

## 1. PROTOCOL AND AMENDMENTS

Version Number	Date	Title
<a href="#">Amendment 5</a>	03 May 2017	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Sage-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus
<a href="#">Amendment 5-EU</a>	14 February 2017	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Sage-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus
<a href="#">Amendment 4- Italy</a>	20 September 2016	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Sage-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus
<a href="#">Amendment 4- Adults Only Sweden</a>	18 August 2016	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Sage-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus
<a href="#">Amendment 4- Adults Only Germany</a>	12 September 2016	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Sage-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus
<a href="#">Amendment 4- Adults Only Denmark</a>	18 August 2016	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Sage-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus
<a href="#">Amendment 4- Adults Only Belgium</a>	18 August 2016	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Sage-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus
<a href="#">Amendment 4- Adults Only</a>	18 August 2016	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Sage-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus
<a href="#">Amendment 4</a>	12 August 2016	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Sage-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus
<a href="#">Amendment 3</a>	22 April 2016	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Sage-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus

Version Number	Date	Title
<a href="#">Amendment 2- Italy</a>	04 February 2016	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Sage-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus
<a href="#">Amendment 2- Adults Only- Sweden</a>	07 December 2015	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Sage-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus
<a href="#">Amendment 2- Adults Only- Germany</a>	21 March 2016	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Sage-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus
<a href="#">Amendment 2- Adults Only</a>	17 November 2015	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Sage-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus
<a href="#">Amendment 2</a>	17 November 2015	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Sage-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus
<a href="#">Amendment 1- Italy</a>	05 December 2015	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Sage-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus
<a href="#">Amendment 1- Denmark</a>	01 March 2016	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Sage-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus
<a href="#">Amendment 1- Adults Only</a>	28 October 2015	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Sage-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus
<a href="#">Amendment 1</a>	27 May 2015	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Sage-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus
<a href="#">Original</a>	09 March 2015	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Sage-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus

**Table 1: Summary of Amendment Changes**

<b>Version</b>	<b>Date</b>
Amendment 1	27 May 2015
Amendment 1- Italy	02 December 2015
Amendment 2	17 November 2015
Amendment 2- Adults Only	17 November 2015
Amendment 2- Adults Only, Sweden	07 December 2015
Amendment 2- Italy	04 February 2016
Amendment 3	22 April 2016
Amendment 4	12 August 2016
Amendment 4- Adults Only	18 August 2016
Amendment 4- Adults Only- Belgium	18 August 2016
Amendment 4- Adults Only Denmark	18 August 2016
Amendment 4- Adults Only Germany	12 September 2016
Amendment 4- Adults Only Sweden	18 August 2016
Amendment 4- Italy	20 September 2016
Amendment 5-EU	14 February 2017
Amendment 5	03 May 2017

**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY  
TO EVALUATE THE EFFICACY AND SAFETY OF SAGE-547 INJECTION  
IN THE TREATMENT OF SUBJECTS WITH SUPER-REFRACTORY  
STATUS EPILEPTICUS**

**PROTOCOL NUMBER: 547-SSE-301/ NCT02477618**

**IND NUMBER: 117901**

**EudraCT Number: 2015-002142-31**

Product: SAGE-547 Injection (allopregnanolone)

Sponsor Contact: [REDACTED], MD

Sage Therapeutics  
215 First Street  
Cambridge, MA 02142  
[REDACTED]

Medical Monitor: [REDACTED], MD

Date of Protocol:	09 March 2015
Date of Amendment One	27 May 2015
Date of Amendment Two	17 November 2015
Date of Amendment Three	22 April 2016
Date of Amendment Four	12 August 2016
Date of Amendment Five	03 May 2017

**Confidentiality Statement**

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.



**PROTOCOL NUMBER: 547-SSE-301**

Sponsor [REDACTED]:

[REDACTED]  
[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]

[REDACTED]

[REDACTED]  
[REDACTED]  
[REDACTED]

Sage Therapeutics

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Sponsor [REDACTED]

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[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

CRO [REDACTED]:

[REDACTED]

## 1. SIGNATURE PAGE

Title of protocol: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus

Protocol No: 547-SSE-301

### Sponsor Approval

[Redacted Signature]

MD

Sage Therapeutics

04 May 2017

Date (dd/mmm/yyyy)

[Redacted Signature]

04 May 2017

Date (dd/mmm/yyyy)

[Redacted Signature]

Sage Therapeutics

[Redacted Signature]

MPH

Sage Therapeutics

04 May 2017

Date (dd/mmm/yyyy)

[Redacted Signature]

[Redacted Signature]

PhD

Sage Therapeutics

04 May 2017

Date (dd/mmm/yyyy)

**Investigator Agreement**

By signing this page, I attest that I have read and understand the contents of Clinical Protocol 547-SSE-301 and any current amendments. I agree to adhere to the design, conduct, and reporting requirements of the study as stated in the clinical protocol and to my obligations to the Sponsor as described in the protocol and executed contracts between myself, my Institution, and the Sponsor. I also agree to adhere to any subsequent amendments to the clinical protocol.

Investigator's Signature: \_\_\_\_\_

Investigator's Name: \_\_\_\_\_

Institution: \_\_\_\_\_

Date (dd/mmm/yyyy): \_\_\_\_\_

## 2. SYNOPSIS

<b>Name of Sponsor:</b> Sage Therapeutics 215 First Street Cambridge, MA 02142																							
<b>Protocol No.</b> 547-SSE-301		<b>Phase:</b> 3																					
<b>Name of Investigational Product:</b> SAGE-547 Injection																							
<b>Name of Active Ingredient:</b> Allopregnanolone																							
<b>Title of the Protocol:</b> A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus																							
<b>Dosing Regimen: SAGE-547 or Placebo Dosing Schedule</b> <table border="1"> <thead> <tr> <th>Hour</th> <th>Type and Duration of SAGE-547 Infusions</th> <th>Dose</th> </tr> </thead> <tbody> <tr> <td>H1</td> <td>One hour loading infusion</td> <td>300 µg/kg/h</td> </tr> <tr> <td>H2 – H120</td> <td>119 hour maintenance infusion</td> <td>90 µg/kg/h</td> </tr> <tr> <td>H121 – H128</td> <td>8 hour taper</td> <td>65 µg/kg/h</td> </tr> <tr> <td>H129 – H136</td> <td>8 hour taper</td> <td>45 µg/kg/h</td> </tr> <tr> <td>H137 – H144</td> <td>8 hour taper</td> <td>25 µg/kg/h</td> </tr> </tbody> </table>			Hour	Type and Duration of SAGE-547 Infusions	Dose	H1	One hour loading infusion	300 µg/kg/h	H2 – H120	119 hour maintenance infusion	90 µg/kg/h	H121 – H128	8 hour taper	65 µg/kg/h	H129 – H136	8 hour taper	45 µg/kg/h	H137 – H144	8 hour taper	25 µg/kg/h			
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<b>Study Sites</b> Up to 180 sites in the USA, Israel, Europe, and Canada.																							
<b>Number of Subjects</b> The study will randomize 126 subjects at up to 180 sites.																							

**Study Population**

Subjects will be aged two years or more, in SRSE<sup>1</sup> (as defined in the Inclusion Criteria [Section 8.1](#)), and being managed in an intensive care setting.

**Duration of Subject Involvement**

Individual subject participation will be up to 30 days.

**Study Design**

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

Patients will follow one of three paths to entry to the study. The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst or seizure suppression with a third-line agent. These subjects will be consented for the study after admission to the intensive care unit, before or after any third-line agents are administered for burst or seizure suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their legally authorized representative (LAR). Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours. Once burst or seizure suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The second path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst or seizure suppression pattern on the EEG. These subjects may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst or seizure suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst or seizure suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst or seizure suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The third path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst

<sup>1</sup> In this study, the term Super-Refractory Status Epilepticus or SRSE is equivalent to “Refractory Status Epilepticus (RSE) that has failed standard treatment” and the two terms are used interchangeably.

or seizure suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These subjects may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 treatment or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within eight hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 63 subjects to be randomized to SAGE-547 and 63 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo).

The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that subjects, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as both the ability to wean the subject off all third-line agents before the end of the infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication infusion, and concurrent signs of physiologic brain activity as determined by EEG. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#) and [Table 2](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo will all subsequently be eligible to be administered SAGE-547 at the higher dose.

### Visit Schedule

The visit schedule and an overview of events at each visit is provided in [Table 1](#), [Table 2](#) and [Table 3](#) Schedule of Assessments.

**Study Objectives*****Primary objective:***

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult and pediatric subjects with SRSE, and for the response to endure at least 24 hours after the end of the SAGE-547 or placebo infusion (primary response).

***Secondary objectives:***

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in the Clinical Global Impression scale (CGI) between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

***Safety objectives:***

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

***Other objectives:***

1. To evaluate the impact of treatment with a higher dose SAGE-547 infusion;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;

3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;
6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS) (age  $\geq 17$  years).

## Endpoints

### *Primary endpoint:*

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### *Secondary endpoints:*

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### *Safety endpoints:*

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.



**Other endpoints:**

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who are treated with a higher dose of SAGE-547.
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS) (age  $\geq 17$  years).

**Inclusion Criteria**

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects two (2) years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed zero, one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst or seizure suppression pattern; or who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst or seizure suppression pattern.

**Exclusion Criteria**

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone or any excipients in SAGE-547.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy with highly malignant/malignant EEG features ([Westhall, Rosetti et al. 2016](#)).

4. Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing underlying neurological disorder.
5. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis but for whatever reason, dialysis that would adequately remove Captisol<sup>®</sup> is not planned;
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the opinion of the investigator, of less than 30 days.
6. Subjects who are being administered more than three third-line agents concomitantly or in whom the qualifying wean cannot be completed within 24 hours, or who are being administered a third-line agent for other indications such as management of raised intra-cranial pressure that would preclude weaning according to this protocol.
7. Subjects with a living will that does not allow heroic measures.
8. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
9. Subjects who have been treated or randomized in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not have received study drug/placebo and then re-enroll).

### **Pharmacogenetic Research**

In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **Statistical Analysis**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

### **Interim Analysis**

When approximately 50% of the subjects have completed the study, an interim analysis may be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

**Analysis of Primary Endpoint**

The analysis of response to treatment between SAGE-547 treated subjects and placebo treated subjects will be performed using a Cochran-Mantel-Haenszel test with variables for treatment, concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). In this analysis, a treatment responder is a subject who is successfully weaned off all third-line agents and blinded study medication prior to the end of study treatment infusion and remains off third-line agents for at least 24 hours following cessation of the blinded study medication, and who has concurrent signs of physiologic brain activity as determined by EEG. The analysis will be based on the ITT Population. The comparison of treatment response rates will be conducted at the 5% level of significance.

**Analysis of Secondary Efficacy Endpoints**

The primary analysis will be repeated for the MITT population. Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section. Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. Secondary analyses will be repeated for the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from Baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third-line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

Summaries of safety endpoints will be based on the overall Safety Population which is defined as all subjects who at least initiated the infusion with blinded study treatment.

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who are treated with a higher dose of SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo. Summary statistics will be presented for subjects who were QW successes.

**Sample Size**

The sample size of this study is based on the assumption of a 25% response rate to placebo treatment, a 30% treatment difference between SAGE-547 and placebo, and a 1:1 randomization schedule. Under these assumptions, with 63 subjects randomized to SAGE-547 and 63 subjects randomized to placebo, there would be >90% power for detecting a significant difference between groups with a 2-sided Chi-squared test at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

**Table 1: Schedule of Assessments for Protocol 547-SSE-301: One Infusion of Study Drug (blinded)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical/SE/Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X	X	X	X	X	X	X	X		X		
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X		X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X		X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X		X	X		X		X		X		
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X			
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>o</sup>											X
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV 3rd-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>p</sup>				
EEG	X	X			X			X	X			
Randomization		X										
Study Drug Administration <sup>q</sup>			X	X	X	X	X	X				
TW Outcome & Open-label Treatment Decision										X <sup>r</sup>		
Physiologic Brain Activity									X			
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

**Table 2: Schedule of Assessments for Protocol 547-SSE-301: Two Infusions of Study Drug (one blinded, one open-label)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V3R
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	0-24h
Eligibility Checklist	X										S
Informed Consent <sup>a</sup>	X										E
Inclusion/Exclusion Criteria	X										E
Demography <sup>b</sup>	X										
Medical and SE and Wean History <sup>c</sup>	X										T
Height	X										A
Weight <sup>d</sup>	X	X	X	X	X	X	X	X		X	B
Serum Pregnancy Test <sup>e</sup>	X										L
Hematology <sup>f</sup>	X		X	X		X		X		X	E
Serum Chemistry and GFR <sup>g</sup>	X		X	X		X		X		X	
Urinalysis <sup>h</sup>	X		X	X		X		X		X	E
Pharmacogenetic sample	X										X
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X	T
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X	E
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X		N
STESS	X										I
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	O
Glasgow Outcome Score (GOS)											N
Supervision Rating Scale (SRS)	X <sup>o</sup>										
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>										
Epilepsy Status	X										N
Clinical Global Impression (CGI)	X										E
Continuous IV Third-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>p</sup>			X
EEG	X	X				X		X	X		T
Randomization		X									
Study Drug Administration <sup>q</sup>			X	X	X	X	X	X			
TW Outcome and Open-label Treatment Decision										X <sup>r</sup>	P
Physiologic Brain Activity									X		
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	A
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	G
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	E
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X	
Pharmacoeconomic Data											
Mortality											

**Table 2 continued**

	V3R	V4R	V5R	V6R	V7R	V8R	V9R	V10R	V11R	V12R
	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3R+14d (±2d)	V3R+21d (±2d)
Weight <sup>d</sup>	X	X	X	X	X	X				
Serum Pregnancy Test <sup>e</sup>										
Hematology <sup>f</sup>	X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X	X		X		X		X		
Vital Signs <sup>i</sup>	X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>	X	X	X	X	X	X	X			
STESS										
FOUR Score <sup>m</sup>	X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)										X
Supervision Rating Scale (SRS)										X
Modified Rankin Score (mRS) <sup>n</sup>										X
Epilepsy Status										X
Clinical Global Impression Scale (CGI)										X
Continuous IV Third-Line Agent(s)	X	X	Wean	Wean	Wean	Wean <sup>p</sup>				
EEG			X			X	X			
Randomization										
Study Drug Administration <sup>q</sup>	X	X	X	X	X	X				
TW Success and Physiologic Brain Activity							X			
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data										X
Mortality										X

**Table 3: Schedule of Assessments for Protocol 547-SSE-301: Qualifying Wean Successes**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical and SE and Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X											
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X											
Serum Chemistry and GFR <sup>f</sup>	X											
Urinalysis <sup>h</sup>	X											
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X											
ECG <sup>j</sup>	X											
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>o</sup>											X
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV Third-Line Agent(s)	X	Wean										
EEG	X	X										
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors <sup>v</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

<sup>a</sup> Written informed consent by proxy (LAR) will be obtained prior to starting any study-related procedures not considered standard of care.

<sup>b</sup> Demographic information will be obtained by proxy and confirmed by the subject when possible.

<sup>c</sup> Medical history will be obtained by proxy and confirmed by the subject when possible. All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Dosing changes with the third-line agent(s) that constitute a wean attempt will be marked as such on the CRF, and the start/stop dates and times of all wean attempts prior to V3 will be recorded, as well as the outcome of the wean attempt.

<sup>d</sup> Weight will be collected at Screening (V1) and prior to administration of the blinded study drug infusion at V2 and the open-label study drug infusion at V10. The weights at V2 and V10 will be used to determine the appropriate infusion rate of the blinded and open-label infusions respectively. If easily obtained (such as via a scale-bed), weight will also be recorded once during each subsequent 24 hour period of the initial study drug infusion period (V3-V8) and second infusion period (V3R-V8R, if applicable).

<sup>e</sup> Serum pregnancy test for females aged 10 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy.

<sup>f</sup> Blood samples will be taken for hematology and serum chemistry and GFR calculation at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will document whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

<sup>g</sup> Blood samples will be taken at V11 or V11R for serum chemistry (renal panel only).

<sup>h</sup> Urine samples will be taken for urinalysis and NAG at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will add a comment about whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

<sup>i</sup> Vital signs will be recorded at the following time points relative to the start of each infusion of study drug: Screening (V1), at 0, 30, 60 minutes ( $\pm 15$  minutes), at 2, 4, and 8 hours ( $\pm 30$  minutes), and at 24, 48, 72, 96, 120, 144, 168, and 192 hours ( $\pm 2$  hours).

<sup>j</sup> For the first 50 subjects randomized in the study, ECG (12-lead) should be performed at Screening (V1) and at the following times relative to the start of study drug infusion. For the blinded (first) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 128, 136, 144, 152, 160, and 192 hours ( $\pm 2$  hours). For the open-label SAGE-547 (second) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 126, 132, 138, 144, 152, 160, and 192 hours ( $\pm 2$  hours). Heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours. If it is not possible to perform ECG immediately after PK sampling up to 160 hours, ECG must be performed within 15 minutes prior to PK sampling up to 160 hours. Following randomization of the first 50 subjects, subsequent subjects randomized in the study will have ECG collected at the following timepoints: Pre-dose and at 1, 12, 24, 48, 72, 96, 120, 144, and 192 hours after the start of the blinded (first) study drug infusion; and, Pre-dose and at 1, 12, 24, 48, 72, 96, 120, 144, and 192 hours after the start of the open-label (second) study drug infusion. It is not necessary for to collect these ECGs with the PK samples at these timepoints and, apart from the 1 h ECG, there is  $\pm 2$  hour time window for these ECGs.

<sup>k</sup> Plasma will be collected to assay for study drug concentrations at the following time points relative to the start of each infusion of study drug: For the blinded (first) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion. For the open-label SAGE-547 (second) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open-label SAGE-547 study drug infusion. Pre-dose samples may be taken within two hours before starting the infusion of study drug; timepoints up to and including 1h will have a time window of  $\pm 5$  minutes; all other timepoints will have a window of  $\pm 15$  minutes.

<sup>m</sup> FOUR Score assessments will be performed at Screening (V1), 24, 48, 72, 96, 120, 144, 168, and 192 hours (all  $\pm 2$  hours) relative to the start of each infusion of study drug, and at V11 or V11R, and at V12 or V12R.

<sup>n</sup> Modified Rankin Score (mRS) applicable for subjects  $\geq 17$  years old only.

<sup>o</sup> SRS at V1 will be a retrospective assessment of the supervision required by the subject immediately prior to admission that includes the index episode of the SE, and mRS at V1 will be a retrospective assessment of the disability and dependence of the subject immediately prior to admission that includes the index episode of the SE.

<sup>p</sup> Target for complete wean of all continuous IV third-line agents by 144 hours at V8/V8R if not completed by 120 hours at V7/V7R.

<sup>q</sup> Study drug infusion is intended for IV administration only with a dedicated peripheral IV line using Sage-approved IV administration bags and lines.

<sup>r</sup> At V10 only a decision to re-treat at a higher dose of SAGE-547 will be made by the Investigator if the continuous IV third-line agent wean has failed or the third-line agent requires re-introduction during V9. Subjects who become eligible for open-label study drug at a higher dose of SAGE-547 will discontinue the planned visit schedule at V10, then repeat V3 (V3R) and all applicable subsequent visits.

<sup>s</sup> AEs will be collected from the time Informed Consent is obtained and prior to the start of study-specific screening procedures not considered standard of care. Collection of AEs will continue throughout the study from V1 through V12 or V12R.



<sup>t</sup> Subjects may enter the study on AEDs and Pressors and be administered AEDs and Pressors during the study. For all randomized and the first 50 QWS subjects, all Concomitant AEDs and Pressors must be recorded on the CRF with details including date and time of starting/stopping each AED and Pressor, the route of administration, changes in doses, and frequency of administration. Details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the CRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”. For subsequent QWS subjects, after the detailed information on all concomitant AEDs and Pressors collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant AED and Pressor and the start and stop dates and times) from Visit 3 to Visit 12 will be recorded in the eCRF.

<sup>u</sup> All third-line agents administered since the diagnosis of SE will be recorded on the CRF. For all randomized and the first 50 QWS subjects, details will include the name of the drug, the start/stop dates and times, and, after consent, the doses with start/stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R. For subsequent QWS subjects, after the detailed information on all concomitant third-line agents collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant third-line agent and the start and stop dates and times) from Visit 3 to Visit 12 will be recorded in the eCRF.

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**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
AE	adverse event
AED	anti-epileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the time-concentration curve
AW	additional weans
BDZ	benzodiazepine
BIEEG	blinded infusion electroencephalogram
BUN	blood urea nitrogen
CBC	complete blood count
CEEG	consent electroencephalogram
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
C <sub>max</sub>	maximum plasma concentration
C <sub>min</sub>	minimum plasma concentration
CNS	central nervous system
CRF	case report form
CSR	clinical study report
CYP2C9	cytochrome P450 enzyme involved in drug metabolism
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EEG	electroencephalogram
EIND	Emergency Use Investigational New Drug Application
EP	European Pharmacopeia
ESETT	Established Status Epilepticus Treatment Trial
FDA	Food and Drug Administration
FOUR	Full Outline of UnResponsiveness
GABA	$\gamma$ -aminobutyric acid
GABA <sub>A</sub>	$\gamma$ -aminobutyric acid-gated chloride channel
GCP	Good Clinical Practice

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
GFR	glomerular filtration rate
GOS	Glasgow Outcome Scale
H	hour
HPLC	high performance liquid chromatography
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent to Treat
IV	intravenous
IVRS	Interactive Voice Randomization System
LAR	legally authorized representative
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent to Treat
mRS-9Q	Modified Rankin Score - 9Q
MS/MS	tandem mass spectrometry
nM	nanomolar
NMDA	n-methyl-D-aspartic acid
OW	other weans
PAEEG	primary endpoint electroencephalogram
PD	pharmacodynamics
PK	pharmacokinetic
QOL	quality of life
QW	qualifying wean
QWEEG	qualifying wean electroencephalogram
RBC	red blood cell
RSE	refractory status epilepticus

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
SAE	serious adverse event
SAP	Statistical Analysis Plan
SE	status epilepticus
SOP	standard operating procedure
SRS	Severity Rating Scale
SRSE	Super-refractory status epilepticus
SSRI	Selective serotonin re-uptake inhibitors
STESS	Status Epilepticus Severity Score
SUSAR	Suspected Unexpected Serious Adverse Reactions
SWFI	Sterile Water for Injection
TAEEG	taper electroencephalogram
T <sub>max</sub>	time at maximum plasma concentration
TW	terminal wean
TWEEG	terminal wean electroencephalogram
US	United States
USP	United States Pharmacopeia

### 3. INTRODUCTION AND RATIONALE

#### 3.1. Status Epilepticus

Status epilepticus (SE) is a life-threatening seizure condition in which the brain is in a state of persistent seizure triggered by neuronal hyperexcitability. The Neurocritical Care Society defines SE as one continuous unremitting seizure lasting longer than five minutes or recurrent seizures without regaining consciousness between seizures for greater than five minutes (Brophy, Bell et al. 2012). Common causes of SE include preexisting epilepsy, cerebrovascular disease (in adults), electrolyte and metabolic disturbances, anoxia, encephalopathies, head trauma, high fever (in children, especially in the first year of life) and drug or substance intoxication. SE is associated with substantial morbidity and mortality.

##### 3.1.1. Epidemiology of SE

Geography, sex, age, and race influence the epidemiology of SE, whose incidence has a bimodal distribution, peaking in infants/young children and the elderly (Hauser 1990; DeLorenzo, Pellock et al. 1995; Wu, Shek et al. 2002). The incidence of SE in the elderly population is at least twice that in the general population. Concurrent medical conditions often exist in the elderly population, which can complicate therapy and worsen the prognosis of SE (Chapman, Smith et al. 2001).

The annual incidence of SE in the US is generally quoted to be within the range of 18/100,000 to 61/100,000, based on a 19-year retrospective study in Rochester, Minnesota (Hesdorffer, Logroscino et al. 1998) and a 2-year prospective study in Richmond, Virginia (DeLorenzo, Pellock et al. 1995), respectively. Two studies from Europe give annual incidences of a similar magnitude, ranging between 9.9/100,000 and 15.8/100,000 (Coeytaux, Jallon et al. 2000; Knake, Rosenow et al. 2001). It is thus estimated that in the United States each year there are as many as 150,000 cases of SE (DeLorenzo, Pellock et al. 1995).

#### 3.2. Refractory SE

When a patient begins to seize, the emergency medical technician will administer a first-line intravenous (IV) benzodiazepine (BDZ), such as diazepam, lorazepam or midazolam (Silbergleit, Durkalski et al. 2012), which is done either at the scene of the seizure or in the ambulance. If this is unsuccessful at abating the seizure, additional doses of the first-line therapy will be administered in the emergency room. Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line therapy, which is an IV anti-epileptic drug (AED) such as phenytoin or valproic acid (Novy, Logroscino et al. 2010; Shorvon 2011; Hocker, Britton et al. 2013).

Approximately 20-30% of patients refractory to first-line treatment will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to approximately 70-80% of patients who receive second-line therapy refractory to that therapy.

If a patient's SE continues after administration of BDZs and AEDs, the subject is diagnosed as having refractory status epilepticus (RSE), which must be treated quickly to terminate the seizure activity, maintain the patient's airway, and prevent cerebral damage. RSE

patients are immediately admitted to the Intensive Care Unit (ICU) and placed in a medically-induced coma to stop all seizure-related activity. The drugs used to induce coma are continuously-infused IV agents, commonly propofol, midazolam, or pentobarbital, referred to as third-line agents (Brophy, Bell et al. 2012).

The RSE patient is continually monitored using electroencephalography (EEG) to ensure that seizure and/or burst suppression is achieved. Burst suppression is a pattern of brain waves seen on an EEG, characterized by periods of activity alternating with periods of little or no activity in the brain, informing medical personnel of the effectiveness of the medically-induced coma. The goal of burst suppression is to allow the brain and corresponding neuronal tissue to restore function and reset to normal pre-seizure levels.

### **3.2.1. Epidemiology of RSE**

Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line AED therapy. In turn, approximately 20 – 30% of these patients treated with AEDs will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to 28% of the total estimated SE patient population refractory to second-line therapy. Based on the previously-cited estimated incidence in the US, this means that there are up to 42,000 incident cases of RSE in the USA, annually (DeLorenzo, Pellock et al. 1995).

## **3.3. Super-refractory SE**

After 24 hours of burst or seizure suppression, the patient is weaned off of the third-line therapy. If the weaning is unsuccessful (neuronal activity has not returned to normal), the third-line agent is re-administered or a different third-line agent is started, and the patient is considered to be in super-refractory status epilepticus (SRSE) (Chapman, Smith et al. 2001; Shorvon 2011; Brophy, Bell et al. 2012). SAGE-547 is being developed as an adjunct to third-line therapy in patients in RSE who have failed standard treatment. In this protocol, the term “RSE that has failed standard treatment” is deemed to be equivalent to the term “SRSE” and the two may be used interchangeably.

### **3.3.1. Epidemiology of SRSE**

The incidence of SRSE is very poorly understood, mainly because the diagnostic codes used for SE do not generally differentiate its nature as responding or refractory to treatment. Based on the variable reporting of outcomes data, the incident cases of SRSE could represent between one and two-thirds of the RSE patients (Novy, Logroscino et al. 2010; Ferlisi and Shorvon 2012; Hocker, Britton et al. 2013; Sutter, Marsch et al. 2013). More detailed epidemiology studies are needed to better elucidate the proportion of RSE patients whose condition becomes super-refractory. A recent review of ICU discharge data in the USA suggests an annual incidence of approximately 35,000, based on patients who required at least three days in the ICU for SE [Sage data on file].

### **3.3.2. Outcomes of SRSE**

SE has varying degrees of mortality depending on the underlying etiologies. Table 4 outlines the acute mortality in patients with SE by etiology (Neligan and Shorvon 2010). The mortality rate of SRSE is estimated to be 30% to 50% using current standard of care.

The causes of death from SE (and therefore SRSE) are heterogeneous, resulting from neuronal cell death, complications of underlying medical conditions, or adverse effects of the current standard treatments. Prognosis worsens and mortality increases with longer duration of SE, i.e. with SE that develops into RSE or SRSE (Neligan and Shorvon 2010), and with longer duration of medically-induced coma (Ferlisi and Shorvon 2012). There is an obvious unmet medical need to improve upon the current standard of care treatment regimens.

Morbidity is high and survivors have outcomes ranging from poor function to vegetative state (Shorvon 2011). Approximately one third of patients with RSE and SRSE will recover, but with chronic neurologic or other deficits (Neligan and Shorvon 2010; Hocker, Britton et al. 2013). In all, it is estimated that less than 25-30% of all SRSE patients have a favorable functional outcome.

**Table 4: Approximate Mortality of Status Epilepticus in Different Etiologies**

Underlying Etiology	Associated Acute Mortality in Patients with SE (%)
Drug reduction/withdrawal, poor AED compliance, or low AED levels	0-10
Cerebrovascular Disease	20-60
Metabolic Disorders	10-35
Acute CNS Infection	0-30
Anoxia	60-100
Alcohol Abuse	0-10
Head Trauma	0-25
Drug Overdose/Toxicity	10-25
Brain Tumors	0-20
Cryptogenic/Idiopathic	5-20

### 3.3.3. Unmet Medical Need in Super-refractory Status Epilepticus

Treatment approaches for SRSE consist of diagnosis and treatment of underlying medical conditions, adding and changing anti-seizure drugs, and repeated attempts at weaning from IV anesthetic agents. Treatment of SRSE has three aims:

- to prevent excitotoxicity, which begins within 24 hours of SE onset;
- to prevent cerebral damage by initiating neuroprotective burst or seizure suppression;
- to prevent the complications of extended periods of anesthesia or unconsciousness (Shorvon 2011).

Currently, there are no therapies that have been specifically approved for RSE or SRSE. The primary drugs used to induce coma are continuously infused IV anesthetics such as propofol, midazolam, or pentobarbital/thiopental, known as third-line agents. Use of these drugs to control SRSE has only been studied in small retrospective reviews or small prospective studies without

controls (Hocker, Britton et al. 2013) therefore there is no agreement on which drug is optimal nor on an optimal dosing regimen for the treatments that are used.

The most common adverse effect of the third-line agents is hemodynamic instability; in addition, they are not universally effective, with breakthrough seizures and withdrawal seizures requiring dose adjustments and changes in third-line agent(s). The drug thought to be most effective in SRSE, pentobarbital, is also associated with the most toxic adverse effect profile, comprising decreased blood pressure and cardiorespiratory collapse (Claassen, Hirsch et al. 2002). The ability to wean patients successfully off the third-line agents as quickly as possible is therefore paramount, and an adjunct to SRSE treatment that enhances the success of the third-line agents and supports their successful weaning in a short timeframe would be an important addition to the therapeutic armamentarium. Preliminary clinical data show that SAGE-547 has been a successful adjunct to third-line therapy in this regard.

### 3.4. SAGE-547 Injection

Allopregnanolone is an endogenous, naturally occurring neuroactive steroid formed in the corpus luteum of the ovary, adrenal cortex and central nervous system (CNS) (Holzbauer, Birmingham et al. 1985; Paul and Purdy 1992; Ottander, Poromaa et al. 2005). It is a metabolite of progesterone created by the actions of 5- $\alpha$  reductase and 3- $\alpha$  hydroxy-steroid dehydrogenase. Allopregnanolone is a potent positive allosteric modulator of both synaptic and extra-synaptic GABA<sub>A</sub> receptors.

SAGE-547 Injection (allopregnanolone aqueous formulation in Captisol<sup>®</sup>) is being developed for the treatment of patients in RSE who have not responded to standard treatment. SAGE-547 Injection is a solution of 5 mg/mL allopregnanolone in Sterile Water for Injection (SWFI), USP and 250 mg/mL betadex sulfobutyl-ether sodium, NF. It is further diluted with Sterile Water for Injection, USP (SWFI) in IV bags to achieve an allopregnanolone concentration of approximately 1.67 mg/mL in an approximately isotonic solution and will be administered intravenously.

#### 3.4.1. Scientific Rationale for SAGE-547 in SRSE

Ineffective recruitment of inhibitory neurotransmission, together with excessive neuronal excitation, likely plays a role in the initiation and propagation of the electrical disturbance occurring in SE. GABA ( $\gamma$ -aminobutyric acid), the major inhibitory neurotransmitter in the central nervous system (CNS), is released from GABAergic neurons and binds to several types of GABA receptors (GABA<sub>A</sub>, GABA<sub>B</sub>, and GABA<sub>C</sub>) on target neurons. GABA<sub>A</sub> receptors are macromolecular proteins that form a chloride ion channel complex and contain specific binding sites for GABA and a number of allosteric regulators, including barbiturates, benzodiazepines, and some anesthetic agents. GABA receptor-mediated inhibition contributes significantly to the normal termination of a seizure (Kapur and Macdonald 1997). SAGE-547 is a positive allosteric modulator of the GABA<sub>A</sub> receptor.

The importance of terminating seizure activity as soon as possible is underpinned by a growing body of evidence from research and clinical observation that SE becomes more difficult to control as its duration increases. It has been postulated that this occurs due to a mechanistic shift from inadequate GABAergic inhibitory receptor-mediated transmission to excessive N-methyl-D-aspartic acid (NMDA) excitatory receptor-mediated transmission (Kapur and Macdonald 1997). As prolonged epileptiform bursting results in a reduction of GABA<sub>A</sub>-mediated synaptic

inhibition, antiepileptic treatments which rely on enhancing intrasynaptic GABA<sub>A</sub> neurotransmission become less effective the longer SE continues.

Furthermore, the constitutive process of synaptic GABA<sub>A</sub> receptor internalization is accelerated by the increased neuronal activity associated with seizures. These findings suggest that the rate of GABA<sub>A</sub> receptor internalization is regulated by neuronal activity, and its acceleration contributes to the reduction of inhibitory transmission observed during prolonged seizures (Kapur and Macdonald 1997). Of note is that SAGE-547 binds to extrasynaptic as well as intrasynaptic GABA<sub>A</sub> receptors; extrasynaptic receptors remain active with ongoing seizure activity, resulting in a putative mode of action for SAGE-547 in SRSE.

Status epilepticus induces cerebral damage that includes neuronal cell necrosis, gliosis, and network reorganization. The major cause of cell death in cerebral damage is excitotoxicity, which is initiated by glutaminergic receptor over-activation, causing calcium to flood the cell, thereby leading to apoptosis and necrosis. This process is initiated within a few hours of the start of seizure activity, and provides the medical imperative to terminate SE as quickly as possible. To prevent the consequences of the excitotoxicity cascade, it is recommended that anesthesia be initiated within 1-2 hours of onset of seizures at doses designed to induce EEG suppression patterns (Shorvon and Ferlisi 2011).

### **3.4.2. SAGE-547 Clinical Program in the Treatment of SRSE**

The current SAGE-547 development program includes:

- a completed Phase 2 open-label trial, Study 547-SSE-201;
- this proposed Phase 3 randomized, double-blind, placebo-controlled trial, Study 547-SSE-301;
- an ongoing open-label, expanded access protocol, Study 547-SSE-302;
- a number of EINDs for SAGE-547 in patients with SRSE.

The designs of these studies are all similar, with a five to six day infusion of SAGE-547 (or placebo), during which time attempts are made to wean the subject off all third-line agents. In the Phase 3 studies, those subjects who cannot be weaned off third-line agents while being administered SAGE-547 (or placebo) may be eligible for a second open-label infusion of SAGE-547 at a higher dose. Follow up of subjects is for 21 – 30 days after the first infusion of study medication.

### **3.4.3. Data from the SAGE-547 Development Program**

The data from 30 subjects included in the on-going clinical evaluation of SAGE-547 for the treatment of adults and children with SRSE clearly offers preliminary evidence that SAGE-547 could provide substantial and clinically significant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate. These subjects comprise 20 from the ongoing Phase 2 trial (71% success rate in 12/17 evaluable subjects) and 10 subjects who received EIND treatments (78% success rate in 7/9 evaluable subjects).

Successful therapy of SRSE has been defined as “the SE is completely controlled by the therapy, without breakthrough of withdrawal seizures, or discontinuation due to side effects or death during therapy,” (Ferlisi and Shorvon 2012). By this definition, which is in accord with the



efficacy assessments used in the overall clinical evaluation of SAGE-547, 19 of the 26 (73%) subjects with SRSE who completed the SAGE-547 infusion were treatment successes. As data collection is ongoing, this information is preliminary and subject to change upon further monitoring.

Published reports on RSE and SRSE have stated mortality rate ranges from 35% to 65%. The underlying etiologies of SE in the 547-SAGE-201 study and EINDs are heterogeneous, and each one conveys a different risk of mortality and longer term morbidity. However, the death rate in subjects who have received SAGE-547, 6 out of 30 (20%) subjects, appears to be lower than the published rates. None of the deaths were considered related to SAGE-547: brain tumor, organophosphate toxicity, respiratory failure, respiratory arrest due to ventilator support withdrawal, and breast cancer.

In the Phase 2 study, 20 SAEs (15 non-fatal) have been reported in 13 (65%) subjects, and of these 3 events in 2 subjects (10%) were considered by the investigator to be related to SAGE-547: pulmonary emboli and tracheostomy dehiscence/infection. The Sponsor did not consider these events to be related to SAGE-547, rather to the underlying disease states. Four of the 20 subjects (20%) experienced AEs considered possibly related to SAGE-547 by the investigator, namely moderate myopathy and severe pulmonary emboli in 1 subject, moderate tracheostomy dehiscence and tracheostomy infection in 1 subject, moderate thrombocytosis in 1 subject and moderate BUN, ALT and AST elevation in 1 subject.

Review of the most current safety data from 547-SAGE-201 reveals that there were changes in serum chemistry, hematology, and urinalysis during the study, but that none of those changes were assessed as related to SAGE-547. There were also no SAGE-547-related changes to vital signs.

Despite the heterogeneity in the underlying causes of SE, the ages of the subject, comorbidities, which normally complicate the treatment of SE, and the fact that all subjects had failed current standard of care treatment, a large majority of subjects had a successful therapy outcome, with discontinuation of all third-line agents and resolution of SE.

Refer to the Investigational Brochure for further information on the pre-clinical and clinical data supporting the use of SAGE-547 in SRSE.

### **3.5. Study Rationale - SAGE-547 in SRSE**

#### **3.5.1. Justification for the Control Group**

Although SAGE-547 has demonstrated extremely promising activity in subjects with SRSE, both in the Phase 2 study and during the EINDs, these have been open-label investigations with no control data for comparison. Generally in the literature there are few data describing the success rates of wean attempts of third-line agents, and few comparative data on the effectiveness of the three main third-line agents, propofol, pentobarbital/thiopental, and midazolam.

Several options for a control group in Study 547-SSE-301 were considered:

- No control group was thought to be unacceptable since there are no reliable published data on success rates in this population that could be used for broad comparisons;
- An active control was considered but found to be impractical since none of the third-line agents are approved for their use in SRSE, no standardized dosing regimens or

treatment guidelines have been adopted for the management of SRSE, and clinicians were unlikely to agree which of the available third-line agents would be reserved for the active control arm;

- Historical controls were considered but abandoned because of the practical difficulties of obtaining high quality data, the lack of ability to prospectively match cases, and a suspicion that clinical practice in the standard of care of SRSE is evolving, mandating the use of prospective, concurrent control data;
- Comparison to standard of care alone was considered as a feasible design. However, in a field where no widely adopted treatment guidelines exist, there was a concern that knowledge of the treatment group (SAGE-547 plus standard of care versus standard of care alone) would alter the behavior of the investigators such that they could be more aggressive with weaning in the SAGE-547 group;
- Placebo control is not without its challenges since the preliminary efficacy data for SAGE-547 show that the compound exerts central pharmacological effects and is associated with positive outcomes in around 70% of patients. There is therefore a potential ethical concern about administering placebo to desperately ill patients who have often exhausted all treatment options for SRSE. This concern has been addressed in two ways: firstly all patients receive current standard of care; secondly, all subjects who fail to be weaned from their third-line agents at the end of the blinded infusion of study drug will be administered open-label SAGE-547 without un-blinding their initial treatment allocation, so treatment with the investigational product is not denied, but delayed about a week in the setting of ongoing receipt of full current standard of care.

It was therefore decided that a blinded, placebo-controlled design was appropriate for Study 547-SSE-301.

### **3.5.2. Justification for the Dose Regimen**

The standard dose regimen has been studied in 19 subjects in the 547-SSE-201 Phase 2 trial; the average peak plasma concentration of SAGE-547 at the end of the loading dose was approximately 144 ng/ml. The average plasma concentration during the maintenance infusion was approximately 70 ng/ml. At these concentrations, there were no clear safety signals although two-thirds of subjects experienced an SAE and there were four deaths, all related to the underlying comorbid conditions. The standard dosing regimen was associated with an approximate 70% successful treatment outcome. For these reasons, the standard dosing regimen has been adopted for the initial SAGE-547 infusion to be compared in a blinded fashion to placebo.

In the 547-SSE-201 trial, three subjects have thus far received the higher dose regimen. This dose regimen has also been well tolerated. The average peak plasma concentrations at the end of the loading dose for both dosing regimens will be in the same range, as the loading dose is the same for both regimens. The average plasma concentrations observed during the higher maintenance dose are 102 ng/ml (n=2). The rationale for adopting the higher dose regimen as the open-label infusion of SAGE-547 for subjects who are retreated in this 547-SSE-301 trial is that those who fail on the standard SAGE-547 dose regimen are afforded the opportunity to have access to a higher dose. The justification to also administer the higher dose regimen to failures on placebo is that the regimen has thus far been well tolerated, and this methodology preserves the blind for the initial infusion.

A five-day dosing regimen with SAGE-547 was investigated in the Phase 2 study, 547-SSE-201. There were some cases when weaning off all third-line agents was not possible within 48 hours, but weaning was completed after the end of the infusion of SAGE-547. For this reason, the duration of dosing with SAGE-547 has been increased from 120 hours (five days) in Phase 2 to 144 hours (six days) in this Phase 3 study.

### 3.5.3. Rationale for Genetic Testing Sub-study

Sage Therapeutics intends to perform genetic research in the SAGE-547 development program in order to explore how genetic variations may affect the metabolism and activity of SAGE-547. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials, and, possibly, to genetically-guided treatment strategies for optimizing decision making with respect to individual benefit:risk. Participation of subjects in genetic research as part of the overall clinical study is optional.

## 3.6. Benefit-Risk Evaluation of the Present Study

Previous reports of human administration of exogenous allopregnanolone indicate that for exposures in men and women up to 150 nM, the most commonly reported AEs were sedation (recorded as sleepiness or tiredness), feelings of intoxication (like alcohol), flushing, and mild headache (Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007). No SAEs were reported (Navarro, Kaddouz et al. 2003; Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007; Kask, Backstrom et al. 2008; Kask, Backstrom et al. 2009; Timby, Hedstrom et al. 2011a). In view of the reduced consciousness and sedation of study subjects at entry into this protocol, none of these previously-reported events are likely to impact subjects in this study.

To date, in the SAGE-547 Phase 2 study and the EIND subjects, a majority of subjects demonstrated a successful therapy outcome (>70%). The majority in the clinical trial (65%) have also experienced SAEs, but none has been considered related to SAGE-547 by the Sponsor (SAEs in 2 subjects (10%) were considered possibly related by Investigator). Five deaths have been reported in 30 subjects (20%), all related to the underlying cause of SRSE and not related to SAGE-547 – this is in the context of published mortality rates between 35% and 65%. These preliminary data suggest that SAGE-547 has the potential to provide clinically relevant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate.

The underlying etiologies of SE are heterogeneous, and each one conveys a different risk of mortality. Subjects who survive SRSE still have a high risk of severe morbidity (Neligan and Shorvon 2010). The subjects treated with SAGE-547 in Study 547-SSE-201, are heterogeneous in factors such as age and etiology of SE, factors that usually complicate treatment and can increase morbidity and mortality. Even with this heterogeneity, the preliminary efficacy and safety data for SAGE-547 are very encouraging, and the mortality rate suggests that the risk to benefit assessment of this treatment rests on the side of benefit.

## **4. ETHICS**

### **4.1. Institutional Review Board or Independent Ethics Committee**

This protocol will be reviewed and approved by the Institutional Review Board (IRB) where the study is conducted. The IRB will meet all FDA requirements governing IRBs (CFR, Title 21, Part 56).

### **4.2. Ethical Conduct of the Study**

The Sponsor, the Medical Monitor, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable ICH and GCP guidelines, and must also conduct the study in accordance with local regulations.

### **4.3. Subject Information and Informed Consent**

Subjects prospectively enrolled in this study will be unable to give consent. Therefore, consent will be given by proxy by a legally authorized representative (LAR). Written informed consent is required for each subject prior to any testing under this protocol not considered standard of care, including screening tests and evaluations. Should a subject gain the ability to sufficiently comprehend the situation and consent during the course of the study, written informed consent or verbal assent will be documented as required or recommended by the institution's IRB.

The form of consent to be obtained will depend on the condition of the subject as determined by the Principal Investigator. The informed consent form (ICF), as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50.

It is the responsibility of the Investigator to obtain consent and to provide the subject's LAR with a copy of the signed and dated informed consent form. The informed consent form for subject participation must also be available as part of the subject file for review by the site's dedicated study monitor or any authorized auditor of the Sponsor or regulatory authorities.

All ICFs used in this study must be approved by the appropriate IRB and by the Sponsor. The ICF must not be altered without the prior agreement of the relevant IRB and the Sponsor.

### **4.4. Ethical and Regulatory Considerations for Pharmacogenetic Sub-study**

#### **4.4.1. Informed Consent for Pharmacogenetics**

The genetic component of this study is optional and subjects may participate in other components of the main study without having to agree to participate in the genetic component. If subject chooses to participate in the genetic component of the study, the subject or LAR must sign and date a specific consent form for the genetic component of the study in addition to the main study consent form. The principal investigator(s) is responsible for ensuring that consent is freely given and that the subject understands that they may discontinue from the genetic aspect of the study independent of their decision to remain within or withdrawal from the main study.

#### **4.4.2. Subject Data Protection Relative to Pharmacogenomics**

Sage Therapeutics will not provide individual genotype results to subjects, their family members, their general physician, their employer or any insurance company unless required to do so by law. While extra precautions will be taken to preserve confidentiality and to prevent genetic data from being linked to an individual's identity outside of a restricted access site, in certain exceptional situations (e.g. in case of a medical emergency or as a consequence of a specific regulatory need), certain individuals may see both genetic data and the personal identifiers of a subject; however in all cases a subject's medical information and genetic files will remain physically separated.

### **5. STUDY OBJECTIVES**

#### **5.1. Primary Objective**

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult and pediatric subjects with SRSE, and for the response to endure at least 24 hours after cessation of the SAGE-547 or placebo infusion (primary response).

#### **5.2. Secondary Objectives**

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in Clinical Global Impression Scale between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

#### **5.3. Safety Objectives**

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

## **5.4. Other Objectives**

1. To evaluate the impact of treatment with a higher dose SAGE-547 infusion;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;
6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS) (age  $\geq 17$  years).

## **6. ENDPOINTS**

### **6.1. Primary Endpoint**

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### **6.2. Secondary Endpoints**

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) and to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;

6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### **6.3. Safety Endpoints**

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.

### **6.4. Other Endpoints**

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who are treated with a higher dose of SAGE-547;
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS) (age  $\geq 17$  years).

## **7. INVESTIGATIONAL PLAN**

### **7.1. Overview of Study Design**

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE. [Figure 1](#) provides an overview of the study design and [Figure 2](#) gives the details of treatment and follow-up on the active treatment arm. Patients will follow one of three paths to entry to the study. The first path is for patients who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst or seizure suppression with a third-line agent. These patients will be consented for the study after admission to the intensive care unit, before or after any third-line agents are administered for burst or seizure suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their

LAR. Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours. Once burst or seizure suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned during the QW will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst or seizure suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The second path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst or seizure suppression pattern on the EEG. These patients may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst or seizure suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst or seizure suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst or seizure suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst or seizure suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The third path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst or seizure suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These patients may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst or seizure suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within eight hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 63 subjects to be randomized to SAGE-547 and 63 subjects to be randomized to placebo. Randomization will be



stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third line agent wean attempts prior to randomization (one vs two or more).

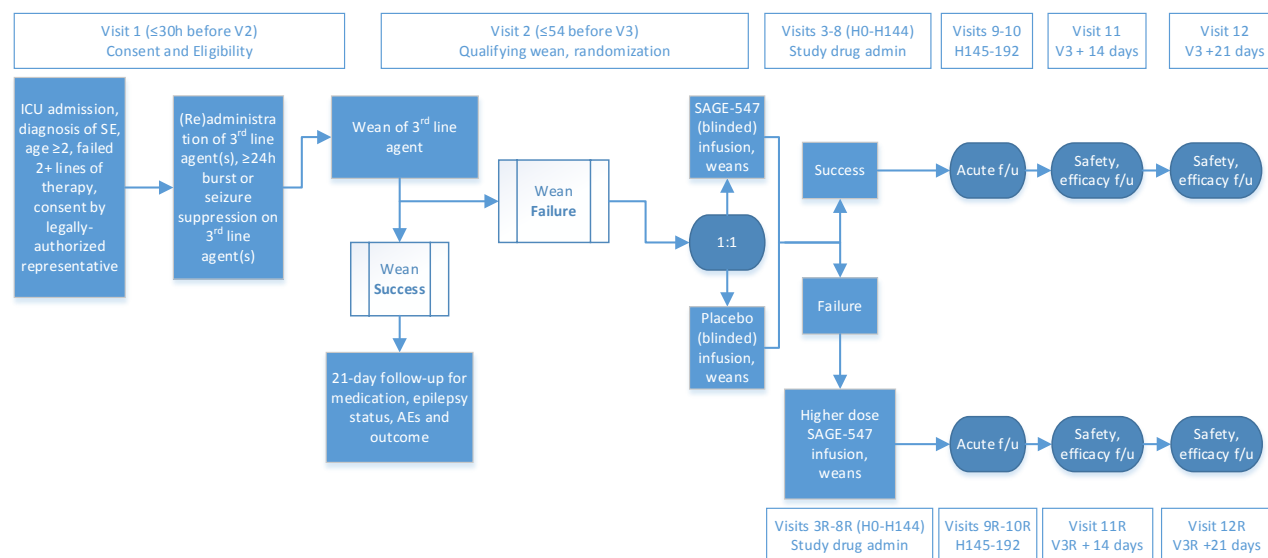
The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as the ability to wean the subject off all third-line agents before the end of the first infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication. Subjects must also have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) at the end of the primary endpoint assessment period as determined by EEG in order to be deemed a success. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#), [Table 2](#) and [Table 3](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion may be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. Eligibility for the open-label treatment must be confirmed in writing by the medical monitor prior to the open-label infusion starting. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo may all subsequently be eligible to be administered SAGE-547 at the higher dose.

**Figure 1: Study Design**



## **7.2. Trial Conduct**

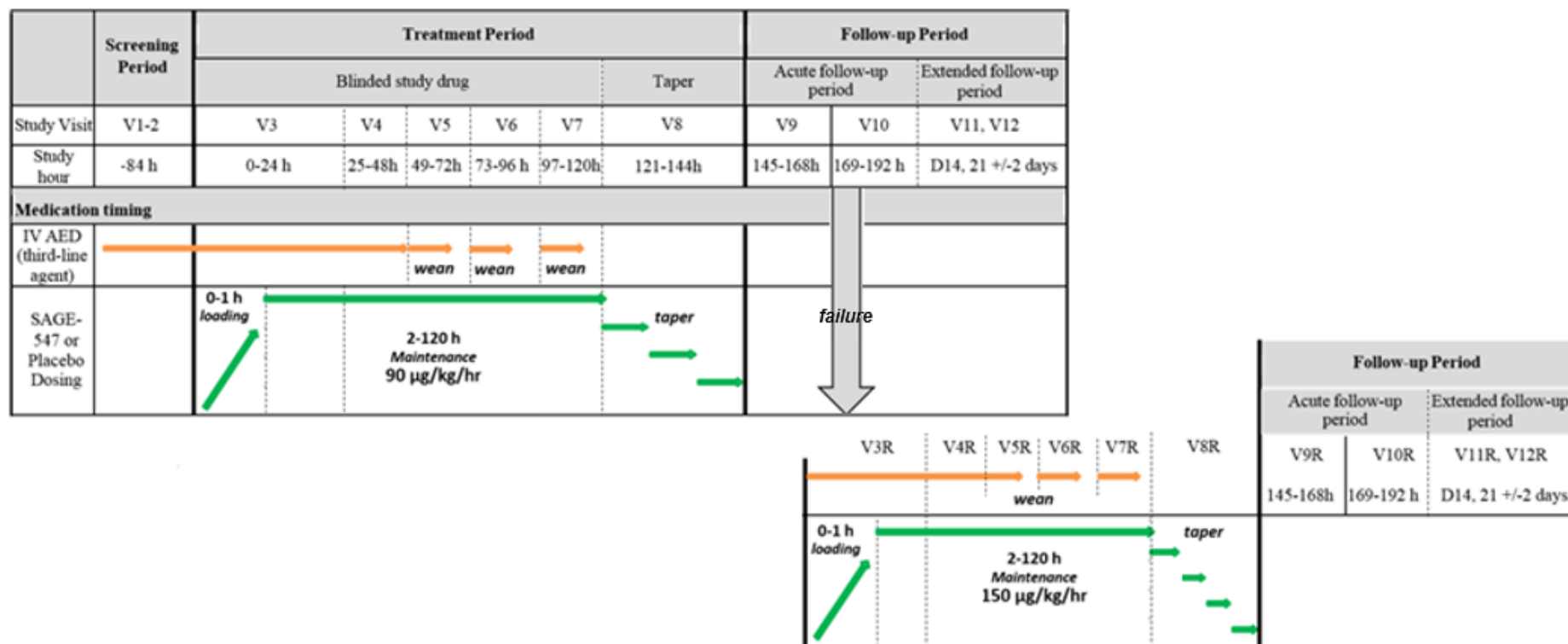
This study will be conducted according to the principles of the World Medical Association Declaration of Helsinki and most recent amendment, and in compliance with the protocol approved by the IRBs/Independent Ethics Committees (IECs), and in accordance with ICH Guidelines on GCP standards.

## **7.3. Blinding and Randomization**

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 63 subjects to be randomized to SAGE-547 and 63 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo). Details of the dynamic randomization process will be included in the SAP.

The randomized portion of the study will be blinded, with the two treatment products (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

The second infusion of SAGE-547 will be administered on an open-label basis to subjects who meet the criteria for open-label treatment.

**Figure 2: Details of Treatment Administration and Follow-up**

## 8. SELECTION AND WITHDRAWAL OF SUBJECTS

The study will randomize 126 patients at up to 180 sites. All subjects deemed eligible to enroll must have written Medical Monitor approval on a case-by-case basis prior to undertaking the qualifying wean.

### 8.1. Inclusion Criteria

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects two (2) years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; *or* who have previously failed zero, one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst or seizure suppression pattern; *or* who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst or seizure suppression pattern.

### 8.2. Exclusion Criteria

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy with highly malignant/malignant EEG features ([Westhall, Rosetti et al. 2016](#)).
4. Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing underlying neurological disorder.
5. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis but for whatever reason, dialysis that would adequately remove Captisol® is not planned;
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;

- d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the experience of the investigator, is less than 30 days.
6. Subjects who are being administered more than three third-line agents concomitantly or for whom the qualifying wean cannot be completed within 24 hours or who are being administered a third-line agent for indications such as raised intra-cranial pressure that would preclude weaning according to this protocol.
7. Subjects with a living will that does not allow heroic measure.
8. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
9. Subjects who have been treated or randomized in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not have received study drug/placebo and then re-enroll).

### **8.3. Selection and Consent of Subjects for Pharmacogenetic Substudy**

All subjects will be asked to participate in pharmacogenetic research; however, participation in research is voluntary and a subject can decide to decline his/her participation without penalty or loss of benefit. Participation or lack thereof will not be a cause for exclusion from any aspect of the main study. In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **8.4. Subject Withdrawal / Study Termination**

#### **8.4.1. Withdrawal/Discontinuation of Individual Subjects**

The reasons for study drug discontinuation and/or subject withdrawal from the study must be recorded in the subject's electronic case report form (eCRF). The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject has been discontinued/withdrawn due to an AE.

##### **8.4.1.1. Withdrawal from the Study**

Subjects or their LAR may withdraw subjects from the study at any time for any reason without compromising the subject's medical care. The Investigator will also withdraw subjects upon the request of Sage Therapeutics or upon termination of the study.

Subjects who withdraw from the study prior to Visit 10 (or 10R) should complete the procedures scheduled for the day of study drug taper (Hour 121-144; Visit8/8R) on the day of their withdrawal, including the SAGE-547 taper schedule, with the addition of the mortality assessment from Visit 12/12R. Subjects who withdraw from the study after Visit 10/10R should undergo study procedures as outlined for Visit 12/12R on the day of their withdrawal. In all cases, the reason for subject withdrawal will be recorded in the eCRF.

Withdrawal of subjects for any reason should be discussed with the Medical Monitor.

#### **8.4.1.2. Discontinuation of Study Drug**

If it is necessary to discontinue the study drug earlier than planned, subjects should continue to be followed per protocol to capture safety and efficacy assessments for the duration of the study period.

The investigator may withdraw the subject from the study drug for the following reasons:

- Upon subject's or LAR's request
- The subject or LAR is unwilling or unable to adhere to the protocol-specified visits
- The subject experiences an intolerable adverse event
- During the course of the study, the subject develops symptoms or conditions listed in the exclusion criteria.
- Other medical reason, at the discretion of the Investigator and/or the Medical Monitor

Subjects who discontinue the study due to an AE considered related to study drug should be followed until the event is resolved, considered stable, or the Investigator determines the event is no longer clinically significant. Study drug discontinuation due to AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

#### **8.4.2. Study Termination**

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of AEs or other findings suggesting unacceptable risk to subjects, administrative or operational reasons. In the event of study termination, Sage Therapeutics will provide written notification to the Investigator. Investigational sites must promptly notify their IRB and initiate withdrawal procedures for participating subjects.

## **9. INVESTIGATIONAL PRODUCT**

### **9.1. Identity of Investigational Product**

SAGE-547 Injection (allopregnanolone)

### **9.2. Clinical Supplies**

#### **9.2.1. SAGE-547**

Adequate supplies of SAGE-547 Injection and materials for intravenous administration will be provided to each site.

SAGE-547 Injection is a clear, colorless sterile solution of allopregnanolone intended for intravenous injection. SAGE-547 Injection is an aqueous solution of 5 mg/mL allopregnanolone in 250 mg/mL Captisol® (betadex sulfobutyl-ether sodium, NF). It is presented either un-buffered or buffered with 10 mM citrate at a pH of 6.0 in either 20 mL or 50 mL vials. SAGE-547 is further diluted according to the Pharmacy Manual to achieve an approximately isotonic solution and will be administered intravenously.

No preservatives are included in the drug product, which is intended to be used as a single-use vial. All inactive components (excipients) used in the formulation are compendial grade and conform to

current USP/EP, and include sodium citrate, citric acid and betadex sulfobutyl-ether sodium (Captisol®).

### **9.2.2. Placebo**

Placebo will be identical to SAGE-547 and presented in identical vials. Placebo will be manufactured in a similar way to SAGE-547 and comprises all excipients but no SAGE-547.

### **9.2.3. Blinding**

The vials of SAGE-547 and placebo will be identical in every way so that they are indistinguishable by the pharmacist, investigator, anyone treating or managing the patient, the monitors, and the sponsor. In this way the first infusion of study drug administered to each patient will be double-blind.

For the blinded study drug infusions, subject-specific dosing kits will be provided. These dosing kits will be pre-labelled with kit number for the first blinded infusion. For the second-infusion, open-label kits will be provided, which will require subject assignment by the pharmacy for reconciliation purposes. The study kits must be stored under refrigerated conditions (2-8 °C). IV administration bags and lines may be provided for the blinded and open-label infusions. Refer to the Pharmacy Manual for additional details.

The label for the SAGE-547 Injection vials will include standard product identification information according to the Code of Federal Regulations, 21CFR 312.6. All study labels will also contain the following statement:

Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use.

## **9.3. Preparation of SAGE-547 or Placebo Injection for Dosing**

The Pharmacy will be responsible for preparing the blinded and open-label study drug for subject dosing. The prepared admixture will be assigned a room temperature (20-25 °C) storage shelf life of 30 hours from time of compounding.

SAGE-547, which is hypertonic, will require dilution with SWFI to achieve an approximately isotonic solution according to the instructions provided in the Pharmacy Manual. Exactly the same procedures will be used to prepare the placebo admixture, so that all site staff remain blinded as to treatment allocation for the first infusion of study drug. SAGE-547 Injection is not intended to be administered to patients undiluted.

Refer to the Pharmacy Manual for specific instructions regarding infusion preparation.

## **9.4. Administration and Accountability**

The Pharmacy will maintain accurate records of all investigational product supplies. Accurate records will be kept regarding the volume of SAGE-547 Injection or placebo used for each IV preparation, as well as the required infusion rate or rates, and the date and time of preparation. Reasons for departure from the expected dosing regimen must also be recorded. To satisfy regulatory requirements regarding drug accountability, all study medication will be reconciled in full. Refer to the Pharmacy Manual for additional details.

## 10. TREATMENT OF SUBJECTS

### 10.1. Dosing Schedule (Blinded Infusions)

SAGE-547 Injection or placebo will be administered according to the dosing schedules in [Table 5](#). The infusion rates to accomplish these  $\mu\text{g/kg/h}$  doses will be calculated according to the weight of the subject obtained within the eight-hour window that follows the declaration of the QW failure at V2 and prior to dosing at V3. The infusion rates will be applied to blinded study drug for the first infusion of study medication.

**Table 5: SAGE-547 or Placebo Dosing Schedule**

Hour	Type and Duration of Study Drug Infusion	Description
H1	One hour loading infusion	300 $\mu\text{g/kg/h}$
H2 – H120	119 hour maintenance infusion	90 $\mu\text{g/kg/h}$
H121 – H128	8 hour taper	65 $\mu\text{g/kg/h}$
H129 – H136	8 hour taper	45 $\mu\text{g/kg/h}$
H137 – H144	8 hour taper	25 $\mu\text{g/kg/h}$

### 10.2. Dosing Schedule (Open-Label Infusions)

Those subjects that qualify for the open-label study drug will be administered SAGE-547 Injection according to the dosing schedule in [Table 6](#). The dose will be administered on a  $\mu\text{g/kg/h}$  basis, and the subject's weight measured prior to dosing during V10 will be used to calculate the doses. These infusion rates will be applied to SAGE-547 treatment for the open-label second infusions of study medication.

**Table 6: SAGE-547 Open-Label Dosing Schedule**

Hour	Type and Duration of SAGE-547 Infusion	Description
H1	One hour loading infusion	300 $\mu\text{g/kg/h}$
H2 – H120	119 hour maintenance infusion	150 $\mu\text{g/kg/h}$
H121 – H126	6 hour taper	125 $\mu\text{g/kg/h}$
H127 – H132	6 hour taper	95 $\mu\text{g/kg/h}$
H133 – H138	6 hour taper	65 $\mu\text{g/kg/h}$
H139 – H144	6 hour taper	35 $\mu\text{g/kg/h}$

### 10.3. Route of Administration

SAGE-547 Injection is intended for IV administration only. The compatibility of SAGE-547 with other drugs is unknown, and the product should be administered via a dedicated peripheral IV line using any Sage-supplied study-specific IV administration bags and lines. In order to preserve blinding, these instructions also apply to the blinded placebo infusions.



## **10.4. Treatment Period**

The treatment period with double-blind SAGE-547 or placebo is six 24-hour periods (144 hours), which may encompass 6-7 calendar days. The open-label study drug treatment period is of identical duration.

## **10.5. Concomitant Medications, Procedures and Treatments**

Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. For all randomized and the first 50 qualifying wean success (QWS) subjects, detailed information on all concomitant medications (concomitant AEDs, third-line agents, pressors, and other concomitant medications), procedures, and treatments should be documented throughout the study from Screening through Visit 12/12R, as described below, and recorded on the eCRF. For subsequent QWS subjects, after the detailed information on all concomitant AEDs, pressors, third-line agents, procedures, and treatments collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant AED or pressor, third-line agent, procedure, and/or treatment, and the start and stop dates and times) from Visit 3 through Visit 12 will be recorded in the eCRF. For subsequent QWS subjects, after the detailed information on all concomitant medications collected during the screening period (Visits 1 and 2) has been recorded, only minimal information, to include the name of the concomitant medications and indication only will be recorded from Visit 3 through Visit 12.

SAGE-547 has demonstrated inhibitory effects on cytochrome P450 isoenzyme 2C9 (CYP2C9). Therefore, AEDs such as phenytoin and phenobarbital that are primarily metabolized by CYP2C9 should be closely monitored during SAGE-547 administration to ensure target exposures are maintained.

### **10.5.1. Concomitant AEDs**

Subjects may enter the study on AEDs, and be administered AEDs during the study. All of these must be recorded on the eCRF with details including date and time of starting and stopping each AED, the route of administration, changes in doses, and frequency of administration. In addition, details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the eCRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.

### **10.5.2. Concomitant Third-Line Agents**

All third-line agents (as defined in [Section 8](#)) administered since the diagnosis of SE will be recorded on the eCRF, whatever path the patient took for entry into the study. Details will include the name of the drug, the start and stop dates and times, and, after consent, the doses with start and stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

In addition, those changes in dose that constitute a wean attempt will be marked as such on the eCRF. In this way the start and stop dates and times of all wean attempts (see [Section 11](#) for definitions) will be recorded, as will the type of wean (QW, OW, or TW) and the outcome of the wean attempt (successful, failed and dose of this third-line agent increased or failed and this third-

line agent stopped and another third-line agent started). Those wean attempts that occur after the TW up to and including Visit 12/12R will be marked “AW”.

Some third-line agents (such as propofol) are also used to induce sedation to facilitate a subject’s ability to tolerate the ventilator. For subjects requiring such sedation, propofol is the preferred agent unless there are contraindications. The eCRF will make clear from the indication for the third-line agent when it is being used for burst or seizure suppression and when it is being used as ventilator support or for another purpose. The investigator will add a note to the eCRF to justify that the doses used are appropriate for sedation and not for seizure or burst suppression. The doses used for ventilator support and other similar uses are usually much lower than those used for seizure or burst suppression, and use of these third-line agents for these other purposes does not constitute a wean failure under this protocol.

### **10.5.3. Concomitant Pressors**

The start and stop dates and times of all pressors will be recorded as well as the start and stop dates and times of all dose changes.

### **10.5.4. Other Concomitant Medications**

All other concomitant medications must be recorded on the eCRF with details including date and time of starting and stopping, the route of administration, dose, and frequency of administration.

## **11. STUDY ASSESSMENTS**

### **11.1. Efficacy Assessments**

#### **11.1.1. Primary Efficacy**

Success or failure will be determined, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo infusion and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the blinded (first) infusion of SAGE-547 or placebo. In addition, subjects must have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) to be deemed to be successes. All subjects who fail to complete their infusion of randomized treatment or do not have at least one attempt during study treatment to wean off all third-line agents will be considered as “failures” for the primary endpoint.

#### **11.1.1.1. Weaning**

Third-line agents are anesthetic agents that are administered in order to reach a seizure or burst suppression EEG pattern. For the purposes of this study, third-line agents are defined as continuous intravenous infusions of pentobarbital/thiopental, midazolam, propofol, and ketamine at maintenance doses alone or in combination sufficient to produce a burst or seizure suppression pattern on the EEG. The following are considered to be minimum maintenance doses of these agents that may be expected alone or in combination to achieve EEG burst suppression. If subjects are on lower doses than these and are not in EEG burst suppression for the first 12 hours of the blinded study drug infusion, they will be considered to be protocol violators and will exit the study.

- Pentobarbital: 1 mg/kg/hour
- Thiopental: 3 mg/kg/hour
- Midazolam: 0.1 mg/kg/hour
- Propofol: 3 mg/kg/hour
- Ketamine 1.2 mg/kg/hour

The timing and nature of the third-line agent weans will be guided by the Clinical Standardization Guidelines for the study, and the clinical judgment of the investigator, and will always be primarily done in the best medical interests of the subject. Advice about weaning may be sought from the Clinical Standardization Team, a group of fellow investigators with experience of performing clinical trials in subjects with SRSE. The Clinical Standardization Team will be able to discuss EEGs related to key study timepoints (terminal wean and the period after the end of the blinded study drug infusion if the terminal wean was successful) in a timely manner in order to provide advice about compliance with the Clinical Standardization Guidelines.

The following guidance for weaning applies to all weans of third-line agents undertaken during the study. Continued determined efforts to liberate subjects from sedation must be undertaken for the entire duration of the blinded study drug infusion. Each failed wean from third-line agents should be followed by a 6-24 hour period of suppression and then another wean attempt, with further optimization of the AED regimen.

Weans include the qualifying wean (QW); the terminal wean (TW), which is the wean of the third-line agent if the subject is on only one third-line agent or the wean of the last third-line agent if the subject is on more than one third-line agent; the other weans (OW), which are the weans of the third-line agents other than the TW if the subject is on more than one third-line agent. The guidance also applies to additional weans (AW), which are the weans from third-line agents that take place after the TW for the first blinded study drug infusion or the second open-label study drug infusion.

### **QW Guidance**

- Wean to be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace that third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Investigators should allow 24 hours to lapse after the end of a “successful” qualifying wean before finally declaring the QW a success. If a third-line agent needs to be re-instituted within that 24 hours, the QW is a failure, and the subject may then be randomized in the study.

### **OW Guidance**

- First OW should not begin before H49 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

- If the subject is on two third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the TW. However the OW may be completed over a shorter or longer time period and may overlap if clinically indicated with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- If the subject is on three third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the wean of the second agent. The second agent should be weaned over 24 hours and that wean completed before starting the TW. However the OWs may be completed over a shorter or longer time period and may overlap if clinically indicated with each other and with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- All OWs should be completed before H96 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **TW Guidance**

- The TW is defined as the wean of the last third-line agent.
- If the subject is on one third-line agent, the TW should not begin before H49 and should begin no later than H97 after starting administration of study drug or starting the open-label infusion of SAGE-547. If the subject has had one or more OWs, the TW should ideally begin as soon as the last OW is complete but in any case not later than H97 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- The TW must be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace this third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Every effort must be made to complete the TW before H120 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547, but the TW must be complete before H144 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **AW Guidance**

- AWs will take place when medically indicated in the opinion of the investigator.

- Ideally the AW should take place over 24 hours, but completion may be over a shorter or longer time period than this. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.

#### 11.1.1.2. EEG

Electroencephalographs (EEGs) that are representative of the intermittent or continuous EEG being used to support key investigator decisions will be collected at the following time points:

- A 24-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst or seizure suppression for the second path to eligibility, and a variable pattern for the third path to eligibility. This EEG also aims to capture the burst or seizure suppression pattern during the 24 hours that precede the QW. If the CEEG does not capture the 24 hours that precede the QW, additional EEG data collected as standard of care prior to the CEEG and prior to the QW may be collected to assess the depth of burst or seizure suppression in the 24 hour period prior to the QW.
- EEG will be performed to cover the qualifying wean (QWEEG). EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for up to 24 hours after the end of the QW. The duration of the QWEEG will be up to 48.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s), the decision to re-institute a third-line agent(s) at doses intended to induce burst or seizure suppression, and the decision that the QW is a success.
- EEG will be performed from three hours prior to the start of the blinded infusion to 12 hours after the start of the blinded infusion. This will be called the BIEEG. The intent of this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG and to assess the depth of burst suppression in the first 12 hours of blinded study drug infusion.
- EEG will be performed to cover the final or terminal wean of third-line agent (TWEEG). The TW is the wean of the final third-line agent during the blinded administration of study drug or the open-label infusion of SAGE-547; if the subject was on one third-line agent, the TW is the wean of that agent. If the subject was on three third-line agents, the TW is the wean of the third and final agent. EEG recording will start 30 minutes prior to the start of the TW, continue for up to 24 hours during the TW, and then continue for the one hour after the end of the TW. The duration of the TWEEG will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the final third-line agent or the decision to re-institute a third-line agent at doses intended to induce burst or seizure suppression because any seizure activity could not be managed using intermittent bolus doses of AEDs.

- EEG will be performed during the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 (TAEED). The TAEED is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the start of the taper (at Hour 119.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours during the taper, and then continue for the one hour after the end of the taper (to Hour 145 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547). The duration of the TAEED will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst or seizure suppression because any seizure activity seen during the taper could not be managed using intermittent bolus doses of AEDs.
- EEG will be obtained to cover the end of the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 and the ensuing 24-hour period, during which the primary endpoint is assessed (PAEED). The PAEED is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the end of taper (at Hour 143.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours after the end of the blinded administration of study treatment or the open-label infusion of SAGE-547, and then continue for the one hour after the end of the 24-hour assessment period (to Hour 169 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547). The duration of the PAEED will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst or seizure suppression because any seizure activity seen in the 24 hours following the end of the blinded administration of study treatment or the open-label infusion of SAGE-547 that could not be managed using intermittent bolus doses of AEDs.

In practice, most subjects are on continuous EEG monitoring or long periods of intermittent EEG monitoring. However, this protocol does not mandate continuous EEG monitoring and breaks from EEG monitoring to provide relief to the scalp from the irritating effects of the electrodes are advised, particularly in children, according to local practice. If a break in EEG monitoring is mandated by local practice guidelines at a time when one of the protocolled EEG segments is to be collected, the break in EEG monitoring will take precedence, with the reason for missing the EEG reading noted on the eCRF. The EEGs obtained for the study are therefore part of the existing EEG record rather than being obtained de-novo at each timepoint. For timepoints where there might be some ambiguity, such as the TWEED, the final EEG record is that of the final attempt to wean the last third-line agent, even if earlier attempts to wean that agent took place. In some cases (the TAEED and PAEED, for instance), the EEG records will overlap, but different cuts are taken to service the different EEG record requirements.

The electronic EEG file will be de-identified, the date and time of the start and stop of the EEG and the subject number will be attached to the file, and the study time point will be indicated (CEEG, QWEED, BIEED, TWEED, TAEED, and PAEED). The PI will indicate on the eCRF what the EEG shows, as follows:

- For the CEEG, the PI will describe the EEG pattern that determined which path to eligibility the subject was on.
- For the QWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure or success on the qualifying wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst or seizure suppression during the qualifying wean constitutes a failure); the QWEEG will extend to cover the 24 hours after the end of third line agents in order to confirm that the QW was a success.
- For the BIEEG, the PI will note the date and time of the start of the EEG and the pattern seen on the EEG.
- For the TWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure on the terminal wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst or seizure suppression during the terminal wean).
- For the TAEED, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst or seizure suppression before the end of the SAGE-547 infusion).
- For the PAEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst or seizure suppression in the 24 hours following the end of the SAGE-547 infusion).

A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm the depth of burst or seizure suppression prior to the QW and during the first 12 hours of the blinded study drug infusion, the PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period (average EEG power at the end of Visit 9 of more than two microvolts):

- All subjects will have the CEEG and QWEEG collected and stored, and the CEEG and QWEEG read;
- Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;
- Those subjects randomized who are not administered the open-label study drug will have the QWEEG, BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the BIEEG, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read;
- Those subjects randomized who later undergo the open-label infusion will have the QWEEG, BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion and the TWEEG, TAEED, and PAEEG related to the open-label study drug

infusion collected and stored, and the BIEEG, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read.

All EEG records may be subject to quantitative EEG analysis.

### **11.1.2. Secondary Efficacy**

#### **11.1.2.1. Clinical Global Impression Scale (CGI)**

The clinical global impression scales are often utilized in clinical trials to allow clinicians to integrate several sources of information into a single rating of the subject's condition. Both the CGI-Severity (Question 1, CGI-S) and the CGI-Improvement (Question 2, CGI-I) employ a 7-point Likert scale measuring severity of the disease state in the subject and improvement, respectively. All severity assessments after initiation of SAGE-547 treatment should consider the general state of the subject over the preceding week. The third question on the scale will not be employed in this trial, and where the scale states "mental illness", this means "physical illness" in this trial.

The CGI-S will be evaluated at Visit 1 and at the last visit, Visit 12 or 12R. The CGI-I will be evaluated at Visit 12 or 12R.

#### **11.1.2.2. Epilepsy Status**

At Visit 1, the diagnosis of epilepsy will be documented as a no/yes question. If there was a previous diagnosis of epilepsy, further details will be documented, including:

- Date of diagnosis;
- Details of anti-epileptic drugs currently being taken;
- Type of epilepsy;
- Seizure frequency in the past month.

Information about the current (index) episode of status epilepticus will be obtained at Visit 1:

- Date of onset
- Date of failure to respond to first line agent(s) and the name(s) of the agent(s)
- Date of failure to respond to second line agent(s) and the name(s) of the agent(s)
- Any previous treatment with third line agents and the response to those agents (details of the third line agent drugs and previous wean attempts will be recorded on the Third Line Agent Medication CRF)
- The cause of the index episode of status epilepticus
- If the subject was transferred from another hospital or from within the hospital, the reason for the transfer will be recorded (such as for study enrollment, due to lack of medical options at original hospital or unit, due to lack of beds at the original hospital or unit, family request, other)

Previous (non-index) diagnosis of status epilepticus will be documented as a no/yes question. If SE did occur in the past 12 months, further information will be gathered, including:



- SE, RSE, or SRSE diagnosis, whichever was the most severe diagnosis for each episode;
- Cause;
- Treatment, including experimental treatments and need for intubation/ventilation;
- Dates of onset and duration.

At Visit 12 or Visit 12R, the following information will be gathered:

- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of SE up to and including Visit 12 or Visit 12R;
- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of seizures (convulsive and non-convulsive) up to and including Visit 12 or Visit 12R;
- Number of separate episodes of SE after H144 at the end of Visit 8 or Visit 8R (no/yes); if yes,
  - SE, RSE, or SRSE diagnosis;
  - Cause;
  - Treatment, including experimental treatments and need for intubation/ventilation;
  - Dates of onset and duration.

Note that a separate episode of SE is defined as an episode of SE separated from other periods of status epilepticus by at least 24 hours.

- Diagnosis of epilepsy since Visit 11 or Visit 11R will be documented as a no/yes question. If a diagnosis of epilepsy has been made, further details will be documented, including:
  - Status as ongoing or new epilepsy since Visit 11 or Visit 11R after initiation of SAGE-547 treatment;
  - Details of anti-epileptic drugs currently being taken;
  - Type of epilepsy and seizure frequency in the past week.

## **11.2. Safety Assessments**

The safety and tolerability of SAGE-547 will be assessed using adverse events, clinical laboratory measures, vital signs, ECG intervals and morphology, and mortality. All safety assessments should be performed per hospital standard of care and will be collected periodically throughout the study according to [Table 1](#), [Table 2](#), and [Table 3](#) (Schedules of Assessments).

### **11.2.1. Adverse Events**

AEs will be collected after informed consent has been signed and prior to study-specific screening procedures not considered standard of care, during subject preparation for SAGE-547 administration and through Visit 12 or Visit 12R. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™) coding system (current version). See [Section 14](#) for additional details.

### **11.2.2. Clinical Laboratory Tests**

Blood samples will be taken for hematology, and serum chemistry and GFR will be calculated at:

- Visit 1 and then at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.
- Blood samples will be taken at Visit 11 or Visit 11R for serum chemistry (renal panel only).

Urine samples (20 ml) will be taken for urinalysis and urine NAG analysis at:

- Visit 1 and at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.

For adults and children  $\geq 30$  kg, these samples will be analyzed at a central laboratory; hour-to-hour medical decisions will be based on sampling for laboratory testing done outside the protocol as part of normal standard of care. GFR will be calculated by the central laboratory. For children under 30 kg, results of local laboratory testing undertaken at the protocolled timepoints may be sent to the central laboratory for inclusion in the central study laboratory database; this obviates the need for additional blood sampling for central laboratory testing.

Any out-of-range values will be flagged by the laboratory; the investigator will add a comment about whether the abnormality is clinically significant. Clinical significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

#### **11.2.2.1. Hematology and Serum Chemistry**

Hematology will include complete blood count (CBC) white blood cell count with differential, platelet count and red blood cell (RBC) count, hemoglobin and hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose. In addition triglycerides will be measured in serum chemistry samples (to aid assessment of lipemia in pharmacokinetic samples).

#### **11.2.2.2. Pregnancy Test**

Females of child-bearing potential will be tested for pregnancy by serum pregnancy test at Visit 1. In this study, since an accurate history of menstruation in girls and menopause in older women may not be available at Visit 1, "child-bearing potential" is taken to mean any female aged 10 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy. Female subjects with a positive pregnancy test will be ineligible for study participation.

#### **11.2.2.3. Urinalysis**

Urinalysis will include assessment of protein, blood, leukocytes, glucose, ketones, urobilinogen, pH, and specific gravity.

### 11.2.3. Vital Signs

Blood pressure, heart rate, and temperature will be recorded at the following time points relative to the first infusion of study drug, and to the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547:

- Visit 1;
- At 0, +30, +60 minutes (+/-15 minutes) and +2, +4 and +8 hours (+/- 30 minutes) after the start of the infusion;
- At +24, +48, +72, +96, +120, +144, +168, and +192 hours (+/- 2 hours) after the start of the infusion.

### 11.2.4. Weight and Height

Weight and height will be measured at Visit 1. Weight will also be obtained at V2, within the eight hour window that follows the declaration of the QW failure and prior to the initiation of the blinded infusion loading dose at H0 of V3, and will be used to calculate the infusion rates throughout the entire blinded treatment course. If a subject qualifies for open-label study drug, the infusion rates for the open-label infusion will be calculated using the subject's weight measured prior to dosing during V10.

If it is not possible to obtain an actual weight at the above-referenced time points, permission from the Clinical Monitor must be obtained to use another method to obtain the subject's weight (such as information from the LAR or estimating using an established local protocol).

In addition, a daily weight will be obtained and recorded if this is easily obtained, such as the use of a scale bed.

### 11.2.5. ECG

For the first 50 subjects randomized in the study, 12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours. If it is not possible to perform ECG immediately after the collection of PK samples up to 160 hours, ECG must be performed within 15 minutes prior to the collection of PK samples up to 160 hours; at other times the allowed time window for ECGs is +/- 2 hours:

- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +128, +136, +144, +152, +160, and +192 hours after the start of the blinded (first) study drug infusion
- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +126, +132, +138, +144, +152, +160, and +192 hours after the start of the open-label (second) study drug

The heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm.

For the subsequent subjects randomized in the study, the following timepoints for ECG will be used:

- pre-dose and at +1, +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the blinded (first) study drug infusion

- pre-dose and at +1, +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the open-label (second) study drug infusion

It is not necessary to collect these ECGs with the PK samples at these timepoints and, apart from the +1h ECG, there is +/- 2 hour time window for these ECGs.

#### **11.2.6. Mortality**

Mortality will be recorded on the Visit 12 or Visit 12R case report form. If the subject has died, the following information will be collected:

- Date of death;
- Cause of death.

As accurate as possible cause of death will be collected, which will be further categorized as due to one of the following causes:

- SE;
- complications of long term intubation and third-line agent infusions;
- underlying cause of qualifying SE;
- co-morbidity existing at the time of the qualifying SE;
- new co-morbidity or trauma;
- study drug;
- other (specify).

#### **11.2.7. Pharmacogenetic Samples**

If a subject's LAR consents to pharmacogenetic sampling, a blood sample for genetic research will be collected at Visit 1 in order to avoid the possible introduction of bias through the exclusion of patients who may withdraw from study due to an AE (a subject population that may be of specific interest for subsequent genetic analysis). If for any reason a sample cannot be taken prior to treatment, a sample can be drawn at any point prior to completion with the restriction that no more than one genetic sample be taken per subject.

The objective of this research is to collect and store blood samples for possible DNA extraction and exploratory research into how genes or specific genetic variation may influence response (i.e. distribution, safety, tolerability, and efficacy) to SAGE-547. Specific genetic variations of interest include but are not limited to: classes of metabolizing enzymes (e.g. Cytochrome P450 supra-family genes), genes encoding enzymes involved in the production and metabolism of allopregnanolone (e.g. AKR1C4 (3 $\alpha$ -hydroxysteroid dehydrogenase)), genes associated with the GABA receptor (e.g. GABRA1-A6, GABRB1-B3, GABRD, GABRE, GABRG1-3) and genes associated with the production and degradation of GABA.

Future research may suggest other genes or gene categories as candidates for influencing not only response to SAGE-547 but also susceptibility to disorders for which SAGE-547 is being evaluated. Thus, the genetic research may involve study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.

### 11.2.7.1. Biological Sampling and Coding Procedures (Pharmacogenetics)

To ensure patient confidentiality, utmost care will be taken in the coding and storage of pharmacogenetic samples.

*Extraction and coding:* DNA will be extracted from the blood sample and the DNA sample will be assigned a unique number replacing information from sampling tube. The assigned DNA number will be used to identify the sample and its corresponding information within Sage Therapeutics or at any designated contract laboratory for the purpose of sequencing of other DNA specific analysis. No personal details sufficient for individual identification will be available to any person (internal or external to Sage Therapeutics) working with the DNA.

*Genotype/Phenotype Analysis:* Samples and data from genetic analysis will be coded. The link between subject enrollment / randomization code and DNA number will be maintained and stored in a secure environment with restricted access. The established link will be used to identify relevant DNA samples for analysis, facilitated correlation of genotype results with clinical data, allow regulatory audit, and to trace samples for destruction in case of withdrawal of consent.

### 11.2.7.2. Retention of Biological Samples for Pharmacogenetic Analysis

Extracted DNA is a finite research that is destroyed in the process of being analyzed. Primary blood samples from which DNA can be extracted will be stored and used until no further analyses are possible, a maximum storage period of 25 years from time of last subject last visit has been reached, or an individual or LAR withdraws his/her or their consent.

### 11.2.8. Other Outcomes

#### 11.2.8.1. Pharmacokinetic Data

Formal plasma analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS)). In addition, all samples will be analyzed for important SAGE-547 metabolites (if and when these are identified) and Captisol® concentrations.

#### Plasma Analysis

Plasma will be collected to assay for SAGE-547 concentrations at the following time points relative to the start of each infusion of study drug:

- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion.
- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open-label SAGE-547 study drug infusion.

- All samples will also be analyzed for plasma concentrations of important metabolites of SAGE-547 if and when these are identified.
- All samples from the first 50 subjects randomized will also be analyzed for plasma concentrations of Captisol®.

The plasma samples will be drawn from the arm contralateral to that used for drug administration. Drawing samples from peripheral arterial or venous lines or from a central line is permissible. PK collection times should be adhered to as strictly as possible. The allowed time window for all samples is: pre-dose in the two hours prior to starting the infusion of study drug; samples up to and including 1h, +/- 5 minutes; subsequent samples, +/- 15 minutes. Subject-specific PK kits for sampling including instructions on collection and processing methods, and storage and shipping conditions, will be provided separately. To maintain the blind, all subjects will have samples taken as outlined above: subjects receiving SAGE-547 will have all samples analyzed for all analytes. Subjects on placebo may have samples analyzed to investigate endogenous allopregnanolone and metabolite concentrations, as well as Captisol® concentrations; experience with the plasma concentration data will determine if and which placebo samples are analyzed.

Each blood sample will be 3 ml in volume for adults and children weighing 30 kg or more, and 1 ml in volume for children weighing less than 30 kg. Separate aliquots will be obtained from each sample to service the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum blood draw for PK analysis for a subject having two infusions of study drug will be 99 ml (33 ml for children weighing less than 30 kg).

Plasma PK parameters for SAGE-547 will be calculated where appropriate (e.g.,  $C_{max}$ ,  $C_{min}$ ,  $t_{max}$ ,  $AUC_{last}$ ,  $AUC_{\infty}$ ,  $CL_s$ ). In addition, similar PK parameters will be calculated for Captisol®. PK parameters for important metabolites of SAGE-547 may be calculated. An evaluation will be made of the feasibility of adopting a population-PK approach to assess drug-drug-interactions with SAGE-547 as victim of AEDs.

In addition, the Visit 9 sample may be analyzed for plasma concentrations of third-line agents.

#### Other Analysis

If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations. The minimum volume of cerebrospinal fluid for analysis is 100 microlitres.

Full details of all pharmacokinetic analyses will be described in the Pharmacokinetic Analysis Plan.

#### **11.2.8.2. Correlation of QT/QTc Changes and Plasma Concentrations of SAGE-547**

An analysis will be performed to determine whether there is any correlation between changes in QT/QTc interval and plasma concentrations of SAGE-547, in order to investigate any effect that SAGE-547 may have on QT/QTc interval.

#### **11.2.8.3. Pharmacoeconomic Data**

At Visit 12 or Visit 12R, the following information will be collected: number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital. If the subject dies before Visit 12 or Visit 12R, data will be collected up to the date of

death. The definition of “hospital” is the institution that the subject was initially treated in. If the subject is transferred to another hospital, that hospital would be the “discharge destination from the hospital” and the “number of days in hospital” would be the number of days in the initial treating hospital.

For those subjects discharged from hospital before Visit 12/12R, the following questions will be asked:

- On what study day was the subject discharged from hospital?
- What type of facility was the subject discharged to (another hospital, a rehabilitation center, a supported care facility, home, other)?
- How many days did the subject stay in this facility?

The following questions will be answered regarding the stay in the ICU and hospital:

- Was the subject still in the ICU at the end of Visit 10/10R?
- If the FOUR Score was  $\geq 12$  at Visit 10/10R and the subject was in the ICU at Visit 10/10R, what was the reason for the subject not being discharged from the ICU (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, other)?
- Was the subject still an in-patient in the hospital at the end of Visit 12/12R?
- If the FOUR Score was  $\geq 15$  at Visit 12/12R and the subject was in the hospital at Visit 12/12R, what was the reason for the subject not being discharged from the hospital (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, unsuitable home circumstances, other)?

#### **11.2.8.4. STESS**

The STESS will be assessed during Visit 1 in order to assess the severity of the status epilepticus.

#### **11.2.8.5. FOUR Score**

The Full Outline of UnResponsiveness or FOUR Score is designed to assess conscious level and unlike other scores, is suitable for subjects who are intubated. It assesses four domains of neurological function (eye responses, motor responses, brainstem reflexes, and breathing pattern).

The FOUR Score will be collected at the following time points relative to each infusion of study drug (the initial blinded infusion and the second open-label infusion if this is administered):

- baseline, +24, +48, +72, +96, +120, +144, +168, and +192 hours (all +/- 2 hours) after the start of the infusion, and at Visit 11/11R and Visit 12/12R.

#### **11.2.8.6. Glasgow Outcome Scale (GOS)**

The GOS is a relatively common assessment scale used to standardize descriptions of the objective degree of recovery from brain injury such as cerebral trauma, or in this case SRSE. It was first used in 1975 ([Jennett and Bond 1975](#)) and allows a prediction of the long-term course of rehabilitation to return to work and everyday life. The scale classifies subjects into 5 groups:

- Death

- Persistent vegetative state
- Severe disability
- Moderate disability
- Good recovery

The GOS will be assessed at Visit 12 or Visit 12R.

#### **11.2.8.7. Supervision Rating Scale (SRS)**

The Supervision Rating (SRS) measures the level of supervision that a patient/subject receives from caregivers. The SRS rates level of supervision on a 13-point ordinal scale that can optionally be grouped into five ranked categories (Independent, Overnight Supervision, Part-Time Supervision, Full-Time Indirect Supervision, and Full-Time Direct Supervision). The SRS was designed to be rated by a clinician based on interviews with the subject and an informant who has observed at first hand the level of supervision received by the subject ([Boake 2000](#)). Scoring is a one-step procedure in which the clinician assigns the rating that is closest to the subject's level. Ratings are based on the level of supervision received, not on how much supervision a subject is judged or predicted to need.

The SRS will be assessed at Visit 1 and Visit 12 or Visit 12R. The Visit 1 assessment will be a retrospective assessment of the supervision required by the subject immediately prior to the admission that included the index episode of status epilepticus.

#### **11.2.8.8. Modified Rankin Scale – 9Q (mRS-9Q)**

The Modified Rankin Scale (mRS) is a commonly used scale to determine disability and functional dependence due to neurological insult such as stroke in adults. The 7-point scale (0 – 6) denotes functional capacity from no symptoms (0) to severe disability (5) and death (6). The Modified Rankin Scale – 9Q is a shortened version consisting of 9 questions that reliably determines the mRS score and was developed to both simplify the assessment and expand the rater base to non- medically trained personnel ([Patel, Rao et al. 2012](#)). The assessment is a web-based tool in the public domain with automatic score calculation and error checking found at [www.modifiedrankin.com](http://www.modifiedrankin.com).

The mRS will be assessed at Visit 1 and at Visit 12 or Visit 12R in subjects  $\geq 17$  years of age. The baseline assessment will be a retrospective assessment of the disability and dependence of the subject immediately prior to the admission that included the index episode of status epilepticus.

## **12. STUDY PROCEDURES**

The study procedures listed below by study day reflect the required data collection times for this protocol. When a time window is necessary, this is specified below. If no time window is specified, the test may be performed at any time within the specified 24-hour period.

### **12.1. Visit 1 (V2- $\leq 30$ h)**

The baseline period will be up to approximately 84 hours prior to starting blinded study treatment and should include the assessments/procedures listed below and summarized in [Table 1](#) and [Table 2](#) (for open-label treatment), the Schedules of Events.



- Informed consent
- Eligibility checklist
- Verification of inclusion/exclusion criteria.
- Demographic information and medical history obtained by proxy and confirmed by the subject when possible.
- SE and wean history
- Blood will be collected from female subjects 10 years to 55 years for a serum pregnancy test unless they are known to be pre-menstrual or post-menopausal or to have had a hysterectomy.
- Blood and urine samples collected for clinical laboratory testing.
- Pharmacogenetic sample will be collected from consenting/eligible subjects.
- Vital signs
- Height
- Weight
- An ECG reading taken.
- Administration of the STESS.
- Administration of the FOUR Score.
- Administration of SRS.
- Administration of the mRS-9Q assessment.
- Assessment of the CGI scale.
- Evaluation of epilepsy status.
- Administration of continuous IV third-line agents.
- Perform EEG.
- Recording of adverse events.
- Recording of previous and concomitant anti-epileptic drugs.
- Recording of previous and concomitant third-line agents.
- Recording of concomitant pressors.
- Recording of other concomitant medications, procedures, and treatments.

## **12.2. Visit 2 (V3-≤54h)**

- Recording of adverse events.
- Recording of concomitant anti-epileptic drugs.
- Recording of concomitant third-line agents.
- Recording of concomitant pressors.

- Recording of other concomitant medications, procedures, and treatments.
- Wean of continuous third-line agent (QW):
  - If wean is successful, subject is followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (these subjects are Qualifying Wean Success subjects or QWS subjects);
  - If wean is not successful, there is ongoing intravenous administration of at least one continuous IV third-line agent and EEG is performed and the subject is randomized.
- Weight
  - Subject weight will be obtained within the eight-hour period from the declaration of failure of QW and prior to the initiation of the blinded infusion loading dose at H0 of V3. This weight will be the dosing weight used to determine the infusion rate for the entire blinded infusion treatment course.

### **12.3. SAGE-547 Treatment Period**

#### **12.3.1. Visit 3/3R (0-24 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs will be recorded at:
  - 0, +30, +60 minutes (+/-15 minutes) and +2, +4, +8 (+/- 30 minutes) and +24 hours (+/- 2 hours) after the start of the infusion
- For the first 50 subjects randomized in the study, ECG readings will be recorded immediately after PK sampling, or within 15 minutes prior to PK sampling, at the following time points:
  - 0 (pre-dose) and at +0.5, +1, +3, +6, +12, and +24 hours after the start of the study drug infusion.
  - Subsequent subjects randomized in the study will have ECG readings recorded at 0 (pre-dose) and +1, +12, and +24 hours after the start of the study drug infusion, it will not be necessary to collect these ECGs with PK samples at these timepoints and, apart from the +1 h ECG, there is +/- 2 hour time window for these ECGs.
- A blood sample for PK analysis should be collected at the following time points (all +/- 15 minutes except where otherwise stated):
  - 0 (pre-dose, within two hours of the start of the infusion) and at +0.5, +1 (+/- 5 minutes), +3, +6, +12, and +24 hours after the start of the study drug infusion.
- Completion of the FOUR Score
  - +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the final declaration of QW success)
- Ongoing intravenous administration of a continuous IV third-line agent.

- Study drug administration in loading (Hour 0-1) and maintenance infusions (at completion of Hour 1).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.3.2. Visit 4/4R (25-48 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +48 hours (+/- 2 hours) after the start of the infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +48 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +48 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +48 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +48 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent.
- Ongoing study drug maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.3.3. Visit 5/5R (49-72 hours)**

- Weight if easily obtained
- Vital signs should be recorded at:
  - +72 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +72 hours after the start of the study drug infusion

- Subsequent subjects randomized in the study will have an ECG reading recorded at +72 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +72 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +72 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.4. Visit 6/6R (73-96 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +96 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +96 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +96 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +96 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +96 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.

- Perform EEG.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.5. Visit 7/7R (97-120 hours)**

- Weight if easily obtained
- Vital signs should be recorded at:
  - +120 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +120 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +120 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +120 hours (+/- 15 minutes) after the start of study drug infusion, immediately prior to the end of the maintenance infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +120 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled. Complete wean by 120 hours if at all possible.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.4. SAGE-547 Taper Period**

#### **12.4.1. Visit 8/8R (121-144 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:

- +144 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after each PK sampling, or within 15 minutes prior to PK sampling at the following time points:
  - +128, +136 hours and +144 hours after the start of the blinded study drug infusion
  - +126, +132, +138 hours and +144 hours after the start of the open-label study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +144 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected (+/- 15 minutes unless otherwise stated):
  - +128 (immediately prior to the end of the first taper step), +136 hours (+/- 5 minutes, immediately prior to the end of the second taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of study drug infusion.
  - During the open-label study drug phase of the study PK blood draws at: +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 hours (+/- 5 minutes, immediately prior to the end of the third taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of the study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +144 hours (+/- 2 hours) after the start of the infusion
- Complete wean of third line agents by H144 if not completed by H120.
- Perform EEG.
- Taper of SAGE-547 infusion begins at hour 121.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## **12.5. Follow-up Period**

### **12.5.1. Visit 9/9R (145-168 hours)**

- Vital signs should be recorded at:
  - +168 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at + 152 hours:
  - +152, +160 hours (+/- 2 hours) after the start of the study drug infusion

- A blood sample for PK analysis should be collected:
  - +152 and +160 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +168 hours (+/- 2 hours) after the start of the infusion
- Perform EEG.
- Assessment of the presence of physiologic brain activity using EEG.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.2. Visit 10/10R (169-192 hours)**

- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +192 hours (+/- 2 hours) after the start of the infusion
- At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine eligibility for the open-label treatment with the higher dose of study drug. This determination may occur at any point during Visit 10: the higher dose open-label infusion must begin within the Visit 10 window. All patients receiving the higher dose open-label treatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.
- Weight if the subject qualifies for the open-label study drug (Visit 10 only, not Visit 10R).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.3. Visit 11/11R (Visit 3/3R + 14d (±2))**

- Blood samples collected for clinical laboratory testing (renal panel only).
- Completion of the FOUR Score (QWS subjects also).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### 12.5.4. Visit 12/12R (Visit 3/3R + 21d ( $\pm 2$ ))

All assessments also performed for QWS subjects.

- Completion of the FOUR Score.
- Administration of the GOS.
- Administration of the SRS.
- Administration of the mRS-9Q assessment.
- Evaluation of epilepsy status (see [Section 11.1.2.2](#) for details).
- Assessment of the CGI Scale.
- Recording of adverse events.
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications.
- Collection of pharmacoeconomic data.
- Mortality will be assessed throughout the study period.

### 13. STATISTICS

#### 13.1. Statistical Plan

Complete details for the analysis and reporting of data from this study will be contained in the Statistical Analysis Plan (SAP).

##### 13.1.1. Interim Analysis

When approximately 50% of subjects have completed the study, an interim analysis may be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

##### 13.1.2. Study Populations

The **Safety Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to actual treatment. This analysis population will be used for all safety analyses.

The **Intent to Treat Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to randomized treatment. This analysis population will be used for all efficacy analyses.

The **Modified Intent to Treat Population** is defined as all subjects who:

1. complete their initial course of blinded SAGE-547 or placebo treatment unless the non-completion was due a drug-related adverse event; and



2. have at least one attempt to wean from third-line agents prior to the end of blinded study treatment infusion unless the failure to wean was because seizures were not controlled.

Subjects will be classified according to randomized treatment. This analysis population will be used for sensitivity analyses of the primary endpoint and select secondary efficacy endpoints.

Narratives will be prepared for all subjects who do not complete the infusion of blinded study medication or were not subjected to any wean attempts. Narratives will include details of the cause of SE, the comorbid conditions, the adverse event(s), and reasons for non-completion of the infusion or failure to attempt weaning. This blinded narrative will be reviewed by the medical monitors and the patient adjudicated as MITT eligible or ineligible. Acceptable reasons for defining a subject as MITT ineligible include death or withdrawal of consent due to progression of the underlying cause of SE or comorbid conditions, unless the cause of death or progression of disease were thought by the investigator, sponsor, or DSMB to be related to study drug.

The **Per-Protocol (PP) Population** is defined as a subset of the MITT population but will exclude data from all subjects with significant protocol violations or deviations. Subjects will be classified according to actual treatment received. This data set will be used for sensitivity analyses to examine the robustness of results for the primary and key secondary efficacy endpoints.

The **Pharmacokinetics Population** is defined as all subjects who at least had an infusion of blinded SAGE-547 initiated and have at least one pharmacokinetic sample collected.

The **Pharmacogenetic Population** is defined all subjects who consent to being included in the pharmacogenetic assessment and provide a pharmacogenetic sample.

Summary statistics of all data collected will be presented for subjects who were QW successes.

### 13.1.3. General Aspects

Tabular displays of descriptive statistics will be provided for all variables. Summary tables will include n, mean, mean, standard deviation, minimum and maximum for continuous variable and frequency and percentage for categorical variables.

### 13.1.4. Analysis of Primary Endpoint

The analysis of response to treatment (see [Section 11.1.1](#) for definition of primary endpoint) between SAGE-547 treated subjects and placebo treated subjects will be performed on the ITT population using a Cochran-Mantel-Haenszel (CMH) test with variables for treatment, concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). The CMH general association statistic and its associated p-value will be presented. The comparison of treatment response rates will be conducted at the 5% level of significance. To confirm the CMH results, a permutation test will also be conducted.

An additional analysis of the primary endpoint will also be performed on the MITT population. In addition sensitivity analyses of the primary endpoint will be performed using the ITT population based on:

- the number of third-line agents (one, two, or three) subjects were administered post-randomization; and
- which third line agent was the subject of the first TW.

### **13.1.5. Analysis of Secondary Efficacy Endpoints**

Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section (Section 6). Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. The analysis of the secondary endpoints will also be performed on the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

### **13.1.6. Analysis of Other Endpoints**

Safety and “Other” endpoints will only be summarized by treatment group.

Summaries of safety endpoints will be based on the overall Safety Population.

### **13.1.7. Epilepsy and SRSE Status**

Diagnosis of epilepsy and recurrence of RSE or SRSE will be documented as the percentage of subjects by time point and overall. Kaplan-Meier curves may be plotted if sufficient data are available.

Utilization of AEDs during follow-up and during recurrence will be summarized.

### **13.1.8. Questionnaires**

The data collected from each questionnaire will be interpreted according to the standard methodology for that questionnaire. There will be no adjustment for missing values.

### **13.1.9. Pharmacokinetic Data Analysis**

Details of the pharmacokinetic data analysis will be described in detail in a separate Pharmacokinetic Analysis Plan.

### **13.1.10. Pharmacogenetic Data Analysis**

Any genotype data generated in this study will be stored within a secured database within Sage Therapeutics and / or a third party contracted to work with Sage Therapeutics to analyze the samples. Because the number of subjects agreeing to participate in the genetic research component of the study is unknown, it is not possible to establish, a priori, whether sufficient samples will be obtained to support formal statistical evaluation of data. As a consequence a Pharmacogenetic Analysis Plan will only be prepared where appropriate and the results obtained from any genetic research will be reported in a report separate from the main study CSR.

### **13.1.11. Open-Label Study Drug Subjects**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are treated with SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo.

### **13.1.12. EEG-Responders**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who are classified as EEG-responders/non-responders based on the independent assessment of the PAEEG. Summaries will be derived for the two randomized treatment groups.

### **13.1.13. QT/QTc Assessment**

An analysis of the correlation between changes in QT/QTc intervals and SAGE-547 plasma levels will be performed to investigate if there is a potential effect that SAGE-547 may have on QT/QTc interval. A detailed description of the QT/QTc assessment will be included in the SAP.

### **13.1.14. Quantitative EEG**

The nine EEG records for each subject may be subjected to exploratory quantitative EEG analysis, the details of which will be included in the EEG Analysis Plan. In summary the following comparisons may be made, SAGE-547 versus placebo: the QWEEG versus the TWEEG (main analysis); the CEEG versus PAEEG (subsidiary analysis); and TAEED versus PAEEG (exploratory analysis).

## **13.2. Determination of Sample Size**

The sample size of this study is based on the assumption of a 25% response rate to placebo treatment, a 30% treatment difference between SAGE-547 and placebo, and a 1:1 randomization schedule. Under these assumptions, with 63 subjects randomized to SAGE-547 and 63 subjects randomized to placebo, there would be >90% power for detecting a significant difference between treatment groups with a 2-sided Chi-squared test at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

## **13.3. Statistical Analysis Plan**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

## **14. ADVERSE EVENTS**

The safety procedures in this study will be detailed in a Safety Management Plan, which will be agreed and signed before the first subject is randomized in the study. [Section 14.1](#) summarizes Investigator responsibilities regarding the identification and documentation of AEs, the classification of AEs for relationship to study drug and severity, and the reporting of AE information to the Sponsor and the IRB.

[Section 14.2](#) summarizes Sponsor/Medical Monitor Responsibilities regarding monitoring of AE data and reporting relevant safety information to FDA.

[Section 14.3](#) lists important AE definitions.

## 14.1. Investigator Responsibilities

### 14.1.1. Identification and Documentation of Adverse Events by Investigator

Subjects will be evaluated and questioned generally (if possible) to identify AEs during the course of the study. AEs will be collected from the signature of the consent form through Visit 12/12R. Adverse events that occur prior to completion of screening will be captured on the Medical History eCRF. Adverse events that occur after completion of screening will be recorded on the Adverse Event eCRF.

All AEs revealed by observation, other diagnostic procedures, or spontaneously reported by the subject and/or in response to an open question from study personnel will be recorded on the Adverse Event Form. Any clinically significant deterioration in laboratory assessments or other clinical findings are considered an AE and must be recorded on the Adverse Event Form, unless otherwise stated. AE information recorded will be entered into the database on an ongoing basis.

AEs with a relationship considered related to study drug (probable, possible) should be followed until the event is resolved or the Investigator determines the event is stable or no longer clinically significant. AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

For SAEs, an electronic Serious Adverse Event eCRF must be completed with as much information as possible and submitted in the time frame described below in [Section 14.1.3](#). When new significant information is obtained as well as when the outcome of an event is known, the electronic SAE eCRF should be updated within 24 hours. If the subject was an outpatient at the time of the SAE and was re-hospitalized due to the SAE, a copy of relevant hospital records (e.g., admission report, laboratory test results, discharge summary, etc.) may be requested to be included as part of the subject medical file.

All SAEs will be followed until resolved or until a stable status has been achieved.

### 14.1.2. Adverse Event Classification

#### 14.1.2.1. Relationship to Investigational Drug

None:	No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state.
Possible:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject, but this is not known for sure.
Probable:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

**14.1.2.2. Severity**

Mild	Discomfort noticed, but no disruption to daily activity.  For subjects that are unconscious, this may be a slight or minor change in a lab result or clinical sign or symptom that does not require immediate corrective action.
Moderate	Discomfort sufficient to reduce or affect normal daily activity, but is not hazardous to health; prescription drug therapy may be employed to treat the AE.  For subjects that are unconscious, this may be a clinically meaningful change that may require immediate corrective action.
Severe	Inability to work or perform normal daily activity and represented a definite hazard to health; prescription drug therapy and/or hospitalization may be employed to treat the AE.  For unconscious subjects, this may be a significant clinical change that requires immediate corrective action.

**14.1.2.3. Action Taken with Investigational Drug**

None	Study medication was continued without change.
Discontinued	Study medication was terminated.
Dose adjusted	Study medication dose/infusion rate was changed and then continued per protocol.
Interrupted	Study medication was interrupted and then continued per protocol.
Unknown	The action taken with regard to study medication is unknown.
Not applicable	Administration of study medication was not ongoing.

**14.1.2.4. Assessment of Outcome**

Ongoing	At the end of the study, the event has not resolved or stabilized.
Ongoing and stable	The event is ongoing but has stabilized and is unlikely to change
Resolved	The event has resolved or the subject recovered without sequelae.
Resolved with sequelae	The event has at least one secondary outcome that may result in permanent disability and/or functional limitation.
Unknown	The status of the event is unknown.
Death	The subject has expired.

**14.1.3. Investigator Reporting to Sponsor and Sponsor Emergency Contact**

All new SAEs that come to the Investigator and/or Sponsor's notice during the course of the study (up to and including the last study visit) must be reported by the Investigator on the designated electronic report form within 24 hours of the point in time when the Investigator becomes aware of the SAE. As additional information becomes available, the designated electronic report form must be updated within 24 hours.

Investigators must report any SAE, whether or not considered drug related. The report must include an assessment of whether there is a reasonable possibility that the drug caused the event.

In a medical emergency (i.e., an event that requires immediate attention regarding the treatment of a subject, operation of the clinical study, and/or the use of investigational drug), study site staff will apply appropriate medical intervention according to current standards of care, and contact the Medical Monitor.

**14.1.4. Medical Monitor and Emergency Contact Information**

[REDACTED], MD  
[REDACTED]

In a study related medical emergency situation, when the assigned Medical Monitor cannot be reached by a caller, an on-call Physician can be reached 24 hours per day, 7 days per week via an [REDACTED] Call-Center:

- Telephone: [REDACTED]  
(this is a chargeable telephone number allowing a global reach from both landlines and mobile phones)
- [REDACTED]

On this internet page a list of country-specific toll-free telephone numbers is provided. It should be noted that not all countries globally have access to toll-free numbers as indicated on the "24/7 Medical Help desk" index. Countries without toll-free numbers need to dial the chargeable number as indicated above. Furthermore, toll-free numbers are not available from mobile phones.

**14.1.5. SAE Reporting Contact Information**

Contact information and reporting instructions are provided in the Safety Management Plan.

**14.1.6. Reporting to Institutional Review Boards (IRBs)**

It is the responsibility of the Investigator to promptly notify the institution's IRB of all serious and unexpected suspected adverse reactions (see [Section 14.3](#) for definitions).

## **14.2. Sponsor/Medical Monitor Responsibilities**

### **14.2.1. Monitoring of Adverse Event Data**

The Medical Monitor will review any newly reported adverse events in an ongoing basis. If the aggregate assessment indicates that an event is occurring more frequently than would normally be expected in this population, or as previously observed, and the sponsor believes that the events are causally related to the administration of SAGE-547, the Sponsor will then report that information in an IND safety report.

### **14.2.2. Data Safety Monitoring Board**

An independent DSMB will monitor the clinical, PK and PD data for safety signals throughout the study and will be asked to assess the placebo response rate at the time of the interim analysis (if conducted) to determine final sample size. In order to perform their monitoring function the DSMB will have access to un-blinded safety data as necessary.

The composition and procedures for the board will be described in a separate DSMB Charter.

### **14.2.3. Reporting to FDA**

The Sponsor must report in an IND safety report any suspected adverse reaction to study treatment that is both serious and unexpected (21 CFR 312.32(c)(1)(i)). Before submitting an IND safety report, the Sponsor will ensure the event meets all three of the definitions: (1) suspected adverse reaction, (2) serious, (3) unexpected. If the AE does not meet all three of the definitions, it should not be submitted as an IND safety report. The Sponsor should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the adverse event and, therefore, that the event meets the definition of a suspected adverse reaction.

If there is a serious and unexpected suspected adverse reaction, the Sponsor will notify the appropriate regulatory agency(ies) and all appropriate parties on an expedited basis. In addition, Sponsors must submit expedited reports of an increased rate of occurrence or severity of serious suspected adverse reactions over that listed in the protocol or Investigational Brochure.

SUSARs will be unblinded prior to reporting to FDA. Unless it is necessary to unblind for the safety of the patient, the investigator will not be informed of the unblinding of the subject.

Under 21 CFR 312.32, Sponsors should identify in the protocol SAEs that it does not plan to report individually in an expedited manner, because they are known consequences of the disease or otherwise common in the study population. Given the grave condition and prognosis of SRSE being studied, individual occurrences of seizures or seizure activity will not be reported expeditiously in this study. Regardless of which events are reported in an expedited manner, all adverse events will be closely monitored throughout the study.

### **14.2.4. Reporting to European Regulatory Authorities**

The Sponsor or its designee is responsible for SUSAR notification to the relevant regulatory authorities as outlined in the ICH Guidelines. All investigators participating in the study will also be informed as required by regulations.

Any SUSAR is subject to expedited reporting in the EU. The Sponsor or its designee, will report any single SUSAR to the appropriate National CAs and IECs within 7 days if the SUSAR is life-threatening or fatal (with the relevant follow-up information subsequently communicated within an

additional eight days), and within 15 days if the SUSAR is neither life-threatening nor fatal. SUSARs reported will be those that have arisen in the present clinical trial and SUSARs that have arisen in other clinical trials conducted by the Sponsor with the same medicinal product.

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to competent authorities of the concerned Member States and to IEC(s)/IRBs as required by national laws.

### **14.3. Adverse Event Definitions**

#### **14.3.1. Adverse Event**

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

#### **14.3.2. Suspected Adverse Reaction**

Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

#### **14.3.3. Life-Threatening**

An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

#### **14.3.4. Serious**

An AE or suspected adverse reaction is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE – see definition above
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disability
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

#### **14.3.5. Unexpected**

An AE or suspected adverse reaction is considered “unexpected”:



- If it is not listed in the Investigational Brochure or is not listed at the specificity or severity that has been observed, or
- If an Investigational Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigational Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigational Brochure listed only cerebral vascular accidents.

“Unexpected,” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigational Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

#### **14.4. Emergency Identification of Study Medication**

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject’s treatment in the study via the IVRS; this normally requires prior approval by the medical monitor. However, if the subject is at immediate risk and the Investigator believes that immediate knowledge of the study treatment will alter medical management, discussion with the medical monitor may take place after unblinding. The Investigator will not unblind the medical monitor during that discussion. The process of unblinding will ensure that only the investigator is unblinded; the medical monitor, study management team, and data management team will not be made aware of the treatment allocation of an individual subject. All cases of emergency unblinding will be fully documented in a way that does not unblind the medical monitor, study management team, and data management team.

### **15. STUDY ADMINISTRATIVE CONSIDERATIONS**

#### **15.1. Quality Control and Quality Assurance**

The Investigators and institutions will permit trial related monitoring, audits, IRB review, and regulatory inspections as requested by FDA, the Sponsor, or the Sponsor’s designee, including direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed informed consent forms, etc.) in addition to case report forms.

Quality assurance and quality control systems with written standard operating procedures (SOPs) will be followed to ensure this trial will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The site’s dedicated study monitor will arrange to visit the Investigator at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be identified and resolved. The study monitor will be given access

to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality assurance officers named by Sage Therapeutics or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements, made by the Sponsor with the Investigator/institution and any other parties involved with the clinical trial, will be in writing in a separate agreement.

## **15.2. Data Handling and Recordkeeping**

### **15.2.1. Data Handling**

Procedures for data handling (including electronic data) used in this protocol will be documented in a Data Management Plan.

### **15.2.2. Case Report Form Completion**

eCRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of demographics, study drug administration, study procedures, AEs, questionnaire completion, efficacy assessments and subject status, including survival.

The Investigator will maintain copies of the eCRFs at the study site. For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate eCRF.

### **15.2.3. Retention of Study Records**

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval and until there are no pending or contemplated marketing applications or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to an appropriate person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

## **15.3. Confidentiality**

To maintain subject privacy, all eCRFs, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available trial registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by Sage Therapeutics to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

#### **15.4. Publication Policy**

All information concerning SAGE-547 is considered confidential and shall remain the sole property of Sage Therapeutics. The Investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval from Sage Therapeutics. No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between Sage Therapeutics and the Investigator.

#### **15.5. Protocol Amendments**

Changes to the conduct of the study should be prepared as a protocol amendment by the Sponsor. Protocol amendments should receive written IRB/IEC approval prior to implementation at the investigative site, except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the trial (e.g., change of monitor, telephone numbers). In this case, Sage Therapeutics will amend and implement the protocol change and subsequently notify the regulatory authorities and the Investigative sites who will notify the respective IRB, as appropriate.

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## APPENDIX 1. FOUR SCORE

### FOUR score

#### Full Outline of UnResponsiveness

##### Eye response

- E4: eyelids open or opened, tracking, or blinking to command
- E3: eyelids open but not tracking
- E2: eyelids closed but open to loud voice
- E1: eyelids closed but open to pain
- E0: eyelids remain closed with pain

##### Motor response

- M4: thumbs-up, fist or peace sign
- M3: localizing to pain
- M2: flexion response to pain
- M1: extension response to pain
- M0: no response to pain or generalized myoclonus status

##### Brainstem reflexes

- B4: pupil and corneal reflexes present
- B3: one pupil wide and fixed
- B2: pupil or corneal reflexes absent
- B1: pupil and corneal reflexes absent
- B0: absent pupil, corneal and cough reflex

##### Respiration pattern

- R4: not intubated, regular breathing pattern
- R3: not intubated, Cheyne-Stokes breathing pattern
- R2: not intubated, irregular breathing
- R1: breathes above ventilatory rate
- R0: breathes at ventilator rate or apnea

Reference ([Iyer, Hoel et al. 2009](#)).

**APPENDIX 2. GLASGOW OUTCOME SCALE (GOS)****GLASGOW  
OUTCOME  
SCALE**

Patient Name: \_\_\_\_\_  
 Rater Name: \_\_\_\_\_  
 Date: \_\_\_\_\_

*Note:* The scale presented here is based on the original article by Jennett and Bond. It has become common practice in clinical trial administration, however, to use a modified version that places the scores in reverse order (i.e., "good recovery" = 1, "moderate disability" =2, etc.).

Score	Description
1	DEATH
2	PERSISTENT VEGETATIVE STATE Patient exhibits no <i>obvious cortical</i> function.
3	SEVERE DISABILITY (Conscious but disabled). Patient depends upon others for daily support due to mental or physical disability or both.
4	MODERATE DISABILITY (Disabled but independent). Patient is independent as far as daily life is concerned. The disabilities found include varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes.
5	GOOD RECOVERY Resumption of normal activities even though there may be minor neurological or psychological deficits.

**TOTAL (1-5):** \_\_\_\_\_

Reference ([Jennett and Bond 1975](#)).

## APPENDIX 3. SUPERVISION RATING SCALE (SRS)

### SUPERVISION RATING SCALE (SRS)

**Instructions:** Circle the rating that is closest to the amount of supervision that the patient *actually receives*. "Supervision" means that someone is responsible for being with the patient.

<u>Rating</u>	<u>Description</u>
<b>Level 1: INDEPENDENT</b>	
1	The patient lives alone or independently. Other persons can live with the patient, but they cannot take responsibility for supervision (for example, a child or elderly person).
2	The patient is unsupervised overnight. The patient lives with one or more persons who <i>could</i> be responsible for supervision (for example, a spouse or roommate), but they are <i>all</i> sometimes absent overnight.
<b>Level 2: OVERNIGHT SUPERVISION</b>	
3	The patient is only supervised overnight. One or more supervising persons are always present overnight but they are <i>all</i> sometimes absent for the rest of the day.
<b>Level 3: PART-TIME SUPERVISION</b>	
4	The patient is supervised overnight and part-time during waking hours, but is allowed on independent outings. One or more supervising persons are always present overnight and are also present during part of waking hours every day. However, the patient is sometimes allowed to leave the residence without being accompanied by someone who is responsible for supervision.
5	The patient is supervised overnight and part-time during waking hours, but is unsupervised during working hours. Supervising persons are <i>all</i> sometimes absent for enough time for them to work full-time outside the home.
6	The patient is supervised overnight and during most waking hours. Supervising persons are <i>all</i> sometimes absent for periods longer than one hour, but less than the time needed to hold a full-time job away from home.
7	The patient is supervised overnight and during almost all waking hours. Supervising persons are <i>all</i> sometimes absent for periods shorter than one hour.
<b>Level 4: FULL-TIME INDIRECT SUPERVISION</b>	
8	The patient is under full-time indirect supervision. At least one supervising person is <i>always</i> present, but the supervising person does not check on the patient more than once every 30 minutes.
9	Same as #8 plus requires overnight safety precautions (for example, a deadbolt on outside door).
<b>Level 5: FULL-TIME DIRECT SUPERVISION</b>	
10	The patient is under full-time direct supervision. At least one supervising person is always present and the supervising person checks on the patient more than once every thirty minutes.
11	The patient lives in a setting in which the exits are physically controlled by others (for example, a locked ward).
12	Same as #11 plus a supervising person is designated to provide full-time line-of-sight supervision (for example, an escape watch or suicide watch).
13	The patient is in physical restraints.

3/12/93

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## APPENDIX 4. MODIFIED RANKIN SCALE – LEVEL OF FUNCTION SURVEY (mRS-9Q)

1. Do you have any symptoms that are bothering you? (For example, trouble with reading or writing, trouble speaking, problems with vision, numbness, weakness, balance trouble, or problems with swallowing?)	YES	<input type="radio"/>	NO	<input type="radio"/>
2. Are you able to do the same work as before?	YES	<input type="radio"/>	NO	<input type="radio"/>
3. Are you able to keep up with your hobbies?	YES	<input type="radio"/>	NO	<input type="radio"/>
4. Have you maintained your ties to friends and family?	YES	<input type="radio"/>	NO	<input type="radio"/>
5. Do you need help making a simple meal, doing household chores, or balancing a checkbook?	YES	<input type="radio"/>	NO	<input type="radio"/>
6. Do you need help with shopping or traveling close to home?	YES	<input type="radio"/>	NO	<input type="radio"/>
7. Do you need another person to help you walk?	YES	<input type="radio"/>	NO	<input type="radio"/>
8. Do you need help with eating, going to the toilet, or bathing?	YES	<input type="radio"/>	NO	<input type="radio"/>
9. Do you stay in bed most of the day and need constant nursing care?	YES	<input type="radio"/>	NO	<input type="radio"/>

## APPENDIX 5. CLINICAL GLOBAL IMPRESSION (CGI)

### Clinical Global Impression (CGI)

#### 1. Severity of illness

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- |                             |   |
|-----------------------------|---|
| 0 = Not assessed            | 4 = Moderately ill                        |
| 1 = Normal, not at all ill  | 5 = Markedly ill                          |
| 2 = Borderline mentally ill | 6 = Severely ill                          |
| 3 = Mildly ill              | 7 = Among the most extremely ill patients |

#### 2. Global improvement: Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.

Compared to his condition at admission to the project, how much has he changed?

- |                        |                     |
|------------------------|---------------------|
| 0 = Not assessed       | 4 = No change       |
| 1 = Very much improved | 5 = Minimally worse |
| 2 = Much improved      | 6 = Much worse      |
| 3 = Minimally improved | 7 = Very much worse |

#### 3. Efficacy index: Rate this item on the basis of drug effect only.

Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.

EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect		Side effects			
		None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
<b>Marked</b>	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
<b>Moderate</b>	Decided improvement. Partial remission of symptoms	05	06	07	08
<b>Minimal</b>	Slight improvement which doesn't alter status of care of patient	09	10	11	12
<b>Unchanged or worse</b>		13	14	15	16
Not assessed = 00					

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

**APPENDIX 6. STATUS EPILEPTICUS SEVERITY SCORE (STESS)**

Outcome Predictor	Feature	Score
Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type (prior to first treatment)	Simple-partial, complex-parial, absence, myoclonic (complicating idiopathic generalized epilepsy)	0
	Generalized-convulsive	1
	Nonconvulsive status epilepticus in coma	2
Age	< 65 years	0
	≥ 65 years	2
History of previous seizures	Yes	0
	No or unknown	1
Summed Total		

**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY  
TO EVALUATE THE EFFICACY AND SAFETY OF SAGE-547 INJECTION  
IN THE TREATMENT OF SUBJECTS WITH SUPER-REFRACTORY  
STATUS EPILEPTICUS**

**PROTOCOL NUMBER: 547-SSE-301**

**IND NUMBER: 117901**

**EudraCT Number: 2015-002142-31**

Product: SAGE-547 Injection (allopregnanolone)

Sponsor Contact:

[REDACTED], MD  
Sage Therapeutics  
215 First Street  
Cambridge, MA 02142  
[REDACTED]

Medical Monitor:

[REDACTED], MD  
[REDACTED]

Date of Protocol: 09 March 2015  
Date of Amendment One 27 May 2015  
Date of Amendment Two (Adults Only) 17 November 2015  
Date of Amendment Three (Adults Only 22 April 2016  
[not implemented])  
Date of Amendment Four (Adults Only) 18 August 2016  
Date of Amendment Five 14 February 2017

**Confidentiality Statement**

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

**PROTOCOL NUMBER: 547-SSE-301**

Sponsor [REDACTED]:

[REDACTED]  
[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]  
[REDACTED]

[REDACTED]  
[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]  
[REDACTED]

[REDACTED]  
[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

CRO [REDACTED]:

[REDACTED]

## 1. SIGNATURE PAGE

Title of Protocol:

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus

Protocol No: 547-SSE-301

### Sponsor Approval

\_\_\_\_\_  
[Redacted Signature]

14 February 2017

Date (dd/mmm/yyyy)

[Redacted Signature], MD  
Sage Therapeutics [Redacted Signature]

14 Feb 2017

\_\_\_\_\_  
[Redacted Signature], MPH  
Sage Therapeutics [Redacted Signature]

Date (dd/mmm/yyyy)

14 Feb 2017

\_\_\_\_\_  
[Redacted Signature], MPH  
Sage Therapeutics [Redacted Signature]

Date (dd/mmm/yyyy)

14-FEB-2017

\_\_\_\_\_  
[Redacted Signature]  
Sage Therapeutics

Date (dd/mmm/yyyy)

**Investigator Agreement**

By signing this page I attest that I have read and understand the contents of Clinical Protocol 547-SSE-301 and any current amendments. I agree to adhere to the design, conduct, and reporting requirements of the study as stated in the clinical protocol and to my obligations to the Sponsor as described in the protocol and executed contracts between myself, my Institution, and the Sponsor. I also agree to adhere to any subsequent amendments to the clinical protocol.

Investigator's Signature: \_\_\_\_\_

Investigator's Name: \_\_\_\_\_

Institution: \_\_\_\_\_

Date: \_\_\_\_\_

## 2. SYNOPSIS

<b>Name of Sponsor:</b> Sage Therapeutics 215 First Street Cambridge, MA 02142		
<b>Protocol No.</b> 547-SSE-301	<b>Phase:</b> 3	
<b>Name of Investigational Product:</b> SAGE-547 Injection		
<b>Name of Active Ingredient:</b> Allopregnanolone		
<b>Title of the Protocol:</b> A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus		
<b>Dosing Regimen: SAGE-547 or Placebo Dosing Schedule</b>		
<b>Hour</b>	<b>Type and Duration of SAGE-547 Infusions</b>	<b>Dose</b>
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	90 µg/kg/h
H121 – H128	8 hour taper	65 µg/kg/h
H129 – H136	8 hour taper	45 µg/kg/h
H137 – H144	8 hour taper	25 µg/kg/h
<b>Dosing Regimen: SAGE-547 Open-Label Dosing Schedule</b>		
<b>Hour</b>	<b>Type and Duration of SAGE-547 Infusion</b>	<b>Dose</b>
H1	One hour loading infusion	300 µg/kg/h
H2 –H120	119 hour maintenance infusion	150 µg/kg/h
H121 – H126	6 hour taper	125 µg/kg/h
H127 – H132	6 hour taper	95 µg/kg/h
H133 – H138	6 hour taper	65 µg/kg/h
H139 – H144	6 hour taper	35 µg/kg/h
<b>Study Sites</b> Up to 180 sites in the USA, Israel, Europe, and Canada.		
<b>Number of Subjects</b>		



The study will randomize 140 subjects at up to 180 sites.

### Study Population

Subjects will be aged two years or more, in SRSE<sup>1</sup> (as defined in the Inclusion Criteria [Section 8.1](#)), and being managed in an intensive care setting.

### Duration of Subject Involvement

Individual subject participation will be up to 30 days.

### Study Design

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

Patients will follow one of three paths to entry to the study. The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst or seizure suppression with a third-line agent. These subjects will be consented for the study after admission to the intensive care unit, before or after any third-line agents are administered for burst or seizure suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their legally authorized representative (LAR). Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours. Once burst or seizure suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The second path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst or seizure suppression pattern on the EEG. These subjects may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst or seizure suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst or seizure suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst or seizure suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

<sup>1</sup> In this study, the term Super-Refractory Status Epilepticus or SRSE is equivalent to “Refractory Status Epilepticus (RSE) that has failed standard treatment” and the two terms are used interchangeably.

The third path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst or seizure suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These subjects may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 treatment or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within eight hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo).

The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that subjects, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as both the ability to wean the subject off all third-line agents before the end of the infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication infusion, and concurrent signs of physiologic brain activity as determined by EEG. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#) and [Table 2](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo will all subsequently be eligible to be administered SAGE-547 at the higher dose.

### Visit Schedule

The visit schedule and an overview of events at each visit is provided in [Table 1](#), [Table 2](#) and [Table 3](#) Schedule of Assessments.

**Study Objectives*****Primary objective:***

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult and pediatric subjects with SRSE, and for the response to endure at least 24 hours after the end of the SAGE-547 or placebo infusion (primary response).

***Secondary objectives:***

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in the Clinical Global Impression scale (CGI) between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

***Safety objectives:***

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

***Other objectives:***

1. To evaluate the impact of treatment with a higher dose SAGE-547 infusion;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;

3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;
6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS) (age  $\geq 17$  years).

## Endpoints

### *Primary endpoint:*

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### *Secondary endpoints:*

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### *Safety endpoints:*

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.

**Other endpoints:**

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who are treated with a higher dose of SAGE-547.
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol<sup>®</sup> and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS) (age  $\geq$  17 years).

**Inclusion Criteria**

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects two (2) years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed zero or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst or seizure suppression pattern; or who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst or seizure suppression pattern.

**Exclusion Criteria**

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone or any excipients in SAGE-547.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy with highly malignant/malignant EEG features ([Westhall, Rosetti et al. 2016](#)).

4. Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing underlying neurological disorder.
5. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis but for whatever reason, dialysis that would adequately remove Captisol<sup>®</sup> is not planned;
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the opinion of the investigator, of less than 30 days.
6. Subjects who are being administered more than three third-line agents concomitantly or in whom the qualifying wean cannot be completed within 24 hours, or who are being administered a third-line agent for other indications such as management of raised intra-cranial pressure that would preclude weaning according to this protocol.
7. Subjects with a living will that does not allow heroic measures.
8. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
9. Subjects who have been treated or randomized in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not have received study drug/placebo and then re-enroll).

### **Pharmacogenetic Research**

In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **Statistical Analysis**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

### **Interim Analysis**

When approximately 50% of the subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

**Analysis of Primary Endpoint**

The analysis of response to treatment between SAGE-547 treated subjects and placebo treated subjects will be performed using a Cochran-Mantel-Haenszel test with variables for treatment, concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). In this analysis, a treatment responder is a subject who is successfully weaned off all third-line agents and blinded study medication prior to the end of study treatment infusion and remains off third-line agents for at least 24 hours following cessation of the blinded study medication, and who has concurrent signs of physiologic brain activity as determined by EEG. The analysis will be based on the ITT Population. The comparison of treatment response rates will be conducted at the 5% level of significance.

**Analysis of Secondary Efficacy Endpoints**

The primary analysis will be repeated for the MITT population. Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section. Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. Secondary analyses will be repeated for the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from Baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third-line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

Summaries of safety endpoints will be based on the overall Safety Population which is defined as all subjects who at least initiated the infusion with blinded study treatment.

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects are treated with a higher dose of SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo. Summary statistics will be presented for subjects who were QW successes.

**Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

**Table 1: Schedule of Assessments for Protocol 547-SSE-301: One Infusion of Study Drug (blinded)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical/SE/Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X	X	X	X	X	X	X	X		X		
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X		X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X		X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X		X	X		X		X		X		
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X			
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>n</sup>											X
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>n</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV 3rd-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>p</sup>				
EEG	X	X				X		X	X			
Randomization		X										
Study Drug Administration <sup>p</sup>			X	X	X	X	X	X				
TW Outcome & Open-label Treatment Decision										X <sup>r</sup>		
Physiologic Brain Activity									X			
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X



**Table 2: Schedule of Assessments for Protocol 547-SSE-301: Two Infusions of Study Drug (one blinded, one open-label)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V3R
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	0-24h
Eligibility Checklist	X										S
Informed Consent <sup>a</sup>	X										E
Inclusion/Exclusion Criteria	X										E
Demography <sup>b</sup>	X										
Medical and SE and Wean History <sup>c</sup>	X										T
Height	X										A
Weight <sup>d</sup>	X	X	X	X	X	X	X	X		X	B
Serum Pregnancy Test <sup>e</sup>	X										L
Hematology <sup>f</sup>	X		X	X		X		X		X	E
Serum Chemistry and GFR <sup>f</sup>	X		X	X		X		X		X	
Urinalysis <sup>h</sup>	X		X	X		X		X		X	E
Pharmacogenetic sample	X										X
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X	T
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X	E
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X		N
STESS	X										I
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	O
Glasgow Outcome Score (GOS)											N
Supervision Rating Scale (SRS)	X <sup>n</sup>										
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>n</sup>										
Epilepsy Status	X										N
Clinical Global Impression (CGI)	X										E
Continuous IV Third-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>p</sup>			X
EEG	X	X				X		X	X		T
Randomization		X									
Study Drug Administration <sup>q</sup>			X	X	X	X	X	X			
TW Outcome and Open-label Treatment Decision										X <sup>r</sup>	P
Physiologic Brain Activity									X		
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	A
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	G
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	E
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X	
Pharmacoeconomic Data											
Mortality											

**Table 2 continued**

	V3R	V4R	V5R	V6R	V7R	V8R	V9R	V10R	V11R	V12R
	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3R+14d (±2d)	V3R+21d (±2d)
Weight <sup>d</sup>	X	X	X	X	X	X				
Serum Pregnancy Test <sup>e</sup>										
Hematology <sup>f</sup>	X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X	X		X		X		X		
Vital Signs <sup>i</sup>	X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>	X	X	X	X	X	X	X			
STESS										
FOUR Score <sup>m</sup>	X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)										X
Supervision Rating Scale (SRS)										X
Modified Rankin Score (mRS) <sup>n</sup>										X
Epilepsy Status										X
Clinical Global Impression Scale (CGI)										X
Continuous IV Third-Line Agent(s)	X	X	Wean	Wean	Wean	Wean <sup>p</sup>				
EEG			X			X	X			
Randomization										
Study Drug Administration <sup>q</sup>	X	X	X	X	X	X				
TW Success and Physiologic Brain Activity							X			
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data										X
Mortality										X

**Table 3: Schedule of Assessments for Protocol 547-SSE-301: Qualifying Wean Successes**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical and SE and Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X											
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X											
Serum Chemistry and GFR <sup>f</sup>	X											
Urinalysis <sup>h</sup>	X											
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X											
ECG <sup>j</sup>	X											
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>o</sup>											X
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV Third-Line Agent(s)	X	Wean										
EEG	X	X										
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

<sup>a</sup> Written informed consent by proxy (LAR) will be obtained prior to starting any study-related procedures not considered standard of care.

<sup>b</sup> Demographic information will be obtained by proxy and confirmed by the subject when possible.

<sup>c</sup> Medical history will be obtained by proxy and confirmed by the subject when possible. All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Dosing changes with the third-line agent(s) that constitute a wean attempt will be marked as such on the CRF, and the start/stop dates and times of all wean attempts prior to V3 will be recorded, as well as the outcome of the wean attempt.

<sup>d</sup> Weight will be collected at Screening (V1) and prior to administration of the blinded study drug infusion at V2 and the open-label study drug infusion at V10. The weights at V2 and V10 will be used to determine the appropriate infusion rate of the blinded and open-label infusions respectively. If easily obtained (such as via a scale-bed), weight will also be recorded once during each subsequent 24 hour period of the initial study drug infusion period (V3-V8) and second infusion period (V3R-V8R, if applicable).

<sup>e</sup> Serum pregnancy test for females aged 10 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy.

<sup>f</sup> Blood samples will be taken for hematology and serum chemistry and GFR calculation at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will document whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

<sup>g</sup> Blood samples will be taken at V11 or V11R for serum chemistry (renal panel only).

<sup>h</sup> Urine samples will be taken for urinalysis and NAG at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will add a comment about whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

<sup>i</sup> Vital signs will be recorded at the following time points relative to the start of each infusion of study drug: Screening (V1), at 0, 30, 60 minutes ( $\pm 15$  minutes), at 2, 4, and 8 hours ( $\pm 30$  minutes), and at 24, 48, 72, 96, 120, 144, 168, and 192 hours ( $\pm 2$  hours).

<sup>j</sup> For the first 50 subjects randomized in the study, ECG (12-lead) should be performed at Screening (V1) and at the following times relative to the start of study drug infusion. For the blinded (first) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 128, 136, 144, 152, 160, and 192 hours ( $\pm 2$  hours). For the open-label SAGE-547 (second) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 126, 132, 138, 144, 152, 160, and 192 hours ( $\pm 2$  hours). Heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours. Following randomization of the first 50 subjects, subsequent subjects randomized in the study will have ECG collected at the following timepoints: Pre-dose and at 1, 12, 24, 48, 72, 96, 120, 144, and 192 hours after the start of the blinded (first) study drug infusion; and, Pre-dose and at 1, 12, 24, 48, 72, 96, 120, 144, and 192 hours after the start of the open-label (second) study drug infusion. It is not necessary for to collect these ECGs with the PK samples at these timepoints and, apart from the 1 h ECG, there is  $\pm 2$  hour time window for these ECGs.

<sup>k</sup> Plasma will be collected to assay for study drug concentrations at the following time points relative to the start of each infusion of study drug: For the blinded (first) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion. For the open-label SAGE-547 (second) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open-label SAGE-547 study drug infusion. Pre-dose samples may be taken within two hours before starting the infusion of study drug; timepoints up to and including 1h will have a time window of  $\pm 5$  minutes; all other timepoints will have a window of  $\pm 15$  minutes.

<sup>m</sup> FOUR Score assessments will be performed at Screening (V1), 24, 48, 72, 96, 120, 144, 168, and 192 hours (all  $\pm 2$  hours) relative to the start of each infusion of study drug, and at V11 or V11R, and at V12 or V12R.

<sup>n</sup> Modified Rankin Score (mRS) applicable for subjects  $\geq 17$  years old only.

<sup>o</sup> SRS at V1 will be a retrospective assessment of the supervision required by the subject immediately prior to admission that includes the index episode of the SE, and mRS at V1 will be a retrospective assessment of the disability and dependence of the subject immediately prior to admission that includes the index episode of the SE.

<sup>p</sup> Target for complete wean of all continuous IV third-line agents by 144 hours at V8/V8R if not completed by 120 hours at V7/V7R.

<sup>q</sup> Study drug infusion is intended for IV administration only with a dedicated peripheral IV line using Sage-approved IV administration bags and lines.

<sup>r</sup> At V10 only a decision to re-treat at a higher dose of SAGE-547 will be made by the Investigator if the continuous IV third-line agent wean has failed or the third-line agent requires re-introduction during V9. Subjects who become eligible for open-label study drug at a higher dose of SAGE-547 will discontinue the planned visit schedule at V10, then repeat V3 (V3R) and all applicable subsequent visits.

<sup>s</sup> AEs will be collected from the time Informed Consent is obtained and prior to the start of study-specific screening procedures not considered standard of care. Collection of AEs will continue throughout the study from V1 through V12 or V12R.

<sup>t</sup> Subjects may enter the study on AEDs and Pressors and be administered AEDs and Pressors during the study. For all randomized and the first 50 QWS subjects, all Concomitant AEDs and Pressors must be recorded on the CRF with details including date and time of starting/stopping each AED and Pressor, the route of administration, changes in doses, and frequency of administration. Details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the CRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”. For subsequent QWS subjects, after the detailed information on all concomitant AEDs and Pressors collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant AED and Pressor and the start and stop dates and times) from Visit 3 to Visit 12 will be recorded in the eCRF.

<sup>u</sup> All third-line agents administered since the diagnosis of SE will be recorded on the CRF. For all randomized and the first 50 QWS subjects, details will include the name of the drug, the start/stop dates and times, and, after consent, the doses with start/stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R. For subsequent QWS subjects, after the detailed information on all concomitant third-line agents collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant third-line agent and the start and stop dates and times) from Visit 3 to Visit 12 will be recorded in the eCRF.

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**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
AE	adverse event
AED	anti-epileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the time-concentration curve
AW	additional weans
BDZ	benzodiazepine
BIEEG	blinded infusion electroencephalogram
BUN	blood urea nitrogen
CBC	complete blood count
CEEG	consent electroencephalogram
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
C <sub>max</sub>	maximum plasma concentration
C <sub>min</sub>	minimum plasma concentration
CNS	central nervous system
CRF	case report form
CSR	clinical study report
CYP2C9	cytochrome P450 enzyme involved in drug metabolism
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EEG	electroencephalogram
EIND	Emergency Use Investigational New Drug Application
EP	European Pharmacopeia
ESETT	Established Status Epilepticus Treatment Trial
FDA	Food and Drug Administration
FOUR	Full Outline of UnResponsiveness
GABA	$\gamma$ -aminobutyric acid
GABA <sub>A</sub>	$\gamma$ -aminobutyric acid-gated chloride channel
GCP	Good Clinical Practice

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
GFR	glomerular filtration rate
GOS	Glasgow Outcome Scale
H	hour
HPLC	high performance liquid chromatography
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent to Treat
IV	intravenous
IVRS	Interactive Voice Randomization System
LAR	legally authorized representative
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent to Treat
mRS-9Q	Modified Rankin Score - 9Q
MS/MS	tandem mass spectrometry
nM	nanomolar
NMDA	n-methyl-D-aspartic acid
OW	other weans
PAEEG	primary endpoint electroencephalogram
PD	pharmacodynamics
PK	pharmacokinetic
QOL	quality of life
QW	qualifying wean
QWEEG	qualifying wean electroencephalogram
RBC	red blood cell
RSE	refractory status epilepticus

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
SAE	serious adverse event
SAP	Statistical Analysis Plan
SE	status epilepticus
SOP	standard operating procedure
SRS	Severity Rating Scale
SRSE	Super-refractory status epilepticus
SSRI	Selective serotonin re-uptake inhibitors
STESS	Status Epilepticus Severity Score
SUSAR	Suspected Unexpected Serious Adverse Reactions
SWFI	Sterile Water for Injection
TAEEG	taper electroencephalogram
T <sub>max</sub>	time at maximum plasma concentration
TW	terminal wean
TWEEG	terminal wean electroencephalogram
US	United States
USP	United States Pharmacopeia

### 3. INTRODUCTION AND RATIONALE

#### 3.1. Status Epilepticus

Status epilepticus (SE) is a life-threatening seizure condition in which the brain is in a state of persistent seizure triggered by neuronal hyperexcitability. The Neurocritical Care Society defines SE as one continuous unremitting seizure lasting longer than five minutes or recurrent seizures without regaining consciousness between seizures for greater than five minutes (Brophy, Bell et al. 2012). Common causes of SE include preexisting epilepsy, cerebrovascular disease (in adults), electrolyte and metabolic disturbances, anoxia, encephalopathies, head trauma, high fever (in children, especially in the first year of life) and drug or substance intoxication. SE is associated with substantial morbidity and mortality.

##### 3.1.1. Epidemiology of SE

Geography, sex, age, and race influence the epidemiology of SE, whose incidence has a bimodal distribution, peaking in infants/young children and the elderly (Hauser 1990; DeLorenzo, Pellock et al. 1995; Wu, Shek et al. 2002). The incidence of SE in the elderly population is at least twice that in the general population. Concurrent medical conditions often exist in the elderly population, which can complicate therapy and worsen the prognosis of SE (Chapman, Smith et al. 2001).

The annual incidence of SE in the US is generally quoted to be within the range of 18/100,000 to 61/100,000, based on a 19-year retrospective study in Rochester, Minnesota (Hesdorffer, Logroscino et al. 1998) and a 2-year prospective study in Richmond, Virginia (DeLorenzo, Pellock et al. 1995), respectively. Two studies from Europe give annual incidences of a similar magnitude, ranging between 9.9/100,000 and 15.8/100,000 (Coeytaux, Jallon et al. 2000; Knake, Rosenow et al. 2001). It is thus estimated that in the United States each year there are as many as 150,000 cases of SE (DeLorenzo, Pellock et al. 1995).

#### 3.2. Refractory SE

When a patient begins to seize, the emergency medical technician will administer a first-line intravenous (IV) benzodiazepine (BDZ), such as diazepam, lorazepam or midazolam (Silbergleit, Durkalski et al. 2012), which is done either at the scene of the seizure or in the ambulance. If this is unsuccessful at abating the seizure, additional doses of the first-line therapy will be administered in the emergency room. Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line therapy, which is an IV anti-epileptic drug (AED) such as phenytoin or valproic acid (Novy, Logroscino et al. 2010; Shorvon 2011; Hocker, Britton et al. 2013).

Approximately 20-30% of patients refractory to first-line treatment will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to approximately 70-80% of patients who receive second-line therapy refractory to that therapy.

If a patient's SE continues after administration of BDZs and AEDs, the subject is diagnosed as having refractory status epilepticus (RSE), which must be treated quickly to terminate the seizure activity, maintain the patient's airway, and prevent cerebral damage. RSE patients are immediately admitted to the Intensive Care Unit (ICU) and placed in a medically-induced coma to stop all seizure-related activity. The drugs used to induce coma are continuously-infused IV agents,



commonly propofol, midazolam, or pentobarbital/thiopental, referred to as third-line agents (Brophy, Bell et al. 2012).

The RSE patient is continually monitored using electroencephalography (EEG) to ensure that seizure and/or burst suppression is achieved. Burst suppression is a pattern of brain waves seen on an EEG, characterized by periods of activity alternating with periods of little or no activity in the brain, informing medical personnel of the effectiveness of the medically-induced coma. The goal of burst suppression is to allow the brain and corresponding neuronal tissue to restore function and reset to normal pre-seizure levels.

### **3.2.1. Epidemiology of RSE**

Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line AED therapy. In turn, approximately 20 – 30% of these patients treated with AEDs will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to 28% of the total estimated SE patient population refractory to second-line therapy. Based on the previously-cited estimated incidence in the US, this means that there are up to 42,000 incident cases of RSE in the USA, annually (DeLorenzo, Pellock et al. 1995).

## **3.3. Super-refractory SE**

After 24 hours of burst or seizure suppression, the patient is weaned off of the third-line therapy. If the weaning is unsuccessful (neuronal activity has not returned to normal), the third-line agent is re-administered or a different third-line agent is started, and the patient is considered to be in super-refractory status epilepticus (SRSE) (Chapman, Smith et al. 2001; Shorvon 2011; Brophy, Bell et al. 2012). SAGE-547 is being developed as an adjunct to third-line therapy in patients in RSE who have failed standard treatment. In this protocol, the term “RSE that has failed standard treatment” is deemed to be equivalent to the term “SRSE” and the two may be used interchangeably.

### **3.3.1. Epidemiology of SRSE**

The incidence of SRSE is very poorly understood, mainly because the diagnostic codes used for SE do not generally differentiate its nature as responding or refractory to treatment. Based on the variable reporting of outcomes data, the incident cases of SRSE could represent between one and two-thirds of the RSE patients (Novy, Logroscino et al. 2010; Ferlisi and Shorvon 2012; Hocker, Britton et al. 2013; Sutter, Marsch et al. 2013). More detailed epidemiology studies are needed to better elucidate the proportion of RSE patients whose condition becomes super-refractory. A recent review of ICU discharge data in the USA suggests an annual incidence of approximately 35,000, based on patients who required at least three days in the ICU for SE [Sage data on file].

### **3.3.2. Outcomes of SRSE**

SE has varying degrees of mortality depending on the underlying etiologies. Table 4 outlines the acute mortality in patients with SE by etiology (Neligan and Shorvon 2010). The mortality rate of SRSE is estimated to be 30% to 50% using current standard of care.

The causes of death from SE (and therefore SRSE) are heterogeneous, resulting from neuronal cell death, complications of underlying medical conditions, or adverse effects of the current standard treatments. Prognosis worsens and mortality increases with longer duration of SE, i.e. with SE that develops into RSE or SRSE (Neligan and Shorvon 2010), and with longer duration of

medically-induced coma ([Ferlisi and Shorvon 2012](#)). There is an obvious unmet medical need to improve upon the current standard of care treatment regimens.

Morbidity is high and survivors have outcomes ranging from poor function to vegetative state ([Shorvon 2011](#)). Approximately one third of patients with RSE and SRSE will recover, but with chronic neurologic or other deficits ([Neligan and Shorvon 2010](#); [Hocker, Britton et al. 2013](#)). In all, it is estimated that less than 25-30% of all SRSE patients have a favorable functional outcome.

**Table 4: Approximate Mortality of Status Epilepticus in Different Etiologies**

Underlying Etiology	Associated Acute Mortality in Patients with SE (%)
Drug reduction/withdrawal, poor AED compliance, or low AED levels	0-10
Cerebrovascular Disease	20-60
Metabolic Disorders	10-35
Acute CNS Infection	0-30
Anoxia	60-100
Alcohol Abuse	0-10
Head Trauma	0-25
Drug Overdose/Toxicity	10-25
Brain Tumors	0-20
Cryptogenic/Idiopathic	5-20

### 3.3.3. Unmet Medical Need in Super-refractory Status Epilepticus

Treatment approaches for SRSE consist of diagnosis and treatment of underlying medical conditions, adding and changing anti-seizure drugs, and repeated attempts at weaning from IV anesthetic agents. Treatment of SRSE has three aims:

- to prevent excitotoxicity, which begins within 24 hours of SE onset;
- to prevent cerebral damage by initiating neuroprotective burst or seizure suppression;
- to prevent the complications of extended periods of anesthesia or unconsciousness ([Shorvon 2011](#)).

Currently, there are no therapies that have been specifically approved for RSE or SRSE. The primary drugs used to induce coma are continuously infused IV anesthetics such as propofol, midazolam, or pentobarbital/thiopental, known as third-line agents. Use of these drugs to control SRSE has only been studied in small retrospective reviews or small prospective studies without controls ([Hocker, Britton et al. 2013](#)) therefore there is no agreement on which drug is optimal nor on an optimal dosing regimen for the treatments that are used.

The most common adverse effect of the third-line agents is hemodynamic instability; in addition, they are not universally effective, with breakthrough seizures and withdrawal seizures requiring dose adjustments and changes in third-line agent(s). The drug thought to be most effective in SRSE, pentobarbital, is also associated with the most toxic adverse effect profile, comprising

decreased blood pressure and cardiorespiratory collapse (Claassen, Hirsch et al. 2002). The ability to wean patients successfully off the third-line agents as quickly as possible is therefore paramount, and an adjunct to SRSE treatment that enhances the success of the third-line agents and supports their successful weaning in a short timeframe would be an important addition to the therapeutic armamentarium. Preliminary clinical data show that SAGE-547 has been a successful adjunct to third-line therapy in this regard.

### 3.4. SAGE-547 Injection

Allopregnanolone is an endogenous, naturally occurring neuroactive steroid formed in the corpus luteum of the ovary, adrenal cortex and central nervous system (CNS) (Holzbauer, Birmingham et al. 1985; Paul and Purdy 1992; Ottander, Poromaa et al. 2005). It is a metabolite of progesterone created by the actions of 5- $\alpha$  reductase and 3- $\alpha$  hydroxy-steroid dehydrogenase. Allopregnanolone is a potent positive allosteric modulator of both synaptic and extra-synaptic GABA<sub>A</sub> receptors.

SAGE-547 Injection (allopregnanolone aqueous formulation in Captisol<sup>®</sup>) is being developed for the treatment of patients in RSE who have not responded to standard treatment. SAGE-547 Injection is a solution of 5 mg/mL allopregnanolone in Sterile Water for Injection (SWFI), USP and 250 mg/mL betadex sulfobutyl-ether sodium, NF. It is further diluted with Sterile Water for Injection, USP (SWFI) in IV bags to achieve an allopregnanolone concentration of approximately 1.67 mg/mL in an approximately isotonic solution and will be administered intravenously.

#### 3.4.1. Scientific Rationale for SAGE-547 in SRSE

Ineffective recruitment of inhibitory neurotransmission, together with excessive neuronal excitation, likely plays a role in the initiation and propagation of the electrical disturbance occurring in SE. GABA ( $\gamma$ -aminobutyric acid), the major inhibitory neurotransmitter in the central nervous system (CNS), is released from GABAergic neurons and binds to several types of GABA receptors (GABA<sub>A</sub>, GABA<sub>B</sub>, and GABA<sub>C</sub>) on target neurons. GABA<sub>A</sub> receptors are macromolecular proteins that form a chloride ion channel complex and contain specific binding sites for GABA and a number of allosteric regulators, including barbiturates, benzodiazepines, and some anesthetic agents. GABA receptor-mediated inhibition contributes significantly to the normal termination of a seizure (Kapur and Macdonald 1997). SAGE-547 is a positive allosteric modulator of the GABA<sub>A</sub> receptor.

The importance of terminating seizure activity as soon as possible is underpinned by a growing body of evidence from research and clinical observation that SE becomes more difficult to control as its duration increases. It has been postulated that this occurs due to a mechanistic shift from inadequate GABAergic inhibitory receptor-mediated transmission to excessive N-methyl-D-aspartic acid (NMDA) excitatory receptor-mediated transmission (Kapur and Macdonald 1997). As prolonged epileptiform bursting results in a reduction of GABA<sub>A</sub>-mediated synaptic inhibition, antiepileptic treatments which rely on enhancing intrasynaptic GABA<sub>A</sub> neurotransmission become less effective the longer SE continues.

Furthermore, the constitutive process of synaptic GABA<sub>A</sub> receptor internalization is accelerated by the increased neuronal activity associated with seizures. These findings suggest that the rate of GABA<sub>A</sub> receptor internalization is regulated by neuronal activity, and its acceleration contributes to the reduction of inhibitory transmission observed during prolonged seizures (Kapur and Macdonald 1997). Of note is that SAGE-547 binds to extrasynaptic as well as intrasynaptic GABA<sub>A</sub> receptors;

extrasynaptic receptors remain active with ongoing seizure activity, resulting in a putative mode of action for SAGE-547 in SRSE.

Status epilepticus induces cerebral damage that includes neuronal cell necrosis, gliosis, and network reorganization. The major cause of cell death in cerebral damage is excitotoxicity, which is initiated by glutaminergic receptor over-activation, causing calcium to flood the cell, thereby leading to apoptosis and necrosis. This process is initiated within a few hours of the start of seizure activity, and provides the medical imperative to terminate SE as quickly as possible. To prevent the consequences of the excitotoxicity cascade, it is recommended that anesthesia be initiated within 1-2 hours of onset of seizures at doses designed to induce EEG suppression patterns (Shorvon and Ferlisi 2011).

### **3.4.2. SAGE-547 Clinical Program in the Treatment of SRSE**

The current SAGE-547 development program includes:

- a completed Phase 2 open-label trial, Study 547-SSE-201;
- this proposed Phase 3 randomized, double-blind, placebo-controlled trial, Study 547-SSE-301;
- an ongoing open-label, expanded access protocol, Study 547-SSE-302;
- a number of EINDs for SAGE-547 in patients with SRSE.

The designs of these studies are all similar, with a five to six day infusion of SAGE-547 (or placebo), during which time attempts are made to wean the subject off all third-line agents. In the Phase 3 studies, those subjects who cannot be weaned off third-line agents while being administered SAGE-547 (or placebo) may be eligible for a second open-label infusion of SAGE-547 at a higher dose. Follow up of subjects is for 21 – 30 days after the first infusion of study medication.

### **3.4.3. Data from the SAGE-547 Development Program**

The data from 30 subjects included in the on-going clinical evaluation of SAGE-547 for the treatment of adults and children with SRSE clearly offers preliminary evidence that SAGE-547 could provide substantial and clinically significant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate. These subjects comprise 20 from the ongoing Phase 2 trial (71% success rate in 12/17 evaluable subjects) and 10 subjects who received EIND treatments (78% success rate in 7/9 evaluable subjects).

Successful therapy of SRSE has been defined as “the SE is completely controlled by the therapy, without breakthrough of withdrawal seizures, or discontinuation due to side effects or death during therapy,” (Ferlisi and Shorvon 2012). By this definition, which is in accord with the efficacy assessments used in the overall clinical evaluation of SAGE-547, 19 of the 26 (73%) subjects with SRSE who completed the SAGE-547 infusion were treatment successes. As data collection is ongoing, this information is preliminary and subject to change upon further monitoring.

Published reports on RSE and SRSE have stated mortality rate ranges from 35% to 65%. The underlying etiologies of SE in the 547-SAGE-201 study and EINDs are heterogeneous, and each one conveys a different risk of mortality and longer term morbidity. However, the death rate in subjects who have received SAGE-547, 6 out of 30 (20%) subjects, appears to be lower than the published rates. None of the deaths were considered related to SAGE-547: brain tumor, organophosphate toxicity, respiratory failure, respiratory arrest due to ventilator support withdrawal, and breast cancer.

In the Phase 2 study, 20 SAEs (15 non-fatal) have been reported in 13 (65%) subjects, and of these 3 events in 2 subjects (10%) were considered by the investigator to be related to SAGE-547: pulmonary emboli and tracheostomy dehiscence/infection. The Sponsor did not consider these events to be related to SAGE-547, rather to the underlying disease states. Four of the 20 subjects (20%) experienced AEs considered possibly related to SAGE-547 by the investigator, namely moderate myopathy and severe pulmonary emboli in 1 subject, moderate tracheostomy dehiscence and tracheostomy infection in 1 subject, moderate thrombocytosis in 1 subject and moderate BUN, ALT and AST elevation in 1 subject.

Review of the most current safety data from 547-SAGE-201 reveals that there were changes in serum chemistry, hematology, and urinalysis during the study, but that none of those changes were assessed as related to SAGE-547. There were also no SAGE-547-related changes to vital signs.

Despite the heterogeneity in the underlying causes of SE, the ages of the subject, comorbidities, which normally complicate the treatment of SE, and the fact that all subjects had failed current standard of care treatment, a large majority of subjects had a successful therapy outcome, with discontinuation of all third-line agents and resolution of SE.

Refer to the Investigational Brochure for further information on the pre-clinical and clinical data supporting the use of SAGE-547 in SRSE.

### **3.5. Study Rationale - SAGE-547 in SRSE**

#### **3.5.1. Justification for the Control Group**

Although SAGE-547 has demonstrated extremely promising activity in subjects with SRSE, both in the Phase 2 study and during the EINDs, these have been open-label investigations with no control data for comparison. Generally in the literature there are few data describing the success rates of wean attempts of third-line agents, and few comparative data on the effectiveness of the three main third-line agents, propofol, pentobarbital/thiopental, and midazolam.

Several options for a control group in Study 547-SSE-301 were considered:

- No control group was thought to be unacceptable since there are no reliable published data on success rates in this population that could be used for broad comparisons;
- An active control was considered but found to be impractical since none of the third-line agents are approved for their use in SRSE, no standardized dosing regimens or treatment guidelines have been adopted for the management of SRSE, and clinicians were unlikely to agree which of the available third-line agents would be reserved for the active control arm;
- Historical controls were considered but abandoned because of the practical difficulties of obtaining high quality data, the lack of ability to prospectively match cases, and a suspicion that clinical practice in the standard of care of SRSE is evolving, mandating the use of prospective, concurrent control data;
- Comparison to standard of care alone was considered as a feasible design. However, in a field where no widely adopted treatment guidelines exist, there was a concern that knowledge of the treatment group (SAGE-547 plus standard of care versus standard of care alone) would alter the behavior of the investigators such that they could be more aggressive with weaning in the SAGE-547 group;

- Placebo control is not without its challenges since the preliminary efficacy data for SAGE-547 show that the compound exerts central pharmacological effects and is associated with positive outcomes in around 70% of patients. There is therefore a potential ethical concern about administering placebo to desperately ill patients who have often exhausted all treatment options for SRSE. This concern has been addressed in two ways: firstly all patients receive current standard of care; secondly, all subjects who fail to be weaned from their third-line agents at the end of the blinded infusion of study drug will be administered open-label SAGE-547 without un-blinding their initial treatment allocation, so treatment with the investigational product is not denied, but delayed about a week in the setting of ongoing receipt of full current standard of care.

It was therefore decided that a blinded, placebo-controlled design was appropriate for Study 547-SSE-301.

### **3.5.2. Justification for the Dose Regimen**

The standard dose regimen has been studied in 19 subjects in the 547-SSE-201 Phase 2 trial; the average peak plasma concentration of SAGE-547 at the end of the loading dose was approximately 144 ng/ml. The average plasma concentration during the maintenance infusion was approximately 70 ng/ml. At these concentrations, there were no clear safety signals although two-thirds of subjects experienced an SAE and there were four deaths, all related to the underlying comorbid conditions. The standard dosing regimen was associated with an approximate 70% successful treatment outcome. For these reasons, the standard dosing regimen has been adopted for the initial SAGE-547 infusion to be compared in a blinded fashion to placebo.

In the 547-SSE-201 trial, three subjects have thus far received the higher dose regimen. This dose regimen has also been well tolerated. The average peak plasma concentrations at the end of the loading dose for both dosing regimens will be in the same range, as the loading dose is the same for both regimens. The average plasma concentrations observed during the higher maintenance dose are 102 ng/ml (n=2). The rationale for adopting the higher dose regimen as the open-label infusion of SAGE-547 for subjects who are retreated in this 547-SSE-301 trial is that those who fail on the standard SAGE-547 dose regimen are afforded the opportunity to have access to a higher dose. The justification to also administer the higher dose regimen to failures on placebo is that the regimen has thus far been well tolerated, and this methodology preserves the blind for the initial infusion.

A five-day dosing regimen with SAGE-547 was investigated in the Phase 2 study, 547-SSE-201. There were some cases when weaning off all third-line agents was not possible within 48 hours, but weaning was completed after the end of the infusion of SAGE-547. For this reason, the duration of dosing with SAGE-547 has been increased from 120 hours (five days) in Phase 2 to 144 hours (six days) in this Phase 3 study.

### **3.5.3. Rationale for Genetic Testing Sub-study**

Sage Therapeutics intends to perform genetic research in the SAGE-547 development program in order to explore how genetic variations may affect the metabolism and activity of SAGE-547. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials, and, possibly, to genetically-guided treatment strategies for optimizing decision making with respect to individual benefit:risk. Participation of subjects in genetic research as part of the overall clinical study is optional.



### **3.6. Benefit-Risk Evaluation of the Present Study**

Previous reports of human administration of exogenous allopregnanolone indicate that for exposures in men and women up to 150 nM, the most commonly reported AEs were sedation (recorded as sleepiness or tiredness), feelings of intoxication (like alcohol), flushing, and mild headache (Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007). No SAEs were reported (Navarro, Kaddouz et al. 2003; Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007; Kask, Backstrom et al. 2008; Kask, Backstrom et al. 2009; Timby, Hedstrom et al. 2011a). In view of the reduced consciousness and sedation of study subjects at entry into this protocol, none of these previously-reported events are likely to impact subjects in this study.

To date, in the SAGE-547 Phase 2 study and the EIND subjects, a majority of subjects demonstrated a successful therapy outcome (>70%). The majority in the clinical trial (65%) have also experienced SAEs, but none has been considered related to SAGE-547 by the Sponsor (SAEs in 2 subjects (10%) were considered possibly related by Investigator). Five deaths have been reported in 30 subjects (20%), all related to the underlying cause of SRSE and not related to SAGE-547 – this is in the context of published mortality rates between 35% and 65%. These preliminary data suggest that SAGE-547 has the potential to provide clinically relevant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate.

The underlying etiologies of SE are heterogeneous, and each one conveys a different risk of mortality. Subjects who survive SRSE still have a high risk of severe morbidity (Neligan and Shorvon 2010). The subjects treated with SAGE-547 in Study 547-SSE-201, are heterogeneous in factors such as age and etiology of SE, factors that usually complicate treatment and can increase morbidity and mortality. Even with this heterogeneity, the preliminary efficacy and safety data for SAGE-547 are very encouraging, and the mortality rate suggests that the risk to benefit assessment of this treatment rests on the side of benefit.

## **4. ETHICS**

### **4.1. Institutional Review Board or Independent Ethics Committee**

This protocol will be reviewed and approved by the Institutional Review Board (IRB) where the study is conducted. The IRB will meet all FDA requirements governing IRBs (CFR, Title 21, Part 56).

### **4.2. Ethical Conduct of the Study**

The Sponsor, the Medical Monitor, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable ICH and GCP guidelines, and must also conduct the study in accordance with local regulations.

### **4.3. Subject Information and Informed Consent**

Subjects prospectively enrolled in this study will be unable to give consent. Therefore, consent will be given by proxy by a legally authorized representative (LAR). Written informed consent is required for each subject prior to any testing under this protocol not considered standard of care, including screening tests and evaluations. Should a subject gain the ability to sufficiently

comprehend the situation and consent during the course of the study, written informed consent or verbal assent will be documented as required or recommended by the institution's IRB.

The form of consent to be obtained will depend on the condition of the subject as determined by the Principal Investigator. The informed consent form (ICF), as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50.

It is the responsibility of the Investigator to obtain consent and to provide the subject's LAR with a copy of the signed and dated informed consent form. The informed consent form for subject participation must also be available as part of the subject file for review by the site's dedicated study monitor or any authorized auditor of the Sponsor or regulatory authorities.

All ICFs used in this study must be approved by the appropriate IRB and by the Sponsor. The ICF must not be altered without the prior agreement of the relevant IRB and the Sponsor.

#### **4.4. Ethical and Regulatory Considerations for Pharmacogenetic Sub-study**

##### **4.4.1. Informed Consent for Pharmacogenetics**

The genetic component of this study is optional and subjects may participate in other components of the main study without having to agree to participate in the genetic component. If subject chooses to participate in the genetic component of the study, the subject or LAR must sign and date a specific consent form for the genetic component of the study in addition to the main study consent form. The principal investigator(s) is responsible for ensuring that consent is freely given and that the subject understands that they may discontinue from the genetic aspect of the study independent of their decision to remain within or withdrawal from the main study.

##### **4.4.2. Subject Data Protection Relative to Pharmacogenomics**

Sage Therapeutics will not provide individual genotype results to subjects, their family members, their general physician, their employer or any insurance company unless required to do so by law. While extra precautions will be taken to preserve confidentiality and to prevent genetic data from being linked to an individual's identity outside of a restricted access site, in certain exceptional situations (e.g. in case of a medical emergency or as a consequence of a specific regulatory need), certain individuals may see both genetic data and the personal identifiers of a subject; however in all cases a subject's medical information and genetic files will remain physically separated.

## **5. STUDY OBJECTIVES**

### **5.1. Primary Objective**

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult and pediatric subjects with SRSE, and for the response to endure at least 24 hours after cessation of the SAGE-547 or placebo infusion (primary response).



## 5.2. Secondary Objectives

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in Clinical Global Impression Scale between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

## 5.3. Safety Objectives

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

## 5.4. Other Objectives

1. To evaluate the impact of retreatment with a higher dose of SAGE-547 infusion;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;

6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS) (age  $\geq 17$  years).

## **6. ENDPOINTS**

### **6.1. Primary Endpoint**

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### **6.2. Secondary Endpoints**

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) and to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### **6.3. Safety Endpoints**

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.

### **6.4. Other Endpoints**

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who are treated with a higher dose of SAGE-547;

2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS) (age  $\geq 17$  years).

## 7. INVESTIGATIONAL PLAN

### 7.1. Overview of Study Design

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

[Figure 1](#) provides an overview of the study design and [Figure 2](#) gives the details of treatment and follow-up on the active treatment arm. Patients will follow one of three paths to entry to the study. The first path is for patients who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst or seizure suppression with a third-line agent. These patients will be consented for the study after admission to the intensive care unit, before or after any third-line agents are administered for burst or seizure suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their LAR. Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours. Once burst or seizure suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned during the QW will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst or seizure suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The second path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst or seizure suppression pattern on the EEG. These patients may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst or seizure suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst or seizure suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst or seizure suppression has been achieved, the third-line agent or agents will

be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst or seizure suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The third path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst or seizure suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These patients may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst or seizure suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within eight hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third line agent wean attempts prior to randomization (one vs two or more).

The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

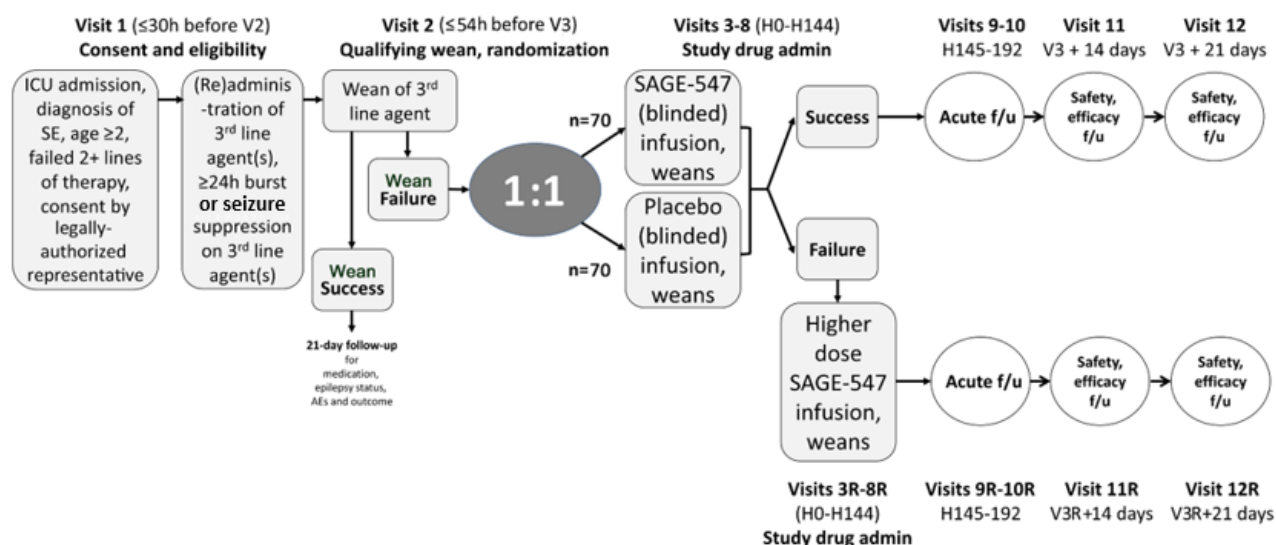
For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as the ability to wean the subject off all third-line agents before the end of the first infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication. Subjects must also have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) at the end of the primary endpoint assessment period as determined by EEG in order to be deemed a success. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#), [Table 2](#) and [Table 3](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion may be eligible to receive an open-label infusion of SAGE-547 at a dose higher than

that administered in the blinded part of the study. Eligibility for the open-label treatment must be confirmed in writing by the medical monitor prior to the open-label infusion starting. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo may all subsequently be eligible to be administered SAGE-547 at the higher dose.

**Figure 1: Study Design**



## 7.2. Trial Conduct

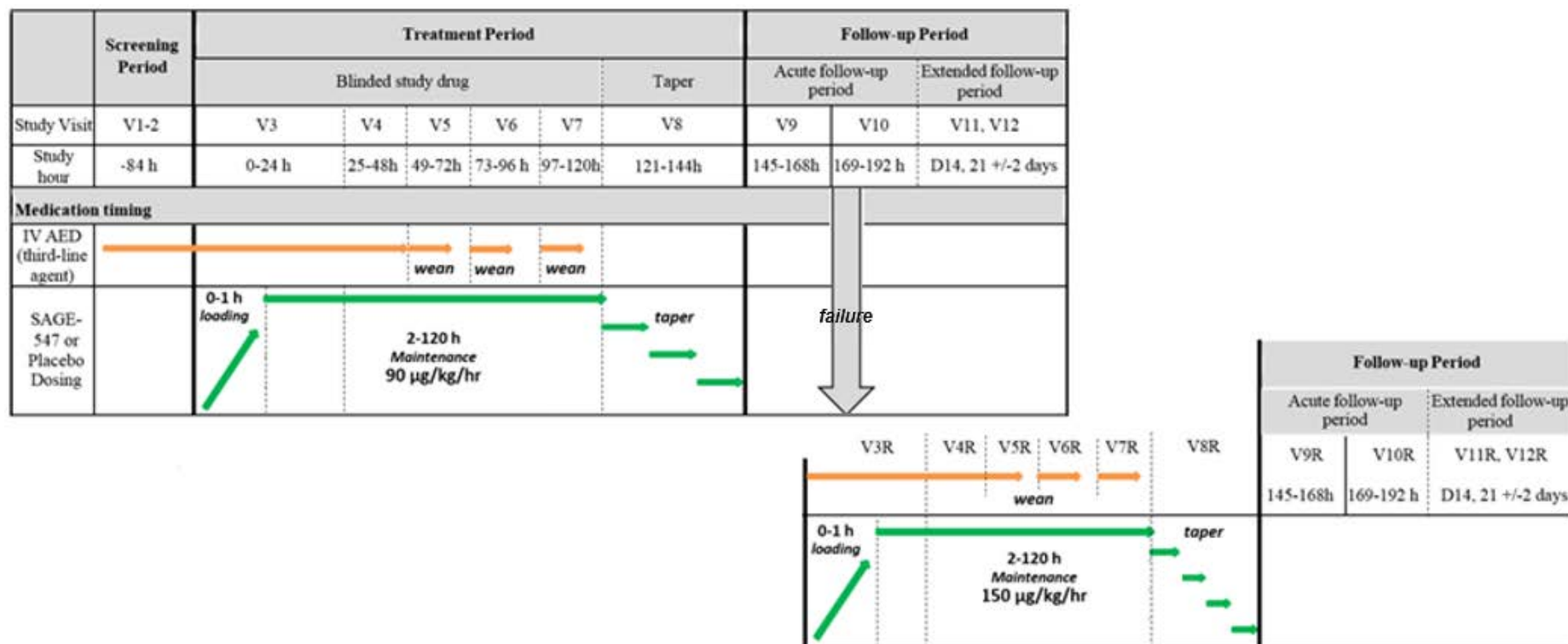
This study will be conducted according to the principles of the World Medical Association Declaration of Helsinki and most recent amendment, and in compliance with the protocol approved by the IRBs/Independent Ethics Committees (IECs), and in accordance with ICH Guidelines on GCP standards.

## 7.3. Blinding and Randomization

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo). Details of the dynamic randomization process will be included in the SAP.

The randomized portion of the study will be blinded, with the two treatment products (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

The second infusion of SAGE-547 will be administered on an open-label basis to subjects who meet the criteria for open-label treatment.

**Figure 2: Details of Treatment Administration and Follow-up**

## 8. SELECTION AND WITHDRAWAL OF SUBJECTS

The study will randomize 140 patients at up to 180 sites. All subjects deemed eligible to enroll must have written Medical Monitor approval on a case-by-case basis prior to undertaking the qualifying wean.

### 8.1. Inclusion Criteria

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects two (2) years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; *or* who have previously failed zero or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst or seizure suppression pattern; *or* who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst or seizure suppression pattern.

### 8.2. Exclusion Criteria

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy with highly malignant/malignant EEG features ([Westhall, Rosetti et al. 2016](#)).
4. Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing underlying neurological disorder.
5. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis but for whatever reason, dialysis that would adequately remove Captisol® is not planned;
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the experience of the investigator, is less than 30 days.

6. Subjects who are being administered more than three third-line agents concomitantly or for whom the qualifying wean cannot be completed within 24 hours or who are being administered a third-line agent for indications such as raised intra-cranial pressure that would preclude weaning according to this protocol.
7. Subjects with a living will that does not allow heroic measure.
8. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
9. Subjects who have been treated or randomized in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not have received study drug/placebo and then re-enroll).

### **8.3. Selection and Consent of Subjects for Pharmacogenetic Substudy**

All subjects will be asked to participate in pharmacogenetic research; however, participation in research is voluntary and a subject can decide to decline his/her participation without penalty or loss of benefit. Participation or lack thereof will not be a cause for exclusion from any aspect of the main study. In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **8.4. Subject Withdrawal / Study Termination**

#### **8.4.1. Withdrawal/Discontinuation of Individual Subjects**

The reasons for study drug discontinuation and/or subject withdrawal from the study must be recorded in the subject's electronic case report form (eCRF). The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject has been discontinued/withdrawn due to an AE.

##### **8.4.1.1. Withdrawal from the Study**

Subjects or their LAR may withdraw subjects from the study at any time for any reason without compromising the subject's medical care. The Investigator will also withdraw subjects upon the request of Sage Therapeutics or upon termination of the study.

Subjects who withdraw from the study prior to Visit 10 (or 10R) should complete the procedures scheduled for the day of study drug taper (Hour 121-144; Visit8/8R) on the day of their withdrawal, including the SAGE-547 taper schedule, with the addition of the mortality assessment from Visit 12/12R. Subjects who withdraw from the study after Visit 10/10R should undergo study procedures as outlined for Visit 12/12R on the day of their withdrawal. In all cases, the reason for subject withdrawal will be recorded in the eCRF.

Withdrawal of subjects for any reason should be discussed with the Medical Monitor.

##### **8.4.1.2. Discontinuation of Study Drug**

If it is necessary to discontinue the study drug earlier than planned, subjects should continue to be followed per protocol to capture safety and efficacy assessments for the duration of the study period.



The investigator may withdraw the subject from the study drug for the following reasons:

- Upon subject's or LAR's request
- The subject or LAR is unwilling or unable to adhere to the protocol-specified visits
- The subject experiences an intolerable adverse event
- During the course of the study, the subject develops symptoms or conditions listed in the exclusion criteria.
- Other medical reason, at the discretion of the Investigator and/or the Medical Monitor

Subjects who discontinue the study due to an AE considered related to study drug should be followed until the event is resolved, considered stable, or the Investigator determines the event is no longer clinically significant. Study drug discontinuation due to AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

#### **8.4.2. Study Termination**

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of AEs or other findings suggesting unacceptable risk to subjects, administrative or operational reasons. In the event of study termination, Sage Therapeutics will provide written notification to the Investigator. Investigational sites must promptly notify their IRB and initiate withdrawal procedures for participating subjects.

## **9. INVESTIGATIONAL PRODUCT**

### **9.1. Identity of Investigational Product**

SAGE-547 Injection (allopregnanolone)

### **9.2. Clinical Supplies**

#### **9.2.1. SAGE-547**

Adequate supplies of SAGE-547 Injection and materials for intravenous administration will be provided to each site.

SAGE-547 Injection is a clear, colorless sterile solution of allopregnanolone intended for intravenous injection. SAGE-547 Injection is an aqueous solution of 5 mg/mL allopregnanolone in 250 mg/mL Captisol® (betadex sulfobutyl-ether sodium, NF). It is presented either un-buffered or buffered with 10 mM citrate at a pH of 6.0 in either 20 mL or 50 mL vials. SAGE-547 is further diluted according to the Pharmacy Manual to achieve an approximately isotonic solution and will be administered intravenously.

No preservatives are included in the drug product, which is intended to be used as a single-use vial. All inactive components (excipients) used in the formulation are compendial grade and conform to current USP/EP, and include sodium citrate, citric acid and betadex sulfobutyl-ether sodium (Captisol®).

### **9.2.2. Placebo**

Placebo will be identical to SAGE-547 and presented in identical vials. Placebo will be manufactured in a similar way to SAGE-547 and comprises all excipients but no SAGE-547.

### **9.2.3. Blinding**

The vials of SAGE-547 and placebo will be identical in every way so that they are indistinguishable by the pharmacist, investigator, anyone treating or managing the patient, the monitors, and the sponsor. In this way the first infusion of study drug administered to each patient will be double-blind.

For the blinded study drug infusions, subject-specific dosing kits will be provided. These dosing kits will be pre-labelled with kit number for the first blinded infusion. For the second-infusion, open-label kits will be provided, which will require subject assignment by the pharmacy for reconciliation purposes. The study kits must be stored under refrigerated conditions (2-8 °C). IV administration bags and lines may be provided for the blinded and open-label infusions. Refer to the Pharmacy Manual for additional details.

The label for the SAGE-547 Injection vials will include standard product identification information according to the Code of Federal Regulations, 21CFR 312.6. All study labels will also contain the following statement:

Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use.

## **9.3. Preparation of SAGE-547 or Placebo Injection for Dosing**

The Pharmacy will be responsible for preparing the blinded and open-label study drug for subject dosing. The prepared admixture will be assigned a room temperature (20-25 °C) storage shelf life of 30 hours from time of compounding.

SAGE-547, which is hypertonic, will require dilution with SWFI to achieve an approximately isotonic solution according to the instructions provided in the Pharmacy Manual. Exactly the same procedures will be used to prepare the placebo admixture, so that all site staff remain blinded as to treatment allocation for the first infusion of study drug. SAGE-547 Injection is not intended to be administered to patients undiluted.

Refer to the Pharmacy Manual for specific instructions regarding infusion preparation.

## **9.4. Administration and Accountability**

The Pharmacy will maintain accurate records of all investigational product supplies. Accurate records will be kept regarding the volume of SAGE-547 Injection or placebo used for each IV preparation, as well as the required infusion rate or rates, and the date and time of preparation. Reasons for departure from the expected dosing regimen must also be recorded. To satisfy regulatory requirements regarding drug accountability, all study medication will be reconciled in full. Refer to the Pharmacy Manual for additional details.

## 10. TREATMENT OF SUBJECTS

### 10.1. Dosing Schedule (Blinded Infusions)

SAGE-547 Injection or placebo will be administered according to the dosing schedules in [Table 5](#). The infusion rates to accomplish these  $\mu\text{g/kg/h}$  doses will be calculated according to the weight of the subject obtained within the eight-hour window that follows the declaration of the QW failure at V2 and prior to dosing at V3. The infusion rates will be applied to blinded study drug for the first infusion of study medication.

**Table 5: SAGE-547 or Placebo Dosing Schedule**

Hour	Type and Duration of Study Drug Infusion	Description
H1	One hour loading Infusion	300 $\mu\text{g/kg/h}$
H2 – H120	119 hour maintenance infusion	90 $\mu\text{g/kg/h}$
H121 – H128	8 hour taper	65 $\mu\text{g/kg/h}$
H129 – H136	8 hour taper	45 $\mu\text{g/kg/h}$
H137 – H144	8 hour taper	25 $\mu\text{g/kg/h}$

### 10.2. Dosing Schedule (Open-Label Infusions)

Those subjects that qualify for the open-label study drug will be administered SAGE-547 Injection will be re-administered according to the dosing schedule in [Table 6](#). The dose will be administered on a  $\mu\text{g/kg/h}$  basis, and the subject's weight measured prior to dosing during V10 will be used to calculate the doses. These infusion rates will be applied to SAGE-547 treatment for the open-label second infusions of study medication.

**Table 6: SAGE-547 Open-Label Dosing Schedule**

Hour	Type and Duration of SAGE-547 Infusion	Description
H1	One hour loading Infusion	300 $\mu\text{g/kg/h}$
H2 –H120	119 hour maintenance infusion	150 $\mu\text{g/kg/h}$
H121 – H126	6 hour taper	125 $\mu\text{g/kg/h}$
H127 – H132	6 hour taper	95 $\mu\text{g/kg/h}$
H133 – H138	6 hour taper	65 $\mu\text{g/kg/h}$
H139 – H144	6 hour taper	35 $\mu\text{g/kg/h}$

### 10.3. Route of Administration

SAGE-547 Injection is intended for IV administration only. The compatibility of SAGE-547 with other drugs is unknown, and the product should be administered via a dedicated peripheral IV line using any Sage-supplied study-specific IV administration bags and lines. In order to preserve blinding, these instructions also apply to the blinded placebo infusions.

## **10.4. Treatment Period**

The treatment period with double-blind SAGE-547 or placebo is six 24-hour periods (144 hours), which may encompass 6-7 calendar days. The open-label study drug treatment period is of identical duration.

## **10.5. Concomitant Medications, Procedures and Treatments**

Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. For all randomized and the first 50 qualifying wean success (QWS) subjects, detailed information on all concomitant medications (concomitant AEDs, third-line agents, pressors, and other concomitant medications), procedures, and treatments should be documented throughout the study from Screening through Visit 12/12R, as described below, and recorded on the eCRF. For subsequent QWS subjects, after the detailed information on all concomitant AEDs, pressors, third-line agents, procedures, and treatments collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant AED or pressor, third-line agent, procedure, and/or treatment, and the start and stop dates and times) from Visit 3 through Visit 12 will be recorded in the eCRF. For subsequent QWS subjects, after the detailed information on all concomitant medications collected during the screening period (Visits 1 and 2) has been recorded, only minimal information, to include the name of the concomitant medications and indication only will be recorded from Visit 3 through Visit 12.

SAGE-547 has demonstrated inhibitory effects on cytochrome P450 isoenzyme 2C9 (CYP2C9). Therefore, AEDs such as phenytoin and phenobarbital that are primarily metabolized by CYP2C9 should be closely monitored during SAGE-547 administration to ensure target exposures are maintained.

### **10.5.1. Concomitant AEDs**

Subjects may enter the study on AEDs, and be administered AEDs during the study. All of these must be recorded on the eCRF with details including date and time of starting and stopping each AED, the route of administration, changes in doses, and frequency of administration. In addition, details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the eCRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.

### **10.5.2. Concomitant Third-Line Agents**

All third-line agents (as defined in [Section 8](#)) administered since the diagnosis of SE will be recorded on the eCRF, whatever path the patient took for entry into the study. Details will include the name of the drug, the start and stop dates and times, and, after consent, the doses with start and stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

In addition, those changes in dose that constitute a wean attempt will be marked as such on the eCRF. In this way the start and stop dates and times of all wean attempts (see [Section 11](#) for definitions) will be recorded, as will the type of wean (QW, OW, or TW) and the outcome of the wean attempt (successful, failed and dose of this third-line agent increased or failed and this third-line agent stopped and another third-line agent started). Those wean attempts that occur after the TW up to and including Visit 12/12R will be marked “AW”.

Some third-line agents (such as propofol) are also used to induce sedation to facilitate a subject's ability to tolerate the ventilator. For subjects requiring such sedation, propofol is the preferred agent unless there are contraindications. The eCRF will make clear from the indication for the third-line agent when it is being used for burst or seizure suppression and when it is being used as ventilator support or for another purpose. The investigator will add a note to the eCRF to justify that the doses used are appropriate for sedation and not for seizure or burst suppression. The doses used for ventilator support and other similar uses are usually much lower than those used for seizure or burst suppression, and use of these third-line agents for these other purposes does not constitute a wean failure under this protocol.

### **10.5.3. Concomitant Pressors**

The start and stop dates and times of all pressors will be recorded as well as the start and stop dates and times of all dose changes.

### **10.5.4. Other Concomitant Medications**

All other concomitant medications must be recorded on the eCRF with details including date and time of starting and stopping, the route of administration, dose, and frequency of administration.

## **11. STUDY ASSESSMENTS**

### **11.1. Efficacy Assessments**

#### **11.1.1. Primary Efficacy**

Success or failure will be determined, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo infusion and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the blinded (first) infusion of SAGE-547 or placebo. In addition, subjects must have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) to be deemed to be successes. All subjects who fail to complete their infusion of randomized treatment or do not have at least one attempt during study treatment to wean off all third-line agents will be considered as "failures" for the primary endpoint.

##### **11.1.1.1. Weaning**

Third-line agents are anesthetic agents that are administered in order to reach a seizure or burst suppression EEG pattern. For the purposes of this study, third-line agents are defined as continuous intravenous infusions of pentobarbital/thiopental, midazolam, propofol, and ketamine at maintenance doses alone or in combination sufficient to produce a burst or seizure suppression pattern on the EEG. The following are considered to be minimum maintenance doses of these agents that may be expected alone or in combination to achieve EEG burst suppression. If subjects are on lower doses than these and are not in EEG burst suppression for the first 12 hours of the blinded study drug infusion, they will be considered to be protocol violators and will exit the study.

- Pentobarbital: 1 mg/kg/hour
- Thiopental: 3mg/kg/hour
- Midazolam: 0.1 mg/kg/hour

- Propofol: 3 mg/kg/hour
- Ketamine 1.2 mg/kg/hour

The timing and nature of the third-line agent weans will be guided by the Clinical Standardization Guidelines for the study, and the clinical judgment of the investigator, and will always be primarily done in the best medical interests of the subject. Advice about weaning may be sought from the Clinical Standardization Team, a group of fellow investigators with experience of performing clinical trials in subjects with SRSE. The Clinical Standardization Team will be able to discuss EEGs in real time related to key study timepoints (terminal wean and the period after the end of the blinded study drug infusion if the terminal wean was successful) in a timely manner in order to provide advice about compliance with the Clinical Standardization Guidelines.

The following guidance for weaning applies to all weans of third-line agents undertaken during the study. Continued determined efforts to liberate subjects from sedation must be undertaken for the entire duration of the blinded study drug infusion. Each failed wean from third-line agents should be followed by a 6-24 hour period of suppression and then another wean attempt, with further optimization of the AED regimen.

Weans include the qualifying wean (QW); the terminal wean (TW), which is the wean of the third-line agent if the subject is on only one third-line agent or the wean of the last third-line agent if the subject is on more than one third-line agent; the other weans (OW), which are the weans of the third-line agents other than the TW if the subject is on more than one third-line agent. The guidance also applies to additional weans (AW), which are the weans from third-line agents that take place after the TW for the first blinded study drug infusion or the second open-label study drug infusion.

### **QW Guidance**

- Wean to be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace that third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Investigators should allow 24 hours to lapse after the end of a “successful” qualifying wean before finally declaring the QW a success. If a third-line agent needs to be re-instituted within that 24 hours, the QW is a failure, and the subject may then be randomized in the study.

### **OW Guidance**

- First OW should not begin before H49 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- If the subject is on two third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the TW. However the OW may be completed over a shorter or longer time period and may overlap if clinically indicated with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be

adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.

- If the subject is on three third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the wean of the second agent. The second agent should be weaned over 24 hours and that wean completed before starting the TW. However the OWs may be completed over a shorter or longer time period and may overlap if clinically indicated with each other and with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- All OWs should be completed before H96 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **TW Guidance**

- The TW is defined as the wean of the last third-line agent.
- If the subject is on one third-line agent, the TW should not begin before H49 and should begin no later than H97 after starting administration of study drug or starting the open-label infusion of SAGE-547. If the subject has had one or more OWs, the TW should ideally begin as soon as the last OW is complete but in any case not later than H97 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- The TW must be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace this third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Every effort must be made to complete the TW before H120 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547, but the TW must be complete before H144 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **AW Guidance**

- AWs will take place when medically indicated in the opinion of the investigator.
- Ideally the AW should take place over 24 hours, but completion may be over a shorter or longer time period than this. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.

### 11.1.1.2. EEG

Electroencephalographs (EEGs) that are representative of the intermittent or continuous EEG being used to support key investigator decisions will be collected at the following time points:

- A 24-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst or seizure suppression for the second path to eligibility, and a variable pattern for the third path to eligibility. This EEG also aims to capture the burst or seizure suppression pattern during the 24 hours that precede the QW. If the CEEG does not capture the 24 hours that precede the QW, additional EEG data collected as standard of care prior to the CEEG and prior to the QW may be collected to assess the depth of burst or seizure suppression in the 24 hour period prior to the QW.
- EEG will be performed to cover the qualifying wean (QWEEG). EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for up to 24 hours after the end of the QW. The duration of the QWEEG will be up to 48.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s), the decision to re-institute a third-line agent(s) at doses intended to induce burst or seizure suppression, and the decision that the QW is a success.
- EEG will be performed from three hours prior to the start of the blinded infusion to 12 hours after the start of the blinded infusion. This will be called the BIEEG. The intent of this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG and to assess the depth of burst suppression in the first 12 hours of blinded study drug infusion.
- EEG will be performed to cover the final or terminal wean of third-line agent (TWEEG). The TW is the wean of the final third-line agent during the blinded administration of study drug or the open-label infusion of SAGE-547; if the subject was on one third-line agent, the TW is the wean of that agent. If the subject was on three third-line agents, the TW is the wean of the third and final agent. EEG recording will start 30 minutes prior to the start of the TW, continue for up to 24 hours during the TW, and then continue for the one hour after the end of the TW. The duration of the TWEEG will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the final third-line agent or the decision to re-institute a third-line agent at doses intended to induce burst or seizure suppression because any seizure activity could not be managed using intermittent bolus doses of AEDs.
- EEG will be performed during the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 (TAEED). The TAEED is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the start of the taper (at Hour 119.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours during the taper, and then continue for the one hour after the end of the taper (to Hour 145 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547). The duration of the TAEED will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst or seizure suppression because



any seizure activity seen during the taper could not be managed using intermittent bolus doses of AEDs.

- EEG will be obtained to cover the end of the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 and the ensuing 24-hour period, during which the primary endpoint is assessed (PAEEG). The PAEEG is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the end of taper (at Hour 143.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours after the end of the blinded administration of study treatment or the open-label infusion of SAGE-547, and then continue for the one hour after the end of the 24-hour assessment period (to Hour 169 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547). The duration of the PAEEG will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst or seizure suppression because any seizure activity seen in the 24 hours following the end of the blinded administration of study treatment or the open-label infusion of SAGE-547 that could not be managed using intermittent bolus doses of AEDs.

In practice, most subjects are on continuous EEG monitoring or long periods of intermittent EEG monitoring. However, this protocol does not mandate continuous EEG monitoring and breaks from EEG monitoring to provide relief to the scalp from the irritating effects of the electrodes are advised, particularly in children, according to local practice. If a break in EEG monitoring is mandated by local practice guidelines at a time when one of the protocolled EEG segments is to be collected, the break in EEG monitoring will take precedence, with the reason for missing the EEG reading noted on the eCRF. The EEGs obtained for the study are therefore part of the existing EEG record rather than being obtained de-novo at each timepoint. For timepoints where there might be some ambiguity, such as the TWEEG, the final EEG record is that of the final attempt to wean the last third-line agent, even if earlier attempts to wean that agent took place. In some cases (the TAEEG and PAEEG, for instance), the EEG records will overlap, but different cuts are taken to service the different EEG record requirements.

The electronic EEG file will be de-identified, the date and time of the start and stop of the EEG and the subject number will be attached to the file, and the study time point will be indicated (CEEG, QWEEG, BIEEG, TWEEG, TAEEG, and PAEEG). The PI will indicate on the eCRF what the EEG shows, as follows:

- For the CEEG, the PI will describe the EEG pattern that determined which path to eligibility the subject was on.
- For the QWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure or success on the qualifying wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst or seizure suppression during the qualifying wean constitutes a failure); the QWEEG will extend to cover the 24 hours after the end of third line agents in order to confirm that the QW was a success.
- For the BIEEG, the PI will note the date and time of the start of the EEG and the pattern seen on the EEG.

- For the TWEEN, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure on the terminal wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst or seizure suppression during the terminal wean).
- For the TAEED, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst or seizure suppression before the end of the SAGE-547 infusion).
- For the PAEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst or seizure suppression in the 24 hours following the end of the SAGE-547 infusion).

A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm the depth of burst or seizure suppression prior to the QW and during the first 12 hours of the blinded study drug infusion, the PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period (average EEG power at the end of Visit 9 of more than two microvolts):

- All subjects will have the CEEG and QWEEN collected and stored, and the CEEG and QWEEN read;
- Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;
- Those subjects randomized who are not administered the open-label study drug will have the QWEEN, BIEEG, TWEEN, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the BIEEG, QWEEN, TWEEN, and PAEEG related to the blinded study drug infusion read;
- Those subjects randomized who later undergo the open-label infusion will have the QWEEN, BIEEG, TWEEN, TAEED and PAEEG related to the blinded study drug infusion and the TWEEN, TAEED, and PAEEG related to the open-label study drug infusion collected and stored, and the BIEEG, QWEEN, TWEEN, and PAEEG related to the blinded study drug infusion read.

All EEG records may be subject to quantitative EEG analysis.

### **11.1.2. Secondary Efficacy**

#### **11.1.2.1. Clinical Global Impression Scale (CGI)**

The clinical global impression scales are often utilized in clinical trials to allow clinicians to integrate several sources of information into a single rating of the subject's condition. Both the CGI-Severity (Question 1, CGI-S) and the CGI-Improvement (Question 2, CGI-I) employ a 7-point Likert scale measuring severity of the disease state in the subject and improvement, respectively. All severity assessments after initiation of SAGE-547 treatment should consider the general state of the subject

over the preceding week. The third question on the scale will not be employed in this trial, and where the scale states “mental illness”, this means “physical illness” in this trial.

The CGI-S will be evaluated at Visit 1 and at the last visit, Visit 12 or 12R. The CGI-I will be evaluated at Visit 12 or 12R.

#### **11.1.2.2. Epilepsy Status**

At Visit 1, the diagnosis of epilepsy will be documented as a no/yes question. If there was a previous diagnosis of epilepsy, further details will be documented, including:

- Date of diagnosis;
- Details of anti-epileptic drugs currently being taken;
- Type of epilepsy;
- Seizure frequency in the past month.

Information about the current (index) episode of status epilepticus will be obtained at Visit 1:

- Date of onset
- Date of failure to respond to first line agent(s) and the name(s) of the agent(s)
- Date of failure to respond to second line agent(s) and the name(s) of the agent(s)
- Any previous treatment with third line agents and the response to those agents (details of the third line agent drugs and previous wean attempts will be recorded on the Third Line Agent Medication CRF)
- The cause of the index episode of status epilepticus
- If the subject was transferred from another hospital or from within the hospital, the reason for the transfer will be recorded (such as for study enrollment, due to lack of medical options at original hospital or unit, due to lack of beds at the original hospital or unit, family request, other)

Previous (non-index) diagnosis of status epilepticus will be documented as a no/yes question. If SE did occur in the past 12 months, further information will be gathered, including:

- SE, RSE, or SRSE diagnosis, whichever was the most severe diagnosis for each episode;
- Cause;
- Treatment, including experimental treatments and need for intubation/ventilation;
- Dates of onset and duration.

At Visit 12 or Visit 12R, the following information will be gathered:

- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of SE up to and including Visit 12 or Visit 12R;
- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of seizures (convulsive and non-convulsive) up to and including Visit 12 or Visit 12R;

- Number of separate episodes of SE after H144 at the end of Visit 8 or Visit 8R (no/yes); if yes,
  - SE, RSE, or SRSE diagnosis;
  - Cause;
  - Treatment, including experimental treatments and need for intubation/ventilation;
  - Dates of onset and duration.

Note that a separate episode of SE is defined as an episode of SE separated from other periods of status epilepticus by at least 24 hours.

- Diagnosis of epilepsy since Visit 11 or Visit 11R will be documented as a no/yes question. If a diagnosis of epilepsy has been made, further details will be documented, including:
  - Status as ongoing or new epilepsy since Visit 11 or Visit 11R after initiation of SAGE-547 treatment;
  - Details of anti-epileptic drugs currently being taken;
  - Type of epilepsy and seizure frequency in the past week.

## 11.2. Safety Assessments

The safety and tolerability of SAGE-547 will be assessed using adverse events, clinical laboratory measures, vital signs, ECG intervals and morphology, and mortality. All safety assessments should be performed per hospital standard of care and will be collected periodically throughout the study according to [Table 1](#), [Table 2](#), and [Table 3](#) (Schedules of Assessments).

### 11.2.1. Adverse Events

AEs will be collected after informed consent has been signed and prior to study-specific screening procedures not considered standard of care, during subject preparation for SAGE-547 administration and through Visit 12 or Visit 12R. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™) coding system (current version). See [Section 14](#) for additional details.

### 11.2.2. Clinical Laboratory Tests

Blood samples will be taken for hematology, and serum chemistry and GFR will be calculated at:

- Visit 1 and then at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.
- Blood samples will be taken at Visit 11 or Visit 11R for serum chemistry (renal panel only).

Urine samples (20 ml) will be taken for urinalysis and urine NAG analysis at:

- Visit 1 and at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.

For adults and children  $\geq 30$  kg, these samples will be analyzed at a central laboratory; hour-to-hour medical decisions will be based on sampling for laboratory testing done outside the protocol as part

of normal standard of care. GFR will be calculated by the central laboratory. For children under 30 kg, results of local laboratory testing undertaken at the protocolled timepoints may be sent to the central laboratory for inclusion in the central study laboratory database; this obviates the need for additional blood sampling for central laboratory testing.

Any out-of-range values will be flagged by the laboratory; the investigator will add a comment about whether the abnormality is clinically significant. Clinical significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

#### **11.2.2.1. Hematology and Serum Chemistry**

Hematology will include complete blood count (CBC) white blood cell count with differential, platelet count and red blood cell (RBC) count, hemoglobin and hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose. In addition triglycerides will be measured in serum chemistry samples (to aid assessment of lipemia in pharmacokinetic samples).

#### **11.2.2.2. Pregnancy Test**

Females of child-bearing potential will be tested for pregnancy by serum pregnancy test at Visit 1. In this study, since an accurate history of menstruation in girls and menopause in older women may not be available at Visit 1, “child-bearing potential” is taken to mean any female aged 10 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy. Female subjects with a positive pregnancy test will be ineligible for study participation.

#### **11.2.2.3. Urinalysis**

Urinalysis will include assessment of protein, blood, leukocytes, glucose, ketones, urobilinogen, pH, and specific gravity.

#### **11.2.3. Vital Signs**

Blood pressure, heart rate, and temperature will be recorded at the following time points relative to the first infusion of study drug, and to the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547:

- Visit 1;
- At 0, +30, +60 minutes (+/-15 minutes) and +2, +4 and +8 hours (+/- 30 minutes) after the start of the infusion;
- At +24, +48, +72, +96, +120, +144, +168, and +192 hours (+/- 2 hours) after the start of the infusion.

#### 11.2.4. Weight and Height

Weight and height will be measured at Visit 1. Weight will also be obtained at V2, within the eight hour window that follows the declaration of the QW failure and prior to the initiation of the blinded infusion loading dose at H0 of V3, and will be used to calculate the infusion rates throughout the entire blinded treatment course. If a subject qualifies for open-label study drug, the infusion rates for the open-label infusion will be calculated using the subject's weight measured prior to dosing during V10.

If it is not possible to obtain the actual weight at the above-referenced timepoints, permission from the Clinical Monitor must be obtained to use another method to obtain the subject's weight (such as information from the LAR or estimating using an established local protocol).

In addition, a daily weight will be obtained and recorded if this is easily obtained, such as the use of a scale bed.

#### 11.2.5. ECG

For the first 50 subjects randomized in the study, 12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours. If it is not possible to perform ECG immediately after the collection of PK samples up to 160 hours, ECG must be performed within 15 minutes prior to the collection of PK samples up to 160 hours; at other times the allowed time window for ECGs is +/- 2 hours:

- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +128, +136, +144, +152, +160, and +192 hours after the start of the blinded (first) study drug infusion
- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +126, +132, +138, +144, +152, +160, and +192 hours after the start of the open-label (second) study drug

The heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm.

For the subsequent subjects randomized in the study, the following timepoints for ECG will be used:

- pre-dose and at +1, +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the blinded (first) study drug infusion
- pre-dose and at +1, +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the open-label (second) study drug infusion

It is not necessary to collect these ECGs with the PK samples at these timepoints and, apart from the +1h ECG, there is +/- 2 hour time window for these ECGs.

#### 11.2.6. Mortality

Mortality will be recorded on the Visit 12 or Visit 12R case report form. If the subject has died, the following information will be collected:

- Date of death;
- Cause of death.

As accurate as possible cause of death will be collected, which will be further categorized as due to one of the following causes:

- SE;
- complications of long term intubation and third-line agent infusions;
- underlying cause of qualifying SE;
- co-morbidity existing at the time of the qualifying SE;
- new co-morbidity or trauma;
- study drug;
- other (specify).

### 11.2.7. Pharmacogenetic Samples

If a subject's LAR consents to pharmacogenetic sampling, a blood sample for genetic research will be collected at Visit 1 in order to avoid the possible introduction of bias through the exclusion of patients who may withdraw from study due to an AE (a subject population that may be of specific interest for subsequent genetic analysis). If for any reason a sample cannot be taken prior to treatment, a sample can be drawn at any point prior to completion with the restriction that no more than one genetic sample be taken per subject.

The objective of this research is to collect and store blood samples for possible DNA extraction and exploratory research into how genes or specific genetic variation may influence response (i.e. distribution, safety, tolerability, and efficacy) to SAGE-547. Specific genetic variations of interest include but are not limited to: classes of metabolizing enzymes (e.g. Cytochrome P450 supra-family genes), genes encoding enzymes involved in the production and metabolism of allopregnanolone (e.g. AKR1C4 (3 $\alpha$ -hydroxysteroid dehydrogenase)), genes associated with the GABA receptor (e.g. GABRA1-A6, GABRB1-B3, GABRD, GABRE, GABRG1-3) and genes associated with the production and degradation of GABA.

Future research may suggest other genes or gene categories as candidates for influencing not only response to SAGE-547 but also susceptibility to disorders for which SAGE-547 is being evaluated. Thus, the genetic research may involve study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.

#### 11.2.7.1. Biological Sampling and Coding Procedures (Pharmacogenetics)

To ensure patient confidentiality, utmost care will be taken in the coding and storage of pharmacogenetic samples.

*Extraction and coding:* DNA will be extracted from the blood sample and the DNA sample will be assigned a unique number replacing information from sampling tube. The assigned DNA number will be used to identify the sample and its corresponding information within Sage Therapeutics or at any designated contract laboratory for the purpose of sequencing of other DNA specific analysis. No personal details sufficient for individual identification will be available to any person (internal or external to Sage Therapeutics) working with the DNA.

*Genotype/Phenotype Analysis:* Samples and data from genetic analysis will be coded. The link between subject enrollment / randomization code and DNA number will be maintained and stored in a secure environment with restricted access. The established link will be used to identify relevant DNA samples for analysis, facilitated correlation of genotype results with clinical data, allow regulatory audit, and to trace samples for destruction in case of withdrawal of consent.

### 11.2.7.2. Retention of Biological Samples for Pharmacogenetic Analysis

Extracted DNA is a finite research that is destroyed in the process of being analyzed. Primary blood samples from which DNA can be extracted will be stored and used until no further analyses are possible, a maximum storage period of 25 years from time of last subject last visit has been reached, or an individual or LAR withdraws his/her or their consent.

### 11.2.8. Other Outcomes

#### 11.2.8.1. Pharmacokinetic Data

Formal plasma analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS)). In addition, all samples will be analyzed for important SAGE-547 metabolites (if and when these are identified) and Captisol<sup>®</sup> concentrations.

#### Plasma Analysis

Plasma will be collected to assay for SAGE-547 concentrations at the following time points relative to the start of each infusion of study drug:

- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion.
- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open-label SAGE-547 study drug infusion.
- All samples will also be analyzed for plasma concentrations of important metabolites of SAGE-547 if and when these are identified.
- All samples from the first 50 subjects randomized will also be analyzed for plasma concentrations of Captisol<sup>®</sup>.

The plasma samples will be drawn from the arm contralateral to that used for drug administration. Drawing samples from peripheral arterial or venous lines or from a central line is permissible. PK collection times should be adhered to as strictly as possible. The allowed time window for all samples is: pre-dose in the two hours prior to starting the infusion of study drug; samples up to and including 1h, +/- 5 minutes; subsequent samples, +/- 15 minutes. Subject-specific PK kits for sampling including instructions on collection and processing methods, and storage and shipping conditions, will be provided separately. To maintain the blind, all subjects will have samples taken as outlined above: subjects receiving SAGE-547 will have all samples analyzed for all analytes. Subjects on placebo may have samples analyzed to investigate endogenous allopregnanolone and metabolite concentrations, as well as Captisol<sup>®</sup> concentrations; experience with the plasma concentration data will determine if and which placebo samples are analyzed.



Each blood sample will be 3 ml in volume for adults and children weighing 30 kg or more, and 1 ml in volume for children weighing less than 30 kg. Separate aliquots will be obtained from each sample to service the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum blood draw for PK analysis for a subject having two infusions of study drug will be 99 ml (33 ml for children weighing less than 30 kg).

Plasma PK parameters for SAGE-547 will be calculated where appropriate (e.g.,  $C_{max}$ ,  $C_{min}$ ,  $t_{max}$ ,  $AUC_{last}$ ,  $AUC_{\infty}$ ,  $CL_s$ ). In addition, similar PK parameters will be calculated for Captisol®. PK parameters for important metabolites of SAGE-547 may be calculated. An evaluation will be made of the feasibility of adopting a population-PK approach to assess drug-drug-interactions with SAGE-547 as victim of AEDs.

In addition, the Visit 9 sample may be analyzed for plasma concentrations of third-line agents.

#### Other Analysis

If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations. The minimum volume of cerebrospinal fluid for analysis is 100 microlitres.

Full details of all pharmacokinetic analyses will be described in the Pharmacokinetic Analysis Plan.

#### **11.2.8.2. Correlation of QT/QTc Changes and Plasma Concentrations of SAGE-547**

An analysis will be performed to determine whether there is any correlation between changes in QT/QTc interval and plasma concentrations of SAGE-547, in order to investigate any effect that SAGE-547 may have on QT/QTc interval.

#### **11.2.8.3. Pharmacoeconomic Data**

At Visit 12 or Visit 12R, the following information will be collected: number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital. If the subject dies before Visit 12 or Visit 12R, data will be collected up to the date of death. The definition of “hospital” is the institution that the subject was initially treated in. If the subject is transferred to another hospital, that hospital would be the “discharge destination from the hospital” and the “number of days in hospital” would be the number of days in the initial treating hospital.

For those subjects discharged from hospital before Visit 12/12R, the following questions will be asked:

- On what study day was the subject discharged from hospital?
- What type of facility was the subject discharged to (another hospital, a rehabilitation center, a supported care facility, home, other)?
- How many days did the subject stay in this facility?

The following questions will be answered regarding the stay in the ICU and hospital:

- Was the subject still in the ICU at the end of Visit 10/10R?

- If the FOUR Score was  $\geq 12$  at Visit 10/10R and the subject was in the ICU at Visit 10/10R, what was the reason for the subject not being discharged from the ICU (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, other)?
- Was the subject still an in-patient in the hospital at the end of Visit 12/12R?
- If the FOUR Score was  $\geq 15$  at Visit 12/12R and the subject was in the hospital at Visit 12/12R, what was the reason for the subject not being discharged from the hospital (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, unsuitable home circumstances, other)?

#### **11.2.8.4. STESS**

The STESS will be assessed during Visit 1 in order to assess the severity of the status epilepticus.

#### **11.2.8.5. FOUR Score**

The Full Outline of UnResponsiveness or FOUR Score is designed to assess conscious level and unlike other scores, is suitable for subjects who are intubated. It assesses four domains of neurological function (eye responses, motor responses, brainstem reflexes, and breathing pattern).

The FOUR Score will be collected at the following time points relative to each infusion of study drug (the initial blinded infusion and the second open-label infusion if this is administered):

- baseline, +24, +48, +72, +96, +120, +144, +168, and +192 hours (all +/- 2 hours) after the start of the infusion, and at Visit 11/11R and Visit 12/12R.

#### **11.2.8.6. Glasgow Outcome Scale (GOS)**

The GOS is a relatively common assessment scale used to standardize descriptions of the objective degree of recovery from brain injury such as cerebral trauma, or in this case SRSE. It was first used in 1975 ([Jennett and Bond 1975](#)) and allows a prediction of the long-term course of rehabilitation to return to work and everyday life. The scale classifies subjects into 5 groups:

- Death
- Persistent vegetative state
- Severe disability
- Moderate disability
- Good recovery

The GOS will be assessed at Visit 12 or Visit 12R.

#### **11.2.8.7. Supervision Rating Scale (SRS)**

The Supervision Rating (SRS) measures the level of supervision that a patient/subject receives from caregivers. The SRS rates level of supervision on a 13-point ordinal scale that can optionally be grouped into five ranked categories (Independent, Overnight Supervision, Part-Time Supervision, Full-Time Indirect Supervision, and Full-Time Direct Supervision). The SRS was designed to be rated by a clinician based on interviews with the subject and an informant who has observed at first hand the level of supervision received by the subject ([Boake 2000](#)). Scoring is a one-step procedure in which the clinician assigns the rating that is closest to the subject's level. Ratings are based on

the level of supervision received, not on how much supervision a subject is judged or predicted to need.

The SRS will be assessed at Visit 1 and Visit 12 or Visit 12R. The Visit 1 assessment will be a retrospective assessment of the supervision required by the subject immediately prior to the admission that included the index episode of status epilepticus.

#### **11.2.8.8. Modified Rankin Scale – 9Q (mRS-9Q)**

The Modified Rankin Scale (mRS) is a commonly used scale to determine disability and functional dependence due to neurological insult such as stroke in adults. The 7-point scale (0 – 6) denotes functional capacity from no symptoms (0) to severe disability (5) and death (6). The Modified Rankin Scale – 9Q is a shortened version consisting of 9 questions that reliably determines the mRS score and was developed to both simplify the assessment and expand the rater base to non- medically trained personnel (Patel, Rao et al. 2012). The assessment is a web-based tool in the public domain with automatic score calculation and error checking found at [www.modifiedrankin.com](http://www.modifiedrankin.com).

The mRS will be assessed at Visit 1 and at Visit 12 or Visit 12R in subjects  $\geq 17$  years of age. The baseline assessment will be a retrospective assessment of the disability and dependence of the subject immediately prior to the admission that included the index episode of status epilepticus.

## 12. STUDY PROCEDURES

The study procedures listed below by study day reflect the required data collection times for this protocol. When a time window is necessary, this is specified below. If no time window is specified, the test may be performed at any time within the specified 24-hour period.

### 12.1. Visit 1 (V2-≤30h)

The baseline period will be up to approximately 84 hours prior to starting blinded study treatment and should include the assessments/procedures listed below and summarized in [Table 1 and Table 2 \(for open-label treatment\)](#), the Schedules of Events.

- Informed consent
- Eligibility checklist
- Verification of inclusion/exclusion criteria.
- Demographic information and medical history obtained by proxy and confirmed by the subject when possible.
- SE and wean history
- Blood will be collected from female subjects 10 years to 55 years for a serum pregnancy test unless they are known to be pre-menstrual or post-menopausal or to have had a hysterectomy.
- Blood and urine samples collected for clinical laboratory testing.
- Pharmacogenetic sample will be collected from consenting/eligible subjects.
- Vital signs
- Height
- Weight
- An ECG reading taken.
- Administration of the STESS.
- Administration of the FOUR Score.
- Administration of SRS.
- Administration of the mRS-9Q assessment.
- Assessment of the CGI scale.
- Evaluation of epilepsy status.
- Administration of continuous IV third-line agents.
- Perform EEG.
- Recording of adverse events.
- Recording of previous and concomitant anti-epileptic drugs.
- Recording of previous and concomitant third-line agents.
- Recording of concomitant pressors.

- Recording of other concomitant medications, procedures, and treatments.

## **12.2. Visit 2 (V3-≤54h)**

- Recording of adverse events.
- Recording of concomitant anti-epileptic drugs.
- Recording of concomitant third-line agents.
- Recording of concomitant pressors.
- Recording of other concomitant medications, procedures, and treatments.
- Wean of continuous third-line agent (QW):
  - If wean is successful, subject is followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (these subjects are Qualifying Wean Success subjects or QWS subjects);
  - If wean is not successful, there is ongoing intravenous administration of at least one continuous IV third-line agent and EEG is performed and the subject is randomized.
- Weight
  - Subject weight will be obtained within the eight-hour period from the declaration of failure of QW and prior to the initiation of the blinded infusion loading dose at H0 of V3. This weight will be the dosing weight used to determine the infusion rate for the entire blinded infusion treatment course.

## **12.3. SAGE-547 Treatment Period**

### **12.3.1. Visit 3/3R (0-24 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs will be recorded at:
  - 0, +30, +60 minutes (+/-15 minutes) and +2, +4, +8 (+/- 30 minutes) and +24 hours (+/- 2 hours) after the start of the infusion
- For the first 50 subjects randomized in the study, ECG readings will be recorded immediately after PK sampling, or within 15 minutes prior to PK sampling, at the following time points:
  - 0 (pre-dose) and at +0.5, +1, +3, +6, +12, and +24 hours after the start of the blinded study drug infusion.
  - Subsequent subjects randomized in the study will have ECG readings recorded at 0 (pre-dose) and +1, +12, and +24 hours after the start of the study drug infusion, it will not be necessary to collect these ECGs with PK samples at these timepoints and, apart from the +1 h ECG, there is +/- 2 hour time window for these ECGs
- A blood sample for PK analysis should be collected at the following time points (all +/- 15 minutes except where otherwise stated):

0 (pre-dose, within two hours of the start of the infusion) and at +0.5, +1 (+/- 5 minutes), +3, +6, +12, and +24 hours after the start of the study drug infusion.

- Completion of the FOUR Score
  - +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the final declaration of QW success)
- Ongoing intravenous administration of a continuous IV third-line agent.
- Study drug administration in loading (Hour 0-1) and maintenance infusions (at completion of Hour 1).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.2. Visit 4/4R (25-48 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +48 hours (+/- 2 hours) after the start of the infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +48 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +48 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +48 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +48 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent.
- Ongoing study drug maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.3. Visit 5/5R (49-72 hours)**

- Weight if easily obtained

- Vital signs should be recorded at:
  - +72 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +72 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +72 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +72 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +72 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.4. Visit 6/6R (73-96 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +96 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +96 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +96 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +96 hours (+/- 15 minutes) after the start of study drug infusion.

- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +96 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Perform EEG.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.5. Visit 7/7R (97-120 hours)**

- Weight if easily obtained
- Vital signs should be recorded at:
  - +120 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +120 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +120 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +120 hours (+/- 15 minutes) after the start of study drug infusion, immediately prior to the end of the maintenance infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +120 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled. Complete wean by 120 hours if at all possible.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).



## 12.4. SAGE-547 Taper Period

### 12.4.1. Visit 8/8R (121-144 hours)

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +144 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after each PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +128, +136 hours and +144 hours after the start of the blinded study drug infusion
  - +126, +132, +138 hours and +144 hours after the start of the open-label study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +144 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected (+/- 15 minutes unless otherwise stated):
  - +128 (immediately prior to the end of the first taper step), +136 hours (+/- 5 minutes, immediately prior to the end of the second taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of study drug infusion.
  - During the open-label study drug phase of the study PK blood draws at: +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 hours (+/- 5 minutes, immediately prior to the end of the third taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of the study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +144 hours (+/- 2 hours) after the start of the infusion
- Complete wean of third line agents by H144 if not completed by H120.
- Perform EEG.
- Taper of SAGE-547 infusion begins at hour 121.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## **12.5. Follow-up Period**

### **12.5.1. Visit 9/9R (145-168 hours)**

- Vital signs should be recorded at:
  - +168 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +152, +160 hours (+/- 2 hours) after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +152 and +160 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +168 hours (+/- 2 hours) after the start of the infusion
- Perform EEG.
- Assessment of the presence of physiologic brain activity using EEG.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.5.2. Visit 10/10R (169-192 hours)**

- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +192 hours (+/- 2 hours) after the start of the infusion
- At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine eligibility for the open-label treatment with the higher dose of study drug. This determination may occur at any point during Visit 10: the higher dose open-label infusion must begin within the Visit 10 window. All patients receiving the higher dose open-label treatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.
- Weight if the subject qualifies for the open-label study drug (Visit 10 only, not Visit 10R).
- Recording of adverse events (QWS subjects also).

- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.3. Visit 11/11R (Visit 3/3R + 14d (±2))**

- Blood samples collected for clinical laboratory testing (renal panel only).
- Completion of the FOUR Score (QWS subjects also).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.4. Visit 12/12R (Visit 3/3R + 21d (±2))**

All assessments also performed for QWS subjects.

- Completion of the FOUR Score.
- Administration of the GOS.
- Administration of the SRS.
- Administration of the mRS-9Q assessment.
- Evaluation of epilepsy status (see [Section 11.1.2.2](#) for details).
- Assessment of the CGI Scale.
- Recording of adverse events.
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications.
- Collection of pharmacoeconomic data.
- Mortality will be assessed throughout the study period.

## **13. STATISTICS**

### **13.1. Statistical Plan**

Complete details for the analysis and reporting of data from this study will be contained in the Statistical Analysis Plan (SAP).

#### **13.1.1. Interim Analysis**

When approximately 50% of subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### 13.1.2. Study Populations

The **Safety Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to actual treatment. This analysis population will be used for all safety analyses.

The **Intent to Treat Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to randomized treatment. This analysis population will be used for all efficacy analyses.

The **Modified Intent to Treat Population** is defined as all subjects who:

1. complete their initial course of blinded SAGE-547 or placebo treatment unless the non-completion was due a drug-related adverse event; and
2. have at least one attempt to wean from third-line agents prior to the end of blinded study treatment infusion unless the failure to wean was because seizures were not controlled.

Subjects will be classified according to randomized treatment. This analysis population will be used for sensitivity analyses of the primary endpoint and select secondary efficacy endpoints.

Narratives will be prepared for all subjects who do not complete the infusion of blinded study medication or were not subjected to any wean attempts. Narratives will include details of the cause of SE, the comorbid conditions, the adverse event(s), and reasons for non-completion of the infusion or failure to attempt weaning. This blinded narrative will be reviewed by the medical monitors and the patient adjudicated as MITT eligible or ineligible. Acceptable reasons for defining a subject as MITT ineligible include death or withdrawal of consent due to progression of the underlying cause of SE or comorbid conditions, unless the cause of death or progression of disease were thought by the investigator, sponsor, or DSMB to be related to study drug.

The **Per-Protocol (PP) Population** is defined as a subset of the MITT population but will exclude data from all subjects with significant protocol violations or deviations. Subjects will be classified according to actual treatment received. This data set will be used for sensitivity analyses to examine the robustness of results for the primary and key secondary efficacy endpoints.

The **Pharmacokinetics Population** is defined as all subjects who at least had an infusion of blinded SAGE-547 initiated and have at least one pharmacokinetic sample collected.

The **Pharmacogenetic Population** is defined all subjects who consent to being included in the pharmacogenetic assessment and provide a pharmacogenetic sample.

Summary statistics of all data collected will be presented for subjects who were QW successes.

### 13.1.3. General Aspects

Tabular displays of descriptive statistics will be provided for all variables. Summary tables will include n, mean, mean, standard deviation, minimum and maximum for continuous variable and frequency and percentage for categorical variables.

### 13.1.4. Analysis of Primary Endpoint

The analysis of response to treatment (see Section 11.1.1 for definition of primary endpoint) between SAGE-547 treated subjects and placebo treated subjects will be performed on the ITT population using a Cochran-Mantel-Haenszel (CMH) test with variables for treatment, concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior

to randomization (one vs two or more). The CMH general association statistic and its associated p-value will be presented. The comparison of treatment response rates will be conducted at the 5% level of significance. To confirm the CMH results, a permutation test will also be conducted.

An additional analysis of the primary endpoint will also be performed on the MITT population. In addition sensitivity analyses of the primary endpoint will be performed using the ITT population based on:

- the number of third-line agents (one, two, or three) subjects were administered post-randomization; and
- which third line agent was the subject of the first TW.

### **13.1.5. Analysis of Secondary Efficacy Endpoints**

Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section ([Section 6](#)). Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. The analysis of the secondary endpoints will also be performed on the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

### **13.1.6. Analysis of Other Endpoints**

Safety and “Other” endpoints will only be summarized by treatment group.

Summaries of safety endpoints will be based on the overall Safety Population.

### **13.1.7. Epilepsy and SRSE Status**

Diagnosis of epilepsy and recurrence of RSE or SRSE will be documented as the percentage of subjects by time point and overall. Kaplan-Meier curves may be plotted if sufficient data are available.

Utilization of AEDs during follow-up and during recurrence will be summarized.

### **13.1.8. Questionnaires**

The data collected from each questionnaire will be interpreted according to the standard methodology for that questionnaire. There will be no adjustment for missing values.

**13.1.9. Pharmacokinetic Data Analysis**

Details of the pharmacokinetic data analysis will be described in detail in a separate Pharmacokinetic Analysis Plan.

**13.1.10. Pharmacogenetic Data Analysis**

Any genotype data generated in this study will be stored within a secured database within Sage Therapeutics and / or a third party contracted to work with Sage Therapeutics to analyze the samples. Because the number of subjects agreeing to participate in the genetic research component of the study is unknown, it is not possible to establish, a priori, whether sufficient samples will be obtained to support formal statistical evaluation of data. As a consequence a Pharmacogenetic Analysis Plan will only be prepared where appropriate and the results obtained from any genetic research will be reported in a report separate from the main study CSR.

**13.1.11. Open-Label Study Drug Subjects**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are treated with SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo.

**13.1.12. EEG-Responders**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who are classified as EEG-responders/non-responders based on the independent assessment of the PAEEG. Summaries will be derived for the two randomized treatment groups.

**13.1.13. QT/QTc Assessment**

An analysis of the correlation between changes in QT/QTc intervals and SAGE-547 plasma levels will be performed to investigate if there is a potential effect that SAGE-547 may have on QT/QTc interval. A detailed description of the QT/QTc assessment will be included in the SAP.

**13.1.14. Quantitative EEG**

The nine EEG records for each subject may be subjected to exploratory quantitative EEG analysis, the details of which will be included in the EEG Analysis Plan. In summary the following comparisons may be made, SAGE-547 versus placebo: the QWEEG versus the TWEEG (main analysis); the CEEG versus PAEEG (subsidiary analysis); and TAEEG versus PAEEG (exploratory analysis).

**13.2. Determination of Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between treatment groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

### **13.3. Statistical Analysis Plan**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

## **14. ADVERSE EVENTS**

The safety procedures in this study will be detailed in a Safety Management Plan, which will be agreed and signed before the first subject is randomized in the study. [Section 14.1](#) summarizes Investigator responsibilities regarding the identification and documentation of AEs, the classification of AEs for relationship to study drug and severity, and the reporting of AE information to the Sponsor and the IRB.

[Section 14.2](#) summarizes Sponsor/Medical Monitor Responsibilities regarding monitoring of AE data and reporting relevant safety information to FDA.

[Section 14.3](#) lists important AE definitions.

### **14.1. Investigator Responsibilities**

#### **14.1.1. Identification and Documentation of Adverse Events by Investigator**

Subjects will be evaluated and questioned generally (if possible) to identify AEs during the course of the study. AEs will be collected from the signature of the consent form through Visit 12/12R. Adverse events that occur prior to completion of screening will be captured on the Medical History eCRF. Adverse events that occur after completion of screening will be recorded on the Adverse Event eCRF.

All AEs revealed by observation, other diagnostic procedures, or spontaneously reported by the subject and/or in response to an open question from study personnel will be recorded on the Adverse Event Form. Any clinically significant deterioration in laboratory assessments or other clinical findings are considered an AE and must be recorded on the Adverse Event Form, unless otherwise stated. AE information recorded will be entered into the database on an ongoing basis.

AEs with a relationship considered related to study drug (probable, possible) should be followed until the event is resolved or the Investigator determines the event is stable or no longer clinically significant. AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

For SAEs, an electronic Serious Adverse Event eCRF must be completed with as much information as possible and submitted in the time frame described below in [Section 14.1.3](#). When new significant information is obtained as well as when the outcome of an event is known, the electronic SAE eCRF should be updated within 24 hours. If the subject was an outpatient at the time of the SAE and was re-hospitalized due to the SAE, a copy of relevant hospital records (e.g., admission report, laboratory test results, discharge summary, etc.) may be requested to be included as part of the subject medical file.

All SAEs will be followed until resolved or until a stable status has been achieved.



**14.1.2. Adverse Event Classification****14.1.2.1. Relationship to Investigational Drug**

None:	No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state.
Possible:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject, but this is not known for sure.
Probable:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

**14.1.2.2. Severity**

Mild	Discomfort noticed, but no disruption to daily activity.  For subjects that are unconscious, this may be a slight or minor change in a lab result or clinical sign or symptom that does not require immediate corrective action.
Moderate	Discomfort sufficient to reduce or affect normal daily activity, but is not hazardous to health; prescription drug therapy may be employed to treat the AE.  For subjects that are unconscious, this may be a clinically meaningful change that may require immediate corrective action.
Severe	Inability to work or perform normal daily activity and represented a definite hazard to health; prescription drug therapy and/or hospitalization may be employed to treat the AE.  For unconscious subjects, this may be a significant clinical change that requires immediate corrective action.

**14.1.2.3. Action Taken with Investigational Drug**

None	Study medication was continued without change.
Discontinued	Study medication was terminated.
Dose adjusted	Study medication dose/infusion rate was changed and then continued per protocol.
Interrupted	Study medication was interrupted and then continued per protocol.
Unknown	The action taken with regard to study medication is unknown.
Not applicable	Administration of study medication was not ongoing.

**14.1.2.4. Assessment of Outcome**

Ongoing	At the end of the study, the event has not resolved or stabilized.
Ongoing and stable	The event is ongoing but has stabilized and is unlikely to change
Resolved	The event has resolved or the subject recovered without sequelae.
Resolved with sequelae	The event has at least one secondary outcome that may result in permanent disability and/or functional limitation.
Unknown	The status of the event is unknown.
Death	The subject has expired.

**14.1.3. Investigator Reporting to Sponsor and Sponsor Emergency Contact**

All new SAEs that come to the Investigator and/or Sponsor's notice during the course of the study (up to and including the last study visit) must be reported by the Investigator on the designated electronic report form within 24 hours of the point in time when the Investigator becomes aware of the SAE. As additional information becomes available, the designated electronic report form must be updated within 24 hours.

Investigators must report any SAE, whether or not considered drug related. The report must include an assessment of whether there is a reasonable possibility that the drug caused the event.

In a medical emergency (ie, an event that requires immediate attention regarding the treatment of a subject, operation of the clinical study, and/or the use of investigational drug), study site staff will apply appropriate medical intervention according to current standards of care, and contact the Medical Monitor.

**14.1.4. Medical Monitor and Emergency Contact Information**

[REDACTED], MD  
[REDACTED]

In a study related medical emergency situation, when the assigned Medical Monitor cannot be reached by a caller, an on-call Physician can be reached 24 hours per day, 7 days per week via an [REDACTED] Call-Center:

- Telephone: [REDACTED]  
(this is a chargeable telephone number allowing a global reach from both landlines and mobile phones)

- 

On this internet page a list of country-specific toll-free telephone numbers is provided. It should be noted that not all countries globally have access to toll-free numbers as indicated on the “24/7 Medical Help desk” index. Countries without toll-free numbers need to dial the chargeable number as indicated above. Furthermore, toll-free numbers are not available from mobile phones.

#### **14.1.5. SAE Reporting Contact Information**

Contact information and reporting instructions are provided in the Safety Management Plan.

#### **14.1.6. Reporting to Institutional Review Boards (IRBs)**

It is the responsibility of the Investigator to promptly notify the institution’s IRB of all serious and unexpected suspected adverse reactions (see [Section 14.3](#) for definitions).

### **14.2. Sponsor/Medical Monitor Responsibilities**

#### **14.2.1. Monitoring of Adverse Event Data**

The Medical Monitor will review any newly reported adverse events in an ongoing basis. If the aggregate assessment indicates that an event is occurring more frequently than would normally be expected in this population, or as previously observed, and the sponsor believes that the events are causally related to the administration of SAGE-547, the Sponsor will then report that information in an IND safety report.

#### **14.2.2. Data Safety Monitoring Board**

An independent DSMB will monitor the clinical, PK and PD data for safety signals throughout the study and will be asked to assess the placebo response rate at the time of the interim analysis to determine final sample size. In order to perform their monitoring function the DSMB will have access to un-blinded safety data as necessary.

The composition and procedures for the board will be described in a separate DSMB Charter.

#### **14.2.3. Reporting to FDA**

The Sponsor must report in an IND safety report any suspected adverse reaction to study treatment that is both serious and unexpected (21 CFR 312.32(c)(1)(i)). Before submitting an IND safety report, the Sponsor will ensure the event meets all three of the definitions: (1) suspected adverse reaction, (2) serious, (3) unexpected. If the AE does not meet all three of the definitions, it should not be submitted as an IND safety report. The Sponsor should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the adverse event and, therefore, that the event meets the definition of a suspected adverse reaction.

If there is a serious and unexpected suspected adverse reaction, the Sponsor will notify the appropriate regulatory agency(ies) and all appropriate parties on an expedited basis. In addition, Sponsors must submit expedited reports of an increased rate of occurrence or severity of serious suspected adverse reactions over that listed in the protocol or Investigational Brochure.

SUSARs will be unblinded prior to reporting to FDA. Unless it is necessary to unblind for the safety of the patient, the investigator will not be informed of the unblinding of the subject.

Under 21 CFR 312.32, Sponsors should identify in the protocol SAEs that it does not plan to report individually in an expedited manner, because they are known consequences of the disease or otherwise common in the study population. Given the grave condition and prognosis of SRSE being studied, individual occurrences of seizures or seizure activity will not be reported expeditiously in this study. Regardless of which events are reported in an expedited manner, all adverse events will be closely monitored throughout the study.

#### **14.2.4. Reporting to European Regulatory Authorities**

The Sponsor or its designee is responsible for SUSAR notification to the relevant regulatory authorities as outlined in the ICH Guidelines. All investigators participating in the study will also be informed as required by regulations.

Any SUSAR is subject to expedited reporting in the EU. The Sponsor or its designee, will report any single SUSAR to the appropriate National CAs and IECs within 7 days if the SUSAR is life-threatening or fatal (with the relevant follow-up information subsequently communicated within an additional eight days), and within 15 days if the SUSAR is neither life-threatening nor fatal. SUSARs reported will be those that have arisen in the present clinical trial and SUSARs that have arisen in other clinical trials conducted by the Sponsor with the same medicinal product.

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to competent authorities of the concerned Member States and to IEC(s)/IRBs as required by national laws.

### **14.3. Adverse Event Definitions**

#### **14.3.1. Adverse Event**

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

#### **14.3.2. Suspected Adverse Reaction**

Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

#### **14.3.3. Life-Threatening**

An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

#### **14.3.4. Serious**

An AE or suspected adverse reaction is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE – see definition above
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disability
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

#### **14.3.5. Unexpected**

An AE or suspected adverse reaction is considered “unexpected”:

- If it is not listed in the Investigational Brochure or is not listed at the specificity or severity that has been observed, or
- If an Investigational Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigational Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigational Brochure listed only cerebral vascular accidents.

“Unexpected,” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigational Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

#### **14.4. Emergency Identification of Study Medication**

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject’s treatment in the study via the IVRS; this normally requires prior approval by the medical monitor. However, if the subject is at immediate risk and the Investigator believes that immediate knowledge of the study treatment will alter medical management, discussion with the medical monitor may take place after unblinding. The Investigator will not unblind the medical monitor during that discussion. The process of unblinding will ensure that only the investigator is unblinded; the medical monitor, study management team, and data management team will not be made aware of the treatment allocation of an individual subject. All

cases of emergency unblinding will be fully documented in a way that does not unblind the medical monitor, study management team, and data management team.

## **15. STUDY ADMINISTRATIVE CONSIDERATIONS**

### **15.1. Quality Control and Quality Assurance**

The Investigators and institutions will permit trial related monitoring, audits, IRB review, and regulatory inspections as requested by FDA, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed informed consent forms, etc.) in addition to case report forms.

Quality assurance and quality control systems with written standard operating procedures (SOPs) will be followed to ensure this trial will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The site's dedicated study monitor will arrange to visit the Investigator at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be identified and resolved. The study monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality assurance officers named by Sage Therapeutics or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements, made by the Sponsor with the Investigator/institution and any other parties involved with the clinical trial, will be in writing in a separate agreement.

### **15.2. Data Handling and Recordkeeping**

#### **15.2.1. Data Handling**

Procedures for data handling (including electronic data) used in this protocol will be documented in a Data Management Plan.

#### **15.2.2. Case Report Form Completion**

eCRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of demographics, study drug administration, study procedures, AEs, questionnaire completion, efficacy assessments and subject status, including survival.

The Investigator will maintain copies of the eCRFs at the study site. For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate eCRF.

### **15.2.3. Retention of Study Records**

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval and until there are no pending or contemplated marketing applications or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to an appropriate person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

## **15.3. Confidentiality**

To maintain subject privacy, all eCRFs, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available trial registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by Sage Therapeutics to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

## **15.4. Publication Policy**

All information concerning SAGE-547 is considered confidential and shall remain the sole property of Sage Therapeutics. The Investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval from Sage Therapeutics. No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between Sage Therapeutics and the Investigator.

## **15.5. Protocol Amendments**

Changes to the conduct of the study should be prepared as a protocol amendment by the Sponsor. Protocol amendments should receive written IRB/IEC approval prior to implementation at the investigative site, except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the trial (eg, change of monitor, telephone numbers). In this case, Sage Therapeutics will amend and implement the protocol change

and subsequently notify the regulatory authorities and the Investigative sites who will notify the respective IRB, as appropriate.



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**APPENDIX 1. APPENDIX 1: FOUR SCORE****FOUR score****Full Outline of UnResponsiveness****Eye response**

- E4: eyelids open or opened, tracking, or blinking to command
- E3: eyelids open but not tracking
- E2: eyelids closed but open to loud voice
- E1: eyelids closed but open to pain
- E0: eyelids remain closed with pain

**Motor response**

- M4: thumbs-up, fist or peace sign
- M3: localizing to pain
- M2: flexion response to pain
- M1: extension response to pain
- M0: no response to pain or generalized myoclonus status

**Brainstem reflexes**

- B4: pupil and corneal reflexes present
- B3: one pupil wide and fixed
- B2: pupil or corneal reflexes absent
- B1: pupil and corneal reflexes absent
- B0: absent pupil, corneal and cough reflex

**Respiration pattern**

- R4: not intubated, regular breathing pattern
- R3: not intubated, Cheyne-Stokes breathing pattern
- R2: not intubated, irregular breathing
- R1: breathes above ventilatory rate
- R0: breathes at ventilator rate or apnea

Reference ([Iyer, Hoel et al. 2009](#)).

**APPENDIX 2. GLASGOW OUTCOME SCALE (GOS)****GLASGOW  
OUTCOME  
SCALE**

Patient Name: \_\_\_\_\_  
 Rater Name: \_\_\_\_\_  
 Date: \_\_\_\_\_

*Note:* The scale presented here is based on the original article by Jennett and Bond. It has become common practice in clinical trial administration, however, to use a modified version that places the scores in reverse order (i.e., "good recovery" = 1, "moderate disability" =2, etc.).

Score	Description
1	DEATH
2	PERSISTENT VEGETATIVE STATE Patient exhibits no <i>obvious cortical</i> function.
3	SEVERE DISABILITY (Conscious but disabled). Patient depends upon others for daily support due to mental or physical disability or both.
4	MODERATE DISABILITY (Disabled but independent). Patient is independent as far as daily life is concerned. The disabilities found include varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes.
5	GOOD RECOVERY Resumption of normal activities even though there may be minor neurological or psychological deficits.

**TOTAL (1-5):** \_\_\_\_\_

Reference ([Jennett and Bond 1975](#)).

## APPENDIX 3. SUPERVISION RATING SCALE (SRS)

### SUPERVISION RATING SCALE (SRS)

**Instructions:** Circle the rating that is closest to the amount of supervision that the patient *actually receives*. "Supervision" means that someone is responsible for being with the patient.

<u>Rating</u>	<u>Description</u>
<b>Level 1: INDEPENDENT</b>	
1	The patient lives alone or independently. Other persons can live with the patient, but they cannot take responsibility for supervision (for example, a child or elderly person).
2	The patient is unsupervised overnight. The patient lives with one or more persons who <i>could</i> be responsible for supervision (for example, a spouse or roommate), but they are <i>all</i> sometimes absent overnight.
<b>Level 2: OVERNIGHT SUPERVISION</b>	
3	The patient is only supervised overnight. One or more supervising persons are always present overnight but they are <i>all</i> sometimes absent for the rest of the day.
<b>Level 3: PART-TIME SUPERVISION</b>	
4	The patient is supervised overnight and part-time during waking hours, but is allowed on independent outings. One or more supervising persons are always present overnight and are also present during part of waking hours every day. However, the patient is sometimes allowed to leave the residence without being accompanied by someone who is responsible for supervision.
5	The patient is supervised overnight and part-time during waking hours, but is unsupervised during working hours. Supervising persons are <i>all</i> sometimes absent for enough time for them to work full-time outside the home.
6	The patient is supervised overnight and during most waking hours. Supervising persons are <i>all</i> sometimes absent for periods longer than one hour, but less than the time needed to hold a full-time job away from home.
7	The patient is supervised overnight and during almost all waking hours. Supervising persons are <i>all</i> sometimes absent for periods shorter than one hour.
<b>Level 4: FULL-TIME INDIRECT SUPERVISION</b>	
8	The patient is under full-time indirect supervision. At least one supervising person is <i>always</i> present, but the supervising person does not check on the patient more than once every 30 minutes.
9	Same as #8 plus requires overnight safety precautions (for example, a deadbolt on outside door).
<b>Level 5: FULL-TIME DIRECT SUPERVISION</b>	
10	The patient is under full-time direct supervision. At least one supervising person is always present and the supervising person checks on the patient more than once every thirty minutes.
11	The patient lives in a setting in which the exits are physically controlled by others (for example, a locked ward).
12	Same as #11 plus a supervising person is designated to provide full-time line-of-sight supervision (for example, an escape watch or suicide watch).
13	The patient is in physical restraints.

3/12/93

Corwin Boake, Ph.D., TIRR, 1333 Moursund, Houston, TX 77030-3405, 713/799-6990

## APPENDIX 4. MODIFIED RANKIN SCALE – LEVEL OF FUNCTION SURVEY (mRS-9Q)

1. Do you have any symptoms that are bothering you? (For example, trouble with reading or writing, trouble speaking, problems with vision, numbness, weakness, balance trouble, or problems with swallowing?)	YES <input type="radio"/>	NO <input type="radio"/>
2. Are you able to do the same work as before?	YES <input type="radio"/>	NO <input type="radio"/>
3. Are you able to keep up with your hobbies?	YES <input type="radio"/>	NO <input type="radio"/>
4. Have you maintained your ties to friends and family?	YES <input type="radio"/>	NO <input type="radio"/>
5. Do you need help making a simple meal, doing household chores, or balancing a checkbook?	YES <input type="radio"/>	NO <input type="radio"/>
6. Do you need help with shopping or traveling close to home?	YES <input type="radio"/>	NO <input type="radio"/>
7. Do you need another person to help you walk?	YES <input type="radio"/>	NO <input type="radio"/>
8. Do you need help with eating, going to the toilet, or bathing?	YES <input type="radio"/>	NO <input type="radio"/>
9. Do you stay in bed most of the day and need constant nursing care?	YES <input type="radio"/>	NO <input type="radio"/>

## APPENDIX 5. CLINICAL GLOBAL IMPRESSION (CGI)

### Clinical Global Impression (CGI)

#### 1. Severity of illness

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- |                             |   |
|-----------------------------|---|
| 0 = Not assessed            | 4 = Moderately ill                        |
| 1 = Normal, not at all ill  | 5 = Markedly ill                          |
| 2 = Borderline mentally ill | 6 = Severely ill                          |
| 3 = Mildly ill              | 7 = Among the most extremely ill patients |

#### 2. Global improvement: Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.

Compared to his condition at admission to the project, how much has he changed?

- |                        |                     |
|------------------------|---------------------|
| 0 = Not assessed       | 4 = No change       |
| 1 = Very much improved | 5 = Minimally worse |
| 2 = Much improved      | 6 = Much worse      |
| 3 = Minimally improved | 7 = Very much worse |

#### 3. Efficacy index: Rate this item on the basis of drug effect only.

Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.

EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect		Side effects			
		None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
<b>Marked</b>	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
<b>Moderate</b>	Decided improvement. Partial remission of symptoms	05	06	07	08
<b>Minimal</b>	Slight improvement which doesn't alter status of care of patient	09	10	11	12
<b>Unchanged or worse</b>		13	14	15	16
Not assessed = 00					

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

**APPENDIX 6. STATUS EPILEPTICUS SEVERITY SCORE (STESS)**

Outcome Predictor	Feature	Score
Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type (prior to first treatment)	Simple-partial, complex-parial, absence, myoclonic (complicating idiopathic generalized epilepsy)	0
	Generalized-convulsive	1
	Nonconvulsive status epilepticus in coma	2
Age	< 65 years	0
	≥ 65 years	2
History of previous seizures	Yes	0
	No or unknown	1
Summed Total		



**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY  
TO EVALUATE THE EFFICACY AND SAFETY OF SAGE-547 INJECTION  
IN THE TREATMENT OF SUBJECTS WITH SUPER-REFRACTORY  
STATUS EPILEPTICUS**

**PROTOCOL NUMBER: 547-SSE-301**

**IND NUMBER: 117901**

**EudraCT Number: 2015-002142-31**

Product: SAGE-547 Injection (allopregnanolone)

Sponsor Contact: [REDACTED], MD

Sage Therapeutics  
215 First Street  
Cambridge, MA 02142

Medical Monitor: [REDACTED], MD

Date of Protocol:	09 March 2015
Date of Amendment One	27 May 2015
Date of Amendment Two (Italy Specific)	04 February 2016
Date of Amendment Three (Italy Specific [not implemented])	22 April 2016
Date of Amendment Four (Italy Specific)	20 September 2016

**Confidentiality Statement**

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

**PROTOCOL NUMBER: 547-SSE-301**

Sponsor [REDACTED]:

[REDACTED]  
[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]  
[REDACTED]

[REDACTED]  
[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]  
[REDACTED]

[REDACTED]  
[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

CRO [REDACTED]:

[REDACTED]

## 1. SIGNATURE PAGE

Title of Protocol:

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus

Protocol No: 547-SSE-301

**Sponsor Approval**

[Redacted Signature]

21 SEP 2016

[Redacted Signature] MD  
Sage Therapeutics

Date (dd/mmm/yyyy)

[Redacted Signature]

23 Sep 2016

[Redacted Signature] MPH  
Sage Therapeutics

Date (dd/mmm/yyyy)

[Redacted Signature]

21 Sep 2016

[Redacted Signature] MPH  
Sage Therapeutics

Date (dd/mmm/yyyy)

[Redacted Signature]

21-SEP-2016

[Redacted Signature]  
Sage Therapeutics

Date (dd/mmm/yyyy)

**Investigator Agreement**

By signing this page I attest that I have read and understand the contents of Clinical Protocol 547-SSE-301 and any current amendments. I agree to adhere to the design, conduct, and reporting requirements of the study as stated in the clinical protocol and to my obligations to the Sponsor as described in the protocol and executed contracts between myself, my Institution, and the Sponsor. I also agree to adhere to any subsequent amendments to the clinical protocol.

Investigator's Signature: \_\_\_\_\_

Investigator's Name: \_\_\_\_\_

Institution: \_\_\_\_\_

Date: \_\_\_\_\_

## 2. SYNOPSIS

<b>Name of Sponsor:</b> Sage Therapeutics 215 First Street Cambridge, MA 02142																							
<b>Protocol No.</b> 547-SSE-301	<b>Phase:</b> 3																						
<b>Name of Investigational Product:</b> SAGE-547 Injection																							
<b>Name of Active Ingredient:</b> Allopregnanolone																							
<b>Title of the Protocol:</b> A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus																							
<b>Dosing Regimen: SAGE-547 or Placebo Dosing Schedule</b> <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 10px;"> <thead> <tr> <th style="width: 20%;">Hour</th> <th style="width: 40%;">Type and Duration of SAGE-547 Infusions</th> <th style="width: 40%;">Dose</th> </tr> </thead> <tbody> <tr> <td>H1</td> <td>One hour loading Infusion</td> <td>300 µg/kg/h</td> </tr> <tr> <td>H2 – H120</td> <td>119 hour maintenance infusion</td> <td>90 µg/kg/h</td> </tr> <tr> <td>H121 – H128</td> <td>8 hour taper</td> <td>65 µg/kg/h</td> </tr> <tr> <td>H129 – H136</td> <td>8 hour taper</td> <td>45 µg/kg/h</td> </tr> <tr> <td>H137 – H144</td> <td>8 hour taper</td> <td>25 µg/kg/h</td> </tr> </tbody> </table>			Hour	Type and Duration of SAGE-547 Infusions	Dose	H1	One hour loading Infusion	300 µg/kg/h	H2 – H120	119 hour maintenance infusion	90 µg/kg/h	H121 – H128	8 hour taper	65 µg/kg/h	H129 – H136	8 hour taper	45 µg/kg/h	H137 – H144	8 hour taper	25 µg/kg/h			
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<b>Study Sites</b> Up to 180 sites in the USA, Israel, Europe, and Canada.																							

**Number of Subjects**

The study will randomize 140 subjects at up to 180 sites.

**Study Population**

Subjects will be aged two years or more, in SRSE<sup>1</sup> (as defined in the Inclusion Criteria [Section 8.1](#)), and being managed in an intensive care setting. Pediatric patients (those < 14 years of age) will be managed in a pediatric intensive care setting.

**Duration of Subject Involvement**

Individual subject participation will be up to 30 days.

**Study Design**

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

Patients will follow one of three paths to entry to the study. The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst or seizure suppression with a third-line agent. These subjects will be consented for the study after admission to the intensive care unit, before or after any third-line agents are administered for burst or seizure suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their legally authorized representative (LAR). Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours. Once burst or seizure suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The second path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst or seizure suppression pattern on the EEG. These subjects may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst or seizure suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst or seizure suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst or seizure suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be

<sup>1</sup> In this study, the term Super-Refractory Status Epilepticus or SRSE is equivalent to “Refractory Status Epilepticus (RSE) that has failed standard treatment” and the two terms are used interchangeably.

randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The third path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst or seizure suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These subjects may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 treatment or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within eight hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo).

The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that subjects, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as both the ability to wean the subject off all third-line agents before the end of the infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication infusion, and concurrent signs of physiologic brain activity as determined by EEG. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#) and [Table 2](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo will all subsequently be eligible to be administered SAGE-547 at the higher dose.

## Visit Schedule

The visit schedule and an overview of events at each visit is provided in [Table 1](#), [Table 2](#) and [Table 3](#) Schedule of Assessments.

## **Study Objectives**

### ***Primary objective:***

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult and pediatric subjects with SRSE, and for the response to endure at least 24 hours after the end of the SAGE-547 or placebo infusion (primary response).

### ***Secondary objectives:***

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in the Clinical Global Impression scale (CGI) between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### ***Safety objectives:***

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

### ***Other objectives:***

1. To evaluate the impact of treatment with a higher dose SAGE-547 infusion;



2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol<sup>®</sup> and identified SAGE-547 metabolite plasma concentrations;
3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;
6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS) (age  $\geq 17$  years).

## Endpoints

### *Primary endpoint:*

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### *Secondary endpoints:*

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### *Safety endpoints:*

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;

## 5. Mortality.

**Other endpoints:**

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who are treated with a higher dose of SAGE-547.
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol<sup>®</sup> and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS) (age  $\geq 17$  years).

**Inclusion Criteria**

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects two (2) years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed zero, one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst or seizure suppression pattern; or who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst or seizure suppression pattern.

**Exclusion Criteria**

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone or any excipients in SAGE-547.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy with highly malignant/malignant EEG features ([Westhall, Rosetti et al. 2016](#)).

4. Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing underlying neurological disorder.
5. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis but for whatever reason, but dialysis that would adequately remove Captisol® is not planned;
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the opinion of the investigator, of less than 30 days.
6. Subjects who are being administered more than three third-line agents concomitantly or in whom the qualifying wean cannot be completed within 24 hours, or who are being administered a third-line agent for other indications such as management of raised intra-cranial pressure that would preclude weaning according to this protocol.
7. Subjects with a living will that does not allow heroic measures.
8. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
9. Subjects who have been treated or randomized in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not have received study drug/placebo and then re-enroll).

### **Pharmacogenetic Research**

In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **Statistical Analysis**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

### **Interim Analysis**

When approximately 50% of the subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### **Analysis of Primary Endpoint**

The analysis of response to treatment between SAGE-547 treated subjects and placebo treated subjects will be performed using a Cochran-Mantel-Haenszel test with variables for treatment, concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). In this analysis, a treatment responder is a subject who is successfully weaned off all third-line agents and blinded study medication prior to the end of study treatment infusion and remains off third-line agents for at least 24 hours following cessation of the blinded study medication, and who has concurrent signs of physiologic brain activity as determined by EEG. The analysis will be based on the ITT Population. The comparison of treatment response rates will be conducted at the 5% level of significance.

### **Analysis of Secondary Efficacy Endpoints**

The primary analysis will be repeated for the MITT population. Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section. Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. Secondary analyses will be repeated for the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from Baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third-line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

Summaries of safety endpoints will be based on the overall Safety Population which is defined as all subjects who at least initiated the infusion with blinded study treatment.

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects are treated with a higher dose of SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo. Summary statistics will be presented for subjects who were QW successes.

### **Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

**Table 1: Schedule of Assessments for Protocol 547-SSE-301: One Infusion of Study Drug (blinded)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical/SE/Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X	X	X	X	X	X	X	X		X		
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X		X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X		X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X		X	X		X		X		X		
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X			
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>o</sup>											X
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV 3rd-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>p</sup>				
EEG	X	X				X		X	X			
Randomization		X										
Study Drug Administration <sup>q</sup>			X	X	X	X	X	X				
TW Outcome & Open-Label Treatment Decision										X <sup>r</sup>		
Physiologic Brain Activity									X			
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

**Table 2: Schedule of Assessments for Protocol 547-SSE-301: Two Infusions of Study Drug (one blinded, one open-label)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V3R
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	0-24h
Eligibility Checklist	X										S
Informed Consent <sup>a</sup>	X										E
Inclusion/Exclusion Criteria	X										E
Demography <sup>b</sup>	X										
Medical and SE and Wean History <sup>c</sup>	X										T
Height	X										A
Weight <sup>d</sup>	X	X	X	X	X	X	X	X		X	B
Serum Pregnancy Test <sup>e</sup>	X										L
Hematology <sup>f</sup>	X		X	X		X		X		X	E
Serum Chemistry and GFR <sup>g</sup>	X		X	X		X		X		X	
Urinalysis <sup>h</sup>	X		X	X		X		X		X	E
Pharmacogenetic sample	X										X
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X	T
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X	E
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X		N
STESS	X										I
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	O
Glasgow Outcome Score (GOS)											N
Supervision Rating Scale (SRS)	X <sup>o</sup>										
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>										
Epilepsy Status	X										N
Clinical Global Impression (CGI)	X										E
Continuous IV Third-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>p</sup>			X
EEG	X	X				X		X	X		T
Randomization		X									
Study Drug Administration <sup>q</sup>			X	X	X	X	X	X			
TW Outcome and Open-Label Treatment Decision										X <sup>r</sup>	P
Physiologic Brain Activity									X		
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	A
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	G
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	E
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X	
Pharmacoeconomic Data											
Mortality											

**Table 2 continued**

	V3R	V4R	V5R	V6R	V7R	V8R	V9R	V10R	V11R	V12R
	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3R+14d (±2d)	V3R+21d (±2d)
Weight <sup>d</sup>	X	X	X	X	X	X				
Serum Pregnancy Test <sup>e</sup>										
Hematology <sup>f</sup>	X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X	X		X		X		X		
Vital Signs <sup>i</sup>	X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>	X	X	X	X	X	X	X			
STESS										
FOUR Score <sup>m</sup>	X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)										X
Supervision Rating Scale (SRS)										X
Modified Rankin Score (mRS) <sup>n</sup>										X
Epilepsy Status										X
Clinical Global Impression Scale (CGI)										X
Continuous IV Third-Line Agent(s)	X	X	Wean	Wean	Wean	Wean <sup>p</sup>				
EEG			X			X	X			
Randomization										
Study Drug Administration <sup>q</sup>	X	X	X	X	X	X				
TW Success and Physiologic Brain Activity							X			
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data										X
Mortality										X

**Table 3: Schedule of Assessments for Protocol 547-SSE-301: Qualifying Wean Successes**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical and SE and Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X											
Serum Pregnancy Test <sup>c</sup>	X											
Hematology <sup>f</sup>	X											
Serum Chemistry and GFR <sup>f</sup>	X											
Urinalysis <sup>h</sup>	X											
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X											
ECG <sup>j</sup>	X											
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>o</sup>											X
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV Third-Line Agent(s)	X	Wean										
EEG	X	X										
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

<sup>a</sup> Written informed consent by proxy (LAR) will be obtained prior to starting any study-related procedures not considered standard of care.

<sup>b</sup> Demographic information will be obtained by proxy and confirmed by the subject when possible.

<sup>c</sup> Medical history will be obtained by proxy and confirmed by the subject when possible. All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Dosing changes with the third-line agent(s) that constitute a wean attempt will be marked as such on the CRF, and the start/stop dates and times of all wean attempts prior to V3 will be recorded, as well as the outcome of the wean attempt.



<sup>d</sup> Weight will be collected at Screening (V1) and prior to administration of the blinded study drug infusion at V2 and the open-label study drug infusion at V10. The weights at V2 and V10 will be used to determine the appropriate infusion rate of the blinded and open-label infusions respectively. If easily obtained (such as via a scale-bed), weight will also be recorded once during each subsequent 24 hour period of the initial study drug infusion period (V3-V8) and second infusion period (V3R-V8R, if applicable).

<sup>e</sup> Serum pregnancy test for females aged 10 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy.

<sup>f</sup> Blood samples will be taken for hematology and serum chemistry and GFR calculation at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will document whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

<sup>g</sup> Blood samples will be taken at V11 or V11R for serum chemistry (renal panel only).

<sup>h</sup> Urine samples will be taken for urinalysis and NAG at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will add a comment about whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

<sup>i</sup> Vital signs will be recorded at the following time points relative to the start of each infusion of study drug: Screening (V1), at 0, 30, 60 minutes ( $\pm 15$  minutes), at 2, 4, and 8 hours ( $\pm 30$  minutes), and at 24, 48, 72, 96, 120, 144, 168, and 192 hours ( $\pm 2$  hours).

<sup>j</sup> For the first 50 subjects randomized in the study, ECG (12-lead) should be performed at Screening (V1) and at the following times relative to the start of study drug infusion. For the blinded (first) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 128, 136, 144, 152, 160, and 192 hours ( $\pm 2$  hours). For the open-label SAGE-547 (second) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 126, 132, 138, 144, 152, 160, and 192 hours ( $\pm 2$  hours). Heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours. If it is not possible to perform ECG immediately after PK sampling up to 160 hours, ECG must be performed within 15 minutes prior to PK sampling up to 160 hours. Following randomization of the first 50 subjects, subsequent subjects randomized in the study will have ECG collected at the following timepoints: Pre-dose and at 1, 12, 24, 48, 72, 96, 120, 144, and 192 hours after the start of the blinded (first) study drug infusion; and, Pre-dose and at 1, 12, 24, 48, 72, 96, 120, 144, and 192 hours after the start of the open-label (second) study drug infusion. It is not necessary for to collect these ECGs with the PK samples at these timepoints and, apart from the 1 h ECG, there is  $\pm 2$  hour time window for these ECGs.

<sup>k</sup> Plasma will be collected to assay for study drug concentrations at the following time points relative to the start of each infusion of study drug: For the blinded (first) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion. For the open-label SAGE-547 (second) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open-label SAGE-547 study drug infusion. Pre-dose samples may be taken within two hours before starting the infusion of study drug; timepoints up to and including 1h will have a time window of  $\pm 5$  minutes; all other timepoints will have a window of  $\pm 15$  minutes.

<sup>m</sup> FOUR Score assessments will be performed at Screening (V1), 24, 48, 72, 96, 120, 144, 168, and 192 hours (all  $\pm 2$  hours) relative to the start of each infusion of study drug, and at V11 or V11R, and at V12 or V12R.

<sup>n</sup> Modified Rankin Score (mRS) applicable for subjects  $\geq 17$  years old only.

<sup>o</sup> SRS at V1 will be a retrospective assessment of the supervision required by the subject immediately prior to admission that includes the index episode of the SE, and mRS at V1 will be a retrospective assessment of the disability and dependence of the subject immediately prior to admission that includes the index episode of the SE.

<sup>p</sup> Target for complete wean of all continuous IV third-line agents by 144 hours at V8/V8R if not completed by 120 hours at V7/V7R.

<sup>q</sup> Study drug infusion is intended for IV administration only with a dedicated peripheral IV line using Sage-approved IV administration bags and lines.

<sup>r</sup> At V10 only a decision to re-treat at a higher dose of SAGE-547 will be made by the Investigator if the continuous IV third-line agent wean has failed or the third-line agent requires re-introduction during V9. Subjects who become eligible for open-label study drug at a higher dose of SAGE-547 will discontinue the planned visit schedule at V10, then repeat V3 (V3R) and all applicable subsequent visits.

<sup>s</sup> AEs will be collected from the time Informed Consent is obtained and prior to the start of study-specific screening procedures not considered standard of care. Collection of AEs will continue throughout the study from V1 through V12 or V12R.

<sup>t</sup> Subjects may enter the study on AEDs and Pressors and be administered AEDs and Pressors during the study. For all randomized and the first 50 QWS subjects, all Concomitant AEDs and Pressors must be recorded on the CRF with details including date and time of starting/stopping each AED and Pressor, the route of administration, changes in doses, and frequency of administration. Details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the CRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”. For subsequent QWS subjects, after the detailed information on all concomitant AEDs and Pressors collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant AED and Pressor and the start and stop dates and times) from Visit 3 to Visit 12 will be recorded in the eCRF.

<sup>u</sup> All third-line agents administered since the diagnosis of SE will be recorded on the CRF. For all randomized and the first 50 QWS subjects, details will include the name of the drug, the start/stop dates and times, and, after consent, the doses with start/stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R. For subsequent QWS subjects, after the detailed information on all concomitant third-line agents collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant third-line agent and the start and stop dates and times) from Visit 3 to Visit 12 will be recorded in the eCRF.

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**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
AE	adverse event
AED	anti-epileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the time-concentration curve
AW	additional weans
BDZ	benzodiazepine
BIEEG	blinded infusion electroencephalogram
BUN	blood urea nitrogen
CBC	complete blood count
CEEG	consent electroencephalogram
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
C <sub>max</sub>	maximum plasma concentration
C <sub>min</sub>	minimum plasma concentration
CNS	central nervous system
CRF	case report form
CSR	clinical study report
CYP2C9	cytochrome P450 enzyme involved in drug metabolism
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EEG	electroencephalogram
EIND	Emergency Use Investigational New Drug Application
EP	European Pharmacopeia
ESETT	Established Status Epilepticus Treatment Trial
FDA	Food and Drug Administration
FOUR	Full Outline of UnResponsiveness
GABA	$\gamma$ -aminobutyric acid
GABA <sub>A</sub>	$\gamma$ -aminobutyric acid-gated chloride channel
GCP	Good Clinical Practice

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
GFR	glomerular filtration rate
GOS	Glasgow Outcome Scale
H	hour
HPLC	high performance liquid chromatography
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent to Treat
IV	intravenous
IVRS	Interactive Voice Randomization System
LAR	legally authorized representative
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent to Treat
mRS-9Q	Modified Rankin Score - 9Q
MS/MS	tandem mass spectrometry
nM	nanomolar
NMDA	n-methyl-D-aspartic acid
OW	other weans
PAEEG	primary endpoint electroencephalogram
PD	pharmacodynamics
PK	pharmacokinetic
QOL	quality of life
QW	qualifying wean
QWEEG	qualifying wean electroencephalogram
RBC	red blood cell
RSE	refractory status epilepticus

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
SAE	serious adverse event
SAP	Statistical Analysis Plan
SE	status epilepticus
SOP	standard operating procedure
SRS	Severity Rating Scale
SRSE	Super-refractory status epilepticus
SSRI	Selective serotonin re-uptake inhibitors
STESS	Status Epilepticus Severity Score
SUSAR	Suspected Unexpected Serious Adverse Reactions
SWFI	Sterile Water for Injection
TAEEG	taper electroencephalogram
T <sub>max</sub>	time at maximum plasma concentration
TW	terminal wean
TWEEG	terminal wean electroencephalogram
US	United States
USP	United States Pharmacopeia

### 3. INTRODUCTION AND RATIONALE

#### 3.1. Status Epilepticus

Status epilepticus (SE) is a life-threatening seizure condition in which the brain is in a state of persistent seizure triggered by neuronal hyperexcitability. The Neurocritical Care Society defines SE as one continuous unremitting seizure lasting longer than five minutes or recurrent seizures without regaining consciousness between seizures for greater than five minutes (Brophy, Bell et al. 2012). Common causes of SE include preexisting epilepsy, cerebrovascular disease (in adults), electrolyte and metabolic disturbances, anoxia, encephalopathies, head trauma, high fever (in children, especially in the first year of life) and drug or substance intoxication. SE is associated with substantial morbidity and mortality.

##### 3.1.1. Epidemiology of SE

Geography, sex, age, and race influence the epidemiology of SE, whose incidence has a bimodal distribution, peaking in infants/young children and the elderly (Hauser 1990; DeLorenzo, Pellock et al. 1995; Wu, Shek et al. 2002). The incidence of SE in the elderly population is at least twice that in the general population. Concurrent medical conditions often exist in the elderly population, which can complicate therapy and worsen the prognosis of SE (Chapman, Smith et al. 2001).

The annual incidence of SE in the US is generally quoted to be within the range of 18/100,000 to 61/100,000, based on a 19-year retrospective study in Rochester, Minnesota (Hesdorffer, Logroscino et al. 1998) and a 2-year prospective study in Richmond, Virginia (DeLorenzo, Pellock et al. 1995), respectively. Two studies from Europe give annual incidences of a similar magnitude, ranging between 9.9/100,000 and 15.8/100,000 (Coeytaux, Jallon et al. 2000; Knake, Rosenow et al. 2001). It is thus estimated that in the United States each year there are as many as 150,000 cases of SE (DeLorenzo, Pellock et al. 1995).

#### 3.2. Refractory SE

When a patient begins to seize, the emergency medical technician will administer a first-line intravenous (IV) benzodiazepine (BDZ), such as diazepam, lorazepam or midazolam (Silbergleit, Durkalski et al. 2012), which is done either at the scene of the seizure or in the ambulance. If this is unsuccessful at abating the seizure, additional doses of the first-line therapy will be administered in the emergency room. Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line therapy, which is an IV anti-epileptic drug (AED) such as phenytoin or valproic acid (Novy, Logroscino et al. 2010; Shorvon 2011; Hocker, Britton et al. 2013).

Approximately 20-30% of patients refractory to first-line treatment will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to approximately 70-80% of patients who receive second-line therapy refractory to that therapy.

If a patient's SE continues after administration of BDZs and AEDs, the subject is diagnosed as having refractory status epilepticus (RSE), which must be treated quickly to terminate the seizure activity, maintain the patient's airway, and prevent cerebral damage. RSE patients are immediately admitted to the Intensive Care Unit (ICU) and placed in a medically-induced coma to stop all seizure-related activity. The drugs used to induce coma are continuously-infused IV agents,

commonly propofol, midazolam, or pentobarbital, referred to as third-line agents (Brophy, Bell et al. 2012).

The RSE patient is continually monitored using electroencephalography (EEG) to ensure that seizure and/or burst suppression is achieved. Burst suppression is a pattern of brain waves seen on an EEG, characterized by periods of activity alternating with periods of little or no activity in the brain, informing medical personnel of the effectiveness of the medically-induced coma. The goal of burst suppression is to allow the brain and corresponding neuronal tissue to restore function and reset to normal pre-seizure levels.

### 3.2.1. Epidemiology of RSE

Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line AED therapy. In turn, approximately 20 – 30% of these patients treated with AEDs will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to 28% of the total estimated SE patient population refractory to second-line therapy. Based on the previously-cited estimated incidence in the US, this means that there are up to 42,000 incident cases of RSE in the USA, annually (DeLorenzo, Pellock et al. 1995).

## 3.3. Super-refractory SE

After 24 hours of burst or seizure suppression, the patient is weaned off of the third-line therapy. If the weaning is unsuccessful (neuronal activity has not returned to normal), the third-line agent is re-administered or a different third-line agent is started, and the patient is considered to be in super-refractory status epilepticus (SRSE) (Chapman, Smith et al. 2001; Shorvon 2011; Brophy, Bell et al. 2012). SAGE-547 is being developed as an adjunct to third-line therapy in patients in RSE who have failed standard treatment. In this protocol, the term “RSE that has failed standard treatment” is deemed to be equivalent to the term “SRSE” and the two may be used interchangeably.

### 3.3.1. Epidemiology of SRSE

The incidence of SRSE is very poorly understood, mainly because the diagnostic codes used for SE do not generally differentiate its nature as responding or refractory to treatment. Based on the variable reporting of outcomes data, the incident cases of SRSE could represent between one and two-thirds of the RSE patients (Novy, Logroscino et al. 2010; Ferlisi and Shorvon 2012; Hocker, Britton et al. 2013; Sutter, Marsch et al. 2013). More detailed epidemiology studies are needed to better elucidate the proportion of RSE patients whose condition becomes super-refractory. A recent review of ICU discharge data in the USA suggests an annual incidence of approximately 35,000, based on patients who required at least three days in the ICU for SE [Sage data on file].

### 3.3.2. Outcomes of SRSE

SE has varying degrees of mortality depending on the underlying etiologies. Table 4 outlines the acute mortality in patients with SE by etiology (Neligan and Shorvon 2010). The mortality rate of SRSE is estimated to be 30% to 50% using current standard of care.

The causes of death from SE (and therefore SRSE) are heterogeneous, resulting from neuronal cell death, complications of underlying medical conditions, or adverse effects of the current standard treatments. Prognosis worsens and mortality increases with longer duration of SE, i.e. with SE that develops into RSE or SRSE (Neligan and Shorvon 2010), and with longer duration of

medically-induced coma (Ferlisi and Shorvon 2012). There is an obvious unmet medical need to improve upon the current standard of care treatment regimens.

Morbidity is high and survivors have outcomes ranging from poor function to vegetative state (Shorvon 2011). Approximately one third of patients with RSE and SRSE will recover, but with chronic neurologic or other deficits (Neligan and Shorvon 2010; Hocker, Britton et al. 2013). In all, it is estimated that less than 25-30% of all SRSE patients have a favorable functional outcome.

**Table 4: Approximate Mortality of Status Epilepticus in Different Etiologies**

Underlying Etiology	Associated Acute Mortality in Patients with SE (%)
Drug reduction/withdrawal, poor AED compliance, or low AED levels	0-10
Cerebrovascular Disease	20-60
Metabolic Disorders	10-35
Acute CNS Infection	0-30
Anoxia	60-100
Alcohol Abuse	0-10
Head Trauma	0-25
Drug Overdose/Toxicity	10-25
Brain Tumors	0-20
Cryptogenic/Idiopathic	5-20

### 3.3.3. Unmet Medical Need in Super-refractory Status Epilepticus

Treatment approaches for SRSE consist of diagnosis and treatment of underlying medical conditions, adding and changing anti-seizure drugs, and repeated attempts at weaning from IV anesthetic agents. Treatment of SRSE has three aims:

- to prevent excitotoxicity, which begins within 24 hours of SE onset;
- to prevent cerebral damage by initiating neuroprotective burst or seizure suppression;
- to prevent the complications of extended periods of anesthesia or unconsciousness (Shorvon 2011).

Currently, there are no therapies that have been specifically approved for RSE or SRSE. The primary drugs used to induce coma are continuously infused IV anesthetics such as propofol, midazolam, or pentobarbital/thiopental, known as third-line agents. Use of these drugs to control SRSE has only been studied in small retrospective reviews or small prospective studies without controls (Hocker, Britton et al. 2013) therefore there is no agreement on which drug is optimal nor on an optimal dosing regimen for the treatments that are used.

The most common adverse effect of the third-line agents is hemodynamic instability; in addition, they are not universally effective, with breakthrough seizures and withdrawal seizures requiring dose adjustments and changes in third-line agent(s). The drug thought to be most effective in SRSE, pentobarbital, is also associated with the most toxic adverse effect profile, comprising

decreased blood pressure and cardiorespiratory collapse (Claassen, Hirsch et al. 2002). The ability to wean patients successfully off the third-line agents as quickly as possible is therefore paramount, and an adjunct to SRSE treatment that enhances the success of the third-line agents and supports their successful weaning in a short timeframe would be an important addition to the therapeutic armamentarium. Preliminary clinical data show that SAGE-547 has been a successful adjunct to third-line therapy in this regard.

### 3.4. SAGE-547 Injection

Allopregnanolone is an endogenous, naturally occurring neuroactive steroid formed in the corpus luteum of the ovary, adrenal cortex and central nervous system (CNS) (Holzbauer, Birmingham et al. 1985; Paul and Purdy 1992; Ottander, Poromaa et al. 2005). It is a metabolite of progesterone created by the actions of 5- $\alpha$  reductase and 3- $\alpha$  hydroxy-steroid dehydrogenase. Allopregnanolone is a potent positive allosteric modulator of both synaptic and extra-synaptic GABA<sub>A</sub> receptors.

SAGE-547 Injection (allopregnanolone aqueous formulation in Captisol<sup>®</sup>) is being developed for the treatment of patients in RSE who have not responded to standard treatment. SAGE-547 Injection is a solution of 5 mg/mL allopregnanolone in Sterile Water for Injection (SWFI), USP and 250 mg/mL betadex sulfobutyl-ether sodium, NF. It is further diluted with Sterile Water for Injection, USP (SWFI) in IV bags to achieve an allopregnanolone concentration of approximately 1.67 mg/mL in an approximately isotonic solution and will be administered intravenously.

#### 3.4.1. Scientific Rationale for SAGE-547 in SRSE

Ineffective recruitment of inhibitory neurotransmission, together with excessive neuronal excitation, likely plays a role in the initiation and propagation of the electrical disturbance occurring in SE. GABA ( $\gamma$ -aminobutyric acid), the major inhibitory neurotransmitter in the central nervous system (CNS), is released from GABAergic neurons and binds to several types of GABA receptors (GABA<sub>A</sub>, GABA<sub>B</sub>, and GABA<sub>C</sub>) on target neurons. GABA<sub>A</sub> receptors are macromolecular proteins that form a chloride ion channel complex and contain specific binding sites for GABA and a number of allosteric regulators, including barbiturates, benzodiazepines, and some anesthetic agents. GABA receptor-mediated inhibition contributes significantly to the normal termination of a seizure (Kapur and Macdonald 1997). SAGE-547 is a positive allosteric modulator of the GABA<sub>A</sub> receptor.

The importance of terminating seizure activity as soon as possible is underpinned by a growing body of evidence from research and clinical observation that SE becomes more difficult to control as its duration increases. It has been postulated that this occurs due to a mechanistic shift from inadequate GABAergic inhibitory receptor-mediated transmission to excessive N-methyl-D-aspartic acid (NMDA) excitatory receptor-mediated transmission (Kapur and Macdonald 1997). As prolonged epileptiform bursting results in a reduction of GABA<sub>A</sub>-mediated synaptic inhibition, antiepileptic treatments which rely on enhancing intrasynaptic GABA<sub>A</sub> neurotransmission become less effective the longer SE continues.

Furthermore, the constitutive process of synaptic GABA<sub>A</sub> receptor internalization is accelerated by the increased neuronal activity associated with seizures. These findings suggest that the rate of GABA<sub>A</sub> receptor internalization is regulated by neuronal activity, and its acceleration contributes to the reduction of inhibitory transmission observed during prolonged seizures (Kapur and Macdonald 1997). Of note is that SAGE-547 binds to extrasynaptic as well as intrasynaptic GABA<sub>A</sub> receptors;



extrasynaptic receptors remain active with ongoing seizure activity, resulting in a putative mode of action for SAGE-547 in SRSE.

Status epilepticus induces cerebral damage that includes neuronal cell necrosis, gliosis, and network reorganization. The major cause of cell death in cerebral damage is excitotoxicity, which is initiated by glutaminergic receptor over-activation, causing calcium to flood the cell, thereby leading to apoptosis and necrosis. This process is initiated within a few hours of the start of seizure activity, and provides the medical imperative to terminate SE as quickly as possible. To prevent the consequences of the excitotoxicity cascade, it is recommended that anesthesia be initiated within 1-2 hours of onset of seizures at doses designed to induce EEG suppression patterns (Shorvon and Ferlisi 2011).

### **3.4.2. SAGE-547 Clinical Program in the Treatment of SRSE**

The current SAGE-547 development program includes:

- a completed Phase 2 open-label trial, Study 547-SSE-201;
- this proposed Phase 3 randomized, double-blind, placebo-controlled trial, Study 547-SSE-301;
- an ongoing open-label, expanded access protocol, Study 547-SSE-302;
- a number of EINDs for SAGE-547 in patients with SRSE.

The designs of these studies are all similar, with a five to six day infusion of SAGE-547 (or placebo), during which time attempts are made to wean the subject off all third-line agents. In the Phase 3 studies, those subjects who cannot be weaned off third-line agents while being administered SAGE-547 (or placebo) may be eligible for a second open-label infusion of SAGE-547 at a higher dose. Follow up of subjects is for 21 – 30 days after the first infusion of study medication.

### **3.4.3. Data from the SAGE-547 Development Program**

The data from 30 subjects included in the on-going clinical evaluation of SAGE-547 for the treatment of adults and children with SRSE clearly offers preliminary evidence that SAGE-547 could provide substantial and clinically significant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate. These subjects comprise 20 from the ongoing Phase 2 trial (71% success rate in 12/17 evaluable subjects) and 10 subjects who received EIND treatments (78% success rate in 7/9 evaluable subjects).

Successful therapy of SRSE has been defined as “the SE is completely controlled by the therapy, without breakthrough of withdrawal seizures, or discontinuation due to side effects or death during therapy,” (Ferlisi and Shorvon 2012). By this definition, which is in accord with the efficacy assessments used in the overall clinical evaluation of SAGE-547, 19 of the 26 (73%) subjects with SRSE who completed the SAGE-547 infusion were treatment successes. As data collection is ongoing, this information is preliminary and subject to change upon further monitoring.

Published reports on RSE and SRSE have stated mortality rate ranges from 35% to 65%. The underlying etiologies of SE in the 547-SAGE-201 study and EINDs are heterogeneous, and each one conveys a different risk of mortality and longer term morbidity. However, the death rate in subjects who have received SAGE-547, 6 out of 30 (20%) subjects, appears to be lower than the published rates. None of the deaths were considered related to SAGE-547: brain tumor, organophosphate toxicity, respiratory failure, respiratory arrest due to ventilator support withdrawal, and breast cancer.

In the Phase 2 study, 20 SAEs (15 non-fatal) have been reported in 13 (65%) subjects, and of these 3 events in 2 subjects (10%) were considered by the investigator to be related to SAGE-547: pulmonary emboli and tracheostomy dehiscence/infection. The Sponsor did not consider these events to be related to SAGE-547, rather to the underlying disease states. Four of the 20 subjects (20%) experienced AEs considered possibly related to SAGE-547 by the investigator, namely moderate myopathy and severe pulmonary emboli in 1 subject, moderate tracheostomy dehiscence and tracheostomy infection in 1 subject, moderate thrombocytosis in 1 subject and moderate BUN, ALT and AST elevation in 1 subject.

Review of the most current safety data from 547-SAGE-201 reveals that there were changes in serum chemistry, hematology, and urinalysis during the study, but that none of those changes were assessed as related to SAGE-547. There were also no SAGE-547-related changes to vital signs.

Despite the heterogeneity in the underlying causes of SE, the ages of the subject, comorbidities, which normally complicate the treatment of SE, and the fact that all subjects had failed current standard of care treatment, a large majority of subjects had a successful therapy outcome, with discontinuation of all third-line agents and resolution of SE.

Refer to the Investigational Brochure for further information on the pre-clinical and clinical data supporting the use of SAGE-547 in SRSE.

### **3.5. Study Rationale - SAGE-547 in SRSE**

#### **3.5.1. Justification for the Control Group**

Although SAGE-547 has demonstrated extremely promising activity in subjects with SRSE, both in the Phase 2 study and during the EINDs, these have been open-label investigations with no control data for comparison. Generally in the literature there are few data describing the success rates of wean attempts of third-line agents, and few comparative data on the effectiveness of the three main third-line agents, propofol, pentobarbital/thiopental, and midazolam.

Several options for a control group in Study 547-SSE-301 were considered:

- No control group was thought to be unacceptable since there are no reliable published data on success rates in this population that could be used for broad comparisons;
- An active control was considered but found to be impractical since none of the third-line agents are approved for their use in SRSE, no standardized dosing regimens or treatment guidelines have been adopted for the management of SRSE, and clinicians were unlikely to agree which of the available third-line agents would be reserved for the active control arm;
- Historical controls were considered but abandoned because of the practical difficulties of obtaining high quality data, the lack of ability to prospectively match cases, and a suspicion that clinical practice in the standard of care of SRSE is evolving, mandating the use of prospective, concurrent control data;
- Comparison to standard of care alone was considered as a feasible design. However, in a field where no widely adopted treatment guidelines exist, there was a concern that knowledge of the treatment group (SAGE-547 plus standard of care versus standard of care alone) would alter the behavior of the investigators such that they could be more aggressive with weaning in the SAGE-547 group;

- Placebo control is not without its challenges since the preliminary efficacy data for SAGE-547 show that the compound exerts central pharmacological effects and is associated with positive outcomes in around 70% of patients. There is therefore a potential ethical concern about administering placebo to desperately ill patients who have often exhausted all treatment options for SRSE. This concern has been addressed in two ways: firstly all patients receive current standard of care; secondly, all subjects who fail to be weaned from their third-line agents at the end of the blinded infusion of study drug will be administered open-label SAGE-547 without un-blinding their initial treatment allocation, so treatment with the investigational product is not denied, but delayed about a week in the setting of ongoing receipt of full current standard of care.

It was therefore decided that a blinded, placebo-controlled design was appropriate for Study 547-SSE-301.

### **3.5.2. Justification for the Dose Regimen**

The standard dose regimen has been studied in 19 subjects in the 547-SSE-201 Phase 2 trial; the average peak plasma concentration of SAGE-547 at the end of the loading dose was approximately 144 ng/ml. The average plasma concentration during the maintenance infusion was approximately 70 ng/ml. At these concentrations, there were no clear safety signals although two-thirds of subjects experienced an SAE and there were four deaths, all related to the underlying comorbid conditions. The standard dosing regimen was associated with an approximate 70% successful treatment outcome. For these reasons, the standard dosing regimen has been adopted for the initial SAGE-547 infusion to be compared in a blinded fashion to placebo.

In the 547-SSE-201 trial, three subjects have thus far received the higher dose regimen. This dose regimen has also been well tolerated. The average peak plasma concentrations at the end of the loading dose for both dosing regimens will be in the same range, as the loading dose is the same for both regimens. The average plasma concentrations observed during the higher maintenance dose are 102 ng/ml (n=2). The rationale for adopting the higher dose regimen as the open-label infusion of SAGE-547 for subjects who are retreated in this 547-SSE-301 trial is that those who fail on the standard SAGE-547 dose regimen are afforded the opportunity to have access to a higher dose. The justification to also administer the higher dose regimen to failures on placebo is that the regimen has thus far been well tolerated, and this methodology preserves the blind for the initial infusion.

A five-day dosing regimen with SAGE-547 was investigated in the Phase 2 study, 547-SSE-201. There were some cases when weaning off all third-line agents was not possible within 48 hours, but weaning was completed after the end of the infusion of SAGE-547. For this reason, the duration of dosing with SAGE-547 has been increased from 120 hours (five days) in Phase 2 to 144 hours (six days) in this Phase 3 study.

### **3.5.3. Rationale for Genetic Testing Sub-study**

Sage Therapeutics intends to perform genetic research in the SAGE-547 development program in order to explore how genetic variations may affect the metabolism and activity of SAGE-547. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials, and, possibly, to genetically-guided treatment strategies for optimizing decision making with respect to individual benefit:risk. Participation of subjects in genetic research as part of the overall clinical study is optional.

### **3.6. Benefit-Risk Evaluation of the Present Study**

Previous reports of human administration of exogenous allopregnanolone indicate that for exposures in men and women up to 150 nM, the most commonly reported AEs were sedation (recorded as sleepiness or tiredness), feelings of intoxication (like alcohol), flushing, and mild headache (Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007). No SAEs were reported (Navarro, Kaddouz et al. 2003; Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007; Kask, Backstrom et al. 2008; Kask, Backstrom et al. 2009; Timby, Hedstrom et al. 2011a). In view of the reduced consciousness and sedation of study subjects at entry into this protocol, none of these previously-reported events are likely to impact subjects in this study.

To date, in the SAGE-547 Phase 2 study and the EIND subjects, a majority of subjects demonstrated a successful therapy outcome (>70%). The majority in the clinical trial (65%) have also experienced SAEs, but none has been considered related to SAGE-547 by the Sponsor (SAEs in 2 subjects (10%) were considered possibly related by Investigator). Five deaths have been reported in 30 subjects (20%), all related to the underlying cause of SRSE and not related to SAGE-547 – this is in the context of published mortality rates between 35% and 65%. These preliminary data suggest that SAGE-547 has the potential to provide clinically relevant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate.

The underlying etiologies of SE are heterogeneous, and each one conveys a different risk of mortality. Subjects who survive SRSE still have a high risk of severe morbidity (Neligan and Shorvon 2010). The subjects treated with SAGE-547 in Study 547-SSE-201, are heterogeneous in factors such as age and etiology of SE, factors that usually complicate treatment and can increase morbidity and mortality. Even with this heterogeneity, the preliminary efficacy and safety data for SAGE-547 are very encouraging, and the mortality rate suggests that the risk to benefit assessment of this treatment rests on the side of benefit.

## **4. ETHICS**

### **4.1. Institutional Review Board or Independent Ethics Committee**

This protocol will be reviewed and approved by the Institutional Review Board (IRB) where the study is conducted. The IRB will meet all FDA requirements governing IRBs (CFR, Title 21, Part 56).

### **4.2. Ethical Conduct of the Study**

The Sponsor, the Medical Monitor, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable ICH and GCP guidelines, and must also conduct the study in accordance with local regulations.

### **4.3. Subject Information and Informed Consent**

Subjects prospectively enrolled in this study will be unable to give consent. Therefore, consent will be given by proxy by a legally authorized representative (LAR). Written informed consent is required for each subject prior to any testing under this protocol not considered standard of care, including screening tests and evaluations. Should a subject gain the ability to sufficiently

comprehend the situation and consent during the course of the study, written informed consent or verbal assent will be documented as required or recommended by the institution's IRB.

The form of consent to be obtained will depend on the condition of the subject as determined by the Principal Investigator. The informed consent form (ICF), as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50.

It is the responsibility of the Investigator to obtain consent and to provide the subject's LAR with a copy of the signed and dated informed consent form. The informed consent form for subject participation must also be available as part of the subject file for review by the site's dedicated study monitor or any authorized auditor of the Sponsor or regulatory authorities.

All ICFs used in this study must be approved by the appropriate IRB and by the Sponsor. The ICF must not be altered without the prior agreement of the relevant IRB and the Sponsor.

#### **4.4. Ethical and Regulatory Considerations for Pharmacogenetic Sub-study**

##### **4.4.1. Informed Consent for Pharmacogenetics**

The genetic component of this study is optional and subjects may participate in other components of the main study without having to agree to participate in the genetic component. If subject chooses to participate in the genetic component of the study, the subject or LAR must sign and date a specific consent form for the genetic component of the study in addition to the main study consent form. The principal investigator(s) is responsible for ensuring that consent is freely given and that the subject understands that they may discontinue from the genetic aspect of the study independent of their decision to remain within or withdrawal from the main study.

##### **4.4.2. Subject Data Protection Relative to Pharmacogenomics**

Sage Therapeutics will not provide individual genotype results to subjects, their family members, their general physician, their employer or any insurance company unless required to do so by law. While extra precautions will be taken to preserve confidentiality and to prevent genetic data from being linked to an individual's identity outside of a restricted access site, in certain exceptional situations (e.g. in case of a medical emergency or as a consequence of a specific regulatory need), certain individuals may see both genetic data and the personal identifiers of a subject; however in all cases a subject's medical information and genetic files will remain physically separated.

## **5. STUDY OBJECTIVES**

### **5.1. Primary Objective**

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult and pediatric subjects with SRSE, and for the response to endure at least 24 hours after cessation of the SAGE-547 or placebo infusion (primary response).

## 5.2. Secondary Objectives

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in Clinical Global Impression Scale between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

## 5.3. Safety Objectives

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

## 5.4. Other Objectives

1. To evaluate the impact of treatment with a higher dose SAGE-547 infusion;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;

6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS) (age  $\geq 17$  years).

## **6. ENDPOINTS**

### **6.1. Primary Endpoint**

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### **6.2. Secondary Endpoints**

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) and to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### **6.3. Safety Endpoints**

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.

### **6.4. Other Endpoints**

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who are treated with a higher dose of SAGE-547;

2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS) (age  $\geq 17$  years).

## 7. INVESTIGATIONAL PLAN

### 7.1. Overview of Study Design

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE. Pediatric patients (those < 14 years of age) will be managed in a pediatric intensive care setting.

Figure 1 provides an overview of the study design and Figure 2 gives the details of treatment and follow-up on the active treatment arm. Patients will follow one of three paths to entry to the study. The first path is for patients who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst or seizure suppression with a third-line agent. These patients will be consented for the study after admission to the intensive care unit, before or after any third-line agents are administered for burst or seizure suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their LAR. Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours. Once burst or seizure suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned during the QW will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see Table 3). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The second path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst or seizure suppression pattern on the EEG. These patients may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst or seizure suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst or seizure suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous



EEG burst or seizure suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The third path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst or seizure suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These patients may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within eight hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third line agent wean attempts prior to randomization (one vs two or more).

The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

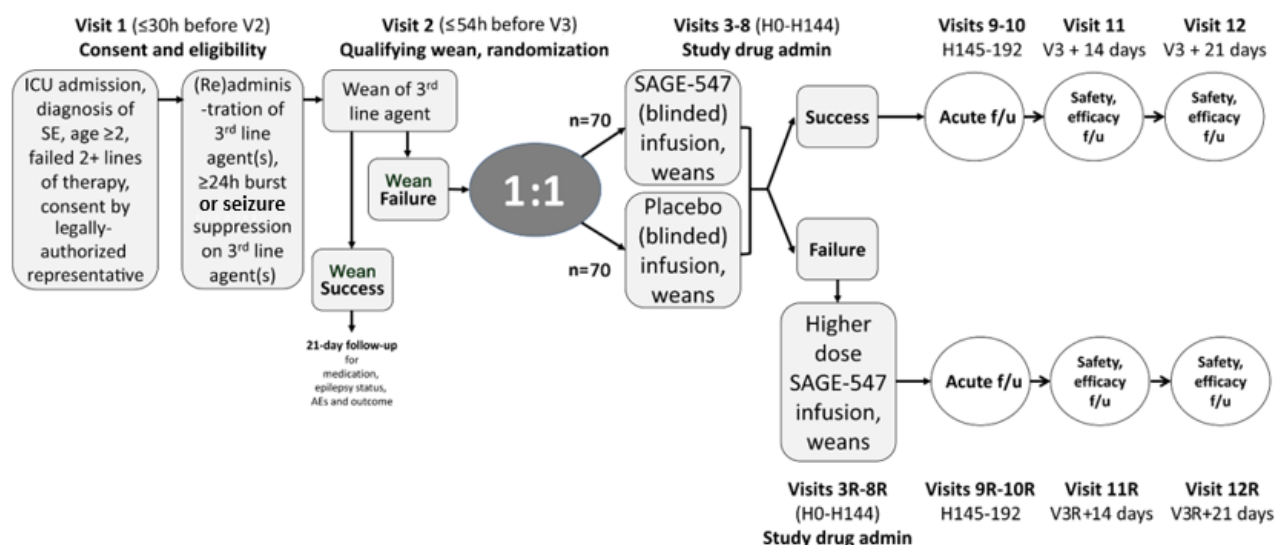
For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as the ability to wean the subject off all third-line agents before the end of the first infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication. Subjects must also have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) at the end of the primary endpoint assessment period as determined by EEG in order to be deemed a success. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#), [Table 2](#) and [Table 3](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion may be eligible to receive an open-label infusion of SAGE-547 at a dose higher than

that administered in the blinded part of the study. Eligibility for the open-label treatment must be confirmed in writing by the medical monitor prior to the open-label infusion starting. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo may all subsequently be eligible to be administered SAGE-547 at the higher dose.

**Figure 1: Study Design**



## 7.2. Trial Conduct

This study will be conducted according to the principles of the World Medical Association Declaration of Helsinki and most recent amendment, and in compliance with the protocol approved by the IRBs/Independent Ethics Committees (IECs), and in accordance with ICH Guidelines on GCP standards.

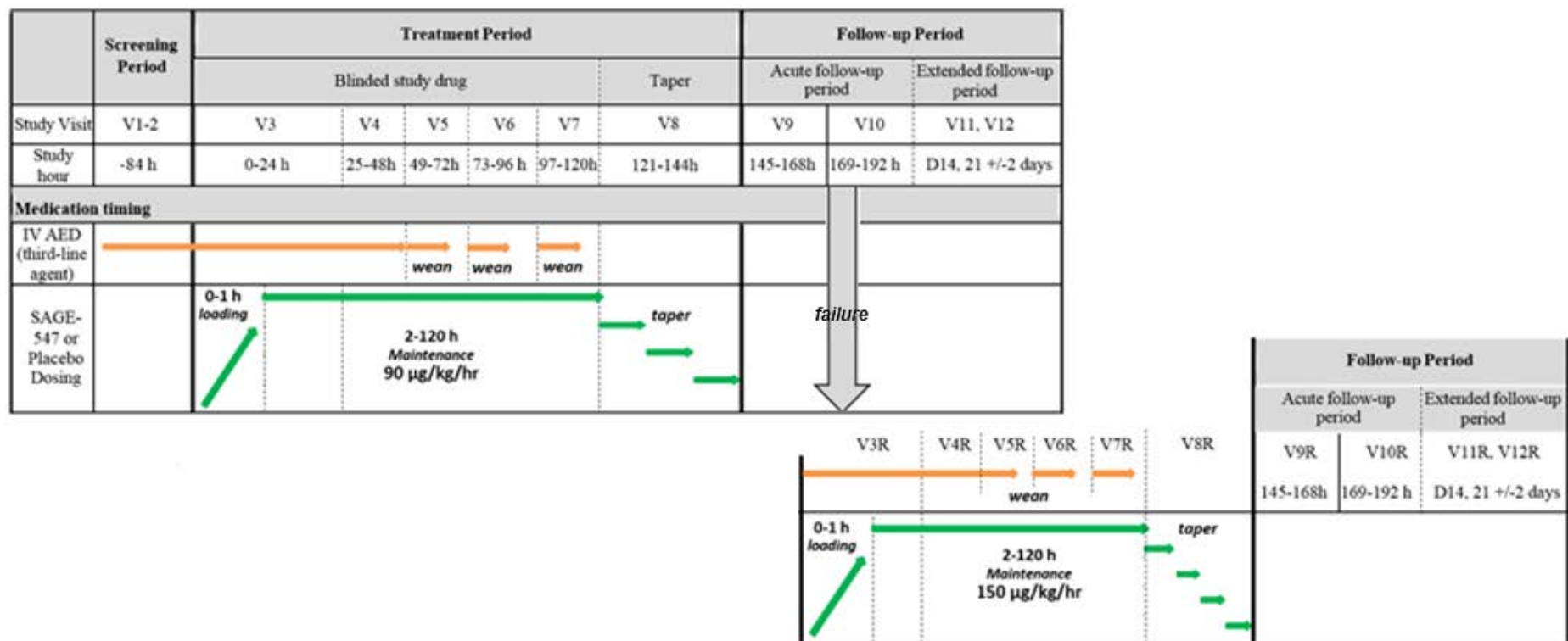
## 7.3. Blinding and Randomization

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo). Details of the dynamic randomization process will be included in the SAP.

The randomized portion of the study will be blinded, with the two treatment products (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

The second infusion of SAGE-547 will be administered on an open-label basis to subjects who meet the criteria for open-label treatment.

### Figure 2: Details of Treatment Administration and Follow-up



## 8. SELECTION AND WITHDRAWAL OF SUBJECTS

The study will randomize 140 patients at up to 180 sites. All subjects deemed eligible to enroll must have written Medical Monitor approval on a case-by-case basis prior to undertaking the qualifying wean.

### 8.1. Inclusion Criteria

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects two (2) years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; *or* who have previously failed zero, one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst or seizure suppression pattern; *or* who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst or seizure suppression pattern.

### 8.2. Exclusion Criteria

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy with highly malignant/malignant EEG features ([Westhall, Rosetti et al. 2016](#)).
4. Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing underlying neurological disorder.
5. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis but for whatever reason, dialysis that would adequately remove Captisol® is not planned;
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the experience of the investigator, is less than 30 days.

6. Subjects who are being administered more than three third-line agents concomitantly or for whom the qualifying wean cannot be completed within 24 hours or who are being administered a third-line agent for indications such as raised intra-cranial pressure that would preclude weaning according to this protocol.
7. Subjects with a living will that does not allow heroic measure.
8. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
9. Subjects who have been treated or randomized in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not have received study drug/placebo and then re-enroll).

### **8.3. Selection and Consent of Subjects for Pharmacogenetic Substudy**

All subjects will be asked to participate in pharmacogenetic research; however, participation in research is voluntary and a subject can decide to decline his/her participation without penalty or loss of benefit. Participation or lack thereof will not be a cause for exclusion from any aspect of the main study. In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **8.4. Subject Withdrawal / Study Termination**

#### **8.4.1. Withdrawal/Discontinuation of Individual Subjects**

The reasons for study drug discontinuation and/or subject withdrawal from the study must be recorded in the subject's electronic case report form (eCRF). The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject has been discontinued/withdrawn due to an AE.

##### **8.4.1.1. Withdrawal from the Study**

Subjects or their LAR may withdraw subjects from the study at any time for any reason without compromising the subject's medical care. The Investigator will also withdraw subjects upon the request of Sage Therapeutics or upon termination of the study.

Subjects who withdraw from the study prior to Visit 10 (or 10R) should complete the procedures scheduled for the day of study drug taper (Hour 121-144; Visit8/8R) on the day of their withdrawal, including the SAGE-547 taper schedule, with the addition of the mortality assessment from Visit 12/12R. Subjects who withdraw from the study after Visit 10/10R should undergo study procedures as outlined for Visit 12/12R on the day of their withdrawal. In all cases, the reason for subject withdrawal will be recorded in the eCRF.

Withdrawal of subjects for any reason should be discussed with the Medical Monitor.

##### **8.4.1.2. Discontinuation of Study Drug**

If it is necessary to discontinue the study drug earlier than planned, subjects should continue to be followed per protocol to capture safety and efficacy assessments for the duration of the study period.

The investigator may withdraw the subject from the study drug for the following reasons:

- Upon subject's or LAR's request
- The subject or LAR is unwilling or unable to adhere to the protocol-specified visits
- The subject experiences an intolerable adverse event
- During the course of the study, the subject develops symptoms or conditions listed in the exclusion criteria.
- Other medical reason, at the discretion of the Investigator and/or the Medical Monitor

Subjects who discontinue the study due to an AE considered related to study drug should be followed until the event is resolved, considered stable, or the Investigator determines the event is no longer clinically significant. Study drug discontinuation due to AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

#### **8.4.2. Study Termination**

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of AEs or other findings suggesting unacceptable risk to subjects, administrative or operational reasons. In the event of study termination, Sage Therapeutics will provide written notification to the Investigator. Investigational sites must promptly notify their IRB and initiate withdrawal procedures for participating subjects.

## **9. INVESTIGATIONAL PRODUCT**

### **9.1. Identity of Investigational Product**

SAGE-547 Injection (allopregnanolone)

### **9.2. Clinical Supplies**

#### **9.2.1. SAGE-547**

Adequate supplies of SAGE-547 Injection and materials for intravenous administration will be provided to each site.

SAGE-547 Injection is a clear, colorless sterile solution of allopregnanolone intended for intravenous injection. SAGE-547 Injection is an aqueous solution of 5 mg/mL allopregnanolone in 250 mg/mL Captisol® (betadex sulfobutyl-ether sodium, NF). It is presented either un-buffered or buffered with 10 mM citrate at a pH of 6.0 in either 20 mL or 50 mL vials. SAGE-547 is further diluted according to the Pharmacy Manual to achieve an approximately isotonic solution and will be administered intravenously.

No preservatives are included in the drug product, which is intended to be used as a single-use vial. All inactive components (excipients) used in the formulation are compendial grade and conform to current USP/EP, and include sodium citrate, citric acid and betadex sulfobutyl-ether sodium (Captisol®).

**9.2.2. Placebo**

Placebo will be identical to SAGE-547 and presented in identical vials. Placebo will be manufactured in a similar way to SAGE-547 and comprises all excipients but no SAGE-547.

**9.2.3. Blinding**

The vials of SAGE-547 and placebo will be identical in every way so that they are indistinguishable by the pharmacist, investigator, anyone treating or managing the patient, the monitors, and the sponsor. In this way the first infusion of study drug administered to each patient will be double-blind.

For the blinded study drug infusions, subject-specific dosing kits will be provided. These dosing kits will be pre-labelled with kit number for the first blinded infusion. For the second-infusion, open-label kits will be provided, which will require subject assignment by the pharmacy for reconciliation purposes. The study kits must be stored under refrigerated conditions (2-8 °C). IV administration bags and lines may be provided for the blinded and open-label infusions. Refer to the Pharmacy Manual for additional details.

The label for the SAGE-547 Injection vials will include standard product identification information according to the Code of Federal Regulations, 21CFR 312.6. All study labels will also contain the following statement:

Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use.

**9.3. Preparation of SAGE-547 or Placebo Injection for Dosing**

The Pharmacy will be responsible for preparing the blinded and open-label study drug for subject dosing. The prepared admixture will be assigned a room temperature (20-25 °C) storage shelf life of 30 hours from time of compounding.

SAGE-547, which is hypertonic, will require dilution with SWFI to achieve an approximately isotonic solution according to the instructions provided in the Pharmacy Manual. Exactly the same procedures will be used to prepare the placebo admixture, so that all site staff remain blinded as to treatment allocation for the first infusion of study drug. SAGE-547 Injection is not intended to be administered to patients undiluted.

Refer to the Pharmacy Manual for specific instructions regarding infusion preparation.

**9.4. Administration and Accountability**

The Pharmacy will maintain accurate records of all investigational product supplies. Accurate records will be kept regarding the volume of SAGE-547 Injection or placebo used for each IV preparation, as well as the required infusion rate or rates, and the date and time of preparation. Reasons for departure from the expected dosing regimen must also be recorded. To satisfy regulatory requirements regarding drug accountability, all study medication will be reconciled in full. Refer to the Pharmacy Manual for additional details.

## 10. TREATMENT OF SUBJECTS

### 10.1. Dosing Schedule (Blinded Infusions)

SAGE-547 Injection or placebo will be administered according to the dosing schedules in Table 5. The infusion rates to accomplish these  $\mu\text{g/kg/h}$  doses will be calculated according to the weight of the subject obtained within the eight-hour window that follows the declaration of the QW failure at V2 and prior to dosing at V3. The infusion rates will be applied to blinded study drug for the first infusion of study medication.

**Table 5: SAGE-547 or Placebo Dosing Schedule**

Hour	Type and Duration of Study Drug Infusion	Description
H1	One hour loading Infusion	300 $\mu\text{g/kg/h}$
H2 – H120	119 hour maintenance infusion	90 $\mu\text{g/kg/h}$
H121 – H128	8 hour taper	65 $\mu\text{g/kg/h}$
H129 – H136	8 hour taper	45 $\mu\text{g/kg/h}$
H137 – H144	8 hour taper	25 $\mu\text{g/kg/h}$

### 10.2. Dosing Schedule (Open-Label Infusions)

Those subjects that qualify for the open-label study drug will be administered SAGE-547 Injection according to the dosing schedule in Table 6. The dose will be administered on a  $\mu\text{g/kg/h}$  basis, and the subject's weight measured prior to dosing during V10 will be used to calculate the doses. These infusion rates will be applied to SAGE-547 treatment for the open-label second infusions of study medication.

**Table 6: SAGE-547 Open-Label Dosing Schedule**

Hour	Type and Duration of SAGE-547 Infusion	Description
H1	One hour loading Infusion	300 $\mu\text{g/kg/h}$
H2 – H120	119 hour maintenance infusion	150 $\mu\text{g/kg/h}$
H121 – H126	6 hour taper	125 $\mu\text{g/kg/h}$
H127 – H132	6 hour taper	95 $\mu\text{g/kg/h}$
H133 – H138	6 hour taper	65 $\mu\text{g/kg/h}$
H139 – H144	6 hour taper	35 $\mu\text{g/kg/h}$

### 10.3. Route of Administration

SAGE-547 Injection is intended for IV administration only. The compatibility of SAGE-547 with other drugs is unknown, and the product should be administered via a dedicated peripheral IV line using any Sage-supplied study-specific IV administration bags and lines. In order to preserve blinding, these instructions also apply to the blinded placebo infusions.



## 10.4. Treatment Period

The treatment period with double-blind SAGE-547 or placebo is six 24-hour periods (144 hours), which may encompass 6-7 calendar days. The open-label study drug treatment period is of identical duration.

## 10.5. Concomitant Medications, Procedures and Treatments

Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. For all randomized and the first 50 qualifying wean success (QWS) subjects, detailed information on all concomitant medications (concomitant AEDs, third-line agents, pressors, and other concomitant medications), procedures, and treatments should be documented throughout the study from Screening through Visit 12/12R, as described below, and recorded on the eCRF. For subsequent QWS subjects, after the detailed information on all concomitant AEDs, pressors, third-line agents, procedures, and treatments collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant AED or pressor, third-line agent, procedure, and/or treatment, and the start and stop dates and times) from Visit 3 through Visit 12 will be recorded in the eCRF. For subsequent QWS subjects, after the detailed information on all concomitant medications collected during the screening period (Visits 1 and 2) has been recorded, only minimal information, to include the name of the concomitant medications and indication only will be recorded from Visit 3 through Visit 12.

SAGE-547 has demonstrated inhibitory effects on cytochrome P450 isoenzyme 2C9 (CYP2C9). Therefore, AEDs such as phenytoin and phenobarbital that are primarily metabolized by CYP2C9 should be closely monitored during SAGE-547 administration to ensure target exposures are maintained.

### 10.5.1. Concomitant AEDs

Subjects may enter the study on AEDs, and be administered AEDs during the study. All of these must be recorded on the eCRF with details including date and time of starting and stopping each AED, the route of administration, changes in doses, and frequency of administration. In addition, details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the eCRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.

### 10.5.2. Concomitant Third-Line Agents

All third-line agents (as defined in [Section 8](#)) administered since the diagnosis of SE will be recorded on the eCRF, whatever path the patient took for entry into the study. Details will include the name of the drug, the start and stop dates and times, and, after consent, the doses with start and stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

In addition, those changes in dose that constitute a wean attempt will be marked as such on the eCRF. In this way the start and stop dates and times of all wean attempts (see [Section 11](#) for definitions) will be recorded, as will the type of wean (QW, OW, or TW) and the outcome of the wean attempt (successful, failed and dose of this third-line agent increased or failed and this third-line agent stopped and another third-line agent started). Those wean attempts that occur after the TW up to and including Visit 12/12R will be marked “AW”.

Some third-line agents (such as propofol) are also used to induce sedation to facilitate a subject's ability to tolerate the ventilator. For subjects requiring such sedation, propofol is the preferred agent unless there are contraindications. The eCRF will make clear from the indication for the third-line agent when it is being used for burst or seizure suppression and when it is being used as ventilator support or for another purpose. The investigator will add a note to the eCRF to justify that the doses used are appropriate for sedation and not for seizure or burst suppression. The doses used for ventilator support and other similar uses are usually much lower than those used for seizure or burst suppression, and use of these third-line agents for these other purposes does not constitute a wean failure under this protocol.

### **10.5.3. Concomitant Pressors**

The start and stop dates and times of all pressors will be recorded as well as the start and stop dates and times of all dose changes.

### **10.5.4. Other Concomitant Medications**

All other concomitant medications must be recorded on the eCRF with details including date and time of starting and stopping, the route of administration, dose, and frequency of administration.

## **11. STUDY ASSESSMENTS**

### **11.1. Efficacy Assessments**

#### **11.1.1. Primary Efficacy**

Success or failure will be determined, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo infusion and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the blinded (first) infusion of SAGE-547 or placebo. In addition, subjects must have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) to be deemed to be successes. All subjects who fail to complete their infusion of randomized treatment or do not have at least one attempt during study treatment to wean off all third-line agents will be considered as "failures" for the primary endpoint.

##### **11.1.1.1. Weaning**

Third-line agents are anesthetic agents that are administered in order to reach a seizure or burst suppression EEG pattern. For the purposes of this study, third-line agents are defined as continuous intravenous infusions of pentobarbital/thiopental, midazolam, propofol, and ketamine at maintenance doses alone or in combination sufficient to produce a burst or seizure suppression pattern on the EEG. The following are considered to be minimum maintenance doses of these agents that may be expected alone or in combination to achieve EEG burst suppression. If subjects are on lower doses than these and are not in EEG burst suppression the first 12 hours of the blinded study drug infusion, they will be considered to be protocol violators and will exit the study.

- Pentobarbital: 1 mg/kg/hour
- Thiopental: 3 mg/kg/hour
- Midazolam: 0.1 mg/kg/hour

- Propofol: 3 mg/kg/hour
- Ketamine 1.2 mg/kg/hour

The timing and nature of the third-line agent weans will be guided by the Clinical Standardization Guidelines for the study, and the clinical judgment of the investigator, and will always be primarily done in the best medical interests of the subject. Advice about weaning may be sought from the Clinical Standardization Team, a group of fellow investigators with experience of performing clinical trials in subjects with SRSE. The Clinical Standardization Team will be able to discuss EEGs related to key study timepoints (terminal wean and the period after the end of the blinded study drug infusion if the terminal wean was successful) in a timely manner in order to provide advice about compliance with the Clinical Standardization Guidelines.

The following guidance for weaning applies to all weans of third-line agents undertaken during the study. Continued determined efforts to liberate subjects from sedation must be undertaken for the entire duration of the blinded study drug infusion. Each failed wean from third-line agents should be followed by a 6-24 hour period of suppression and then another wean attempt, with further optimization of the AED regimen.

Weans include the qualifying wean (QW); the terminal wean (TW), which is the wean of the third-line agent if the subject is on only one third-line agent or the wean of the last third-line agent if the subject is on more than one third-line agent; the other weans (OW), which are the weans of the third-line agents other than the TW if the subject is on more than one third-line agent. The guidance also applies to additional weans (AW), which are the weans from third-line agents that take place after the TW for the first blinded study drug infusion or the second open-label study drug infusion.

### **QW Guidance**

- Wean to be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace that third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Investigators should allow 24 hours to lapse after the end of a “successful” qualifying wean before finally declaring the QW a success. If a third-line agent needs to be re-instituted within that 24 hours, the QW is a failure, and the subject may then be randomized in the study.

### **OW Guidance**

- First OW should not begin before H49 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- If the subject is on two third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the TW. However the OW may be completed over a shorter or longer time period and may overlap if clinically indicated with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be

adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.

- If the subject is on three third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the wean of the second agent. The second agent should be weaned over 24 hours and that wean completed before starting the TW. However the OWs may be completed over a shorter or longer time period and may overlap if clinically indicated with each other and with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- All OWs should be completed before H96 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **TW Guidance**

- The TW is defined as the wean of the last third-line agent.
- If the subject is on one third-line agent, the TW should not begin before H49 and should begin no later than H97 after starting administration of study drug or starting the open-label infusion of SAGE-547. If the subject has had one or more OWs, the TW should ideally begin as soon as the last OW is complete but in any case not later than H97 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- The TW must be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace this third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Every effort must be made to complete the TW before H120 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547, but the TW must be complete before H144 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **AW Guidance**

- AWs will take place when medically indicated in the opinion of the investigator.
- Ideally the AW should take place over 24 hours, but completion may be over a shorter or longer time period than this. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.

### 11.1.1.2. EEG

Electroencephalographs (EEGs) that are representative of the intermittent or continuous EEG being used to support key investigator decisions will be collected at the following time points:

- A 24-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst or seizure suppression for the second path to eligibility, and a variable pattern for the third path to eligibility. This EEG also aims to capture the burst or seizure suppression pattern during the 24 hours that precede the QW. If the CEEG does not capture the 24 hours that precede the QW, additional EEG data collected as standard of care prior to the CEEG and prior to the QW may be collected to assess the depth of burst or seizure suppression in the 24 hour period prior to the QW.
- EEG will be performed to cover the qualifying wean (QWEEG). EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for up to 24 hours after the end of the QW. The duration of the QWEEG will be up to 48.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s), the decision to re-institute a third-line agent(s) at doses intended to induce burst or seizure suppression, and the decision that the QW is a success.
- EEG will be performed from three hours prior to the start of the blinded infusion to 12 hours after the start of the blinded infusion. This will be called the BIEEG. The intent of this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG and to assess the depth of burst suppression in the first 12 hours of blinded study drug infusion.
- EEG will be performed to cover the final or terminal wean of third-line agent (TWEEG). The TW is the wean of the final third-line agent during the blinded administration of study drug or the open-label infusion of SAGE-547; if the subject was on one third-line agent, the TW is the wean of that agent. If the subject was on three third-line agents, the TW is the wean of the third and final agent. EEG recording will start 30 minutes prior to the start of the TW, continue for up to 24 hours during the TW, and then continue for the one hour after the end of the TW. The duration of the TWEEG will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the final third-line agent or the decision to re-institute a third-line agent at doses intended to induce burst or seizure suppression because any seizure activity could not be managed using intermittent bolus doses of AEDs.
- EEG will be performed during the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 (TAEED). The TAEED is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the start of the taper (at Hour 119.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours during the taper, and then continue for the one hour after the end of the taper (to Hour 145 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547). The duration of the TAEED will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst or seizure suppression because

any seizure activity seen during the taper could not be managed using intermittent bolus doses of AEDs.

- EEG will be obtained to cover the end of the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 and the ensuing 24-hour period, during which the primary endpoint is assessed (PAEEG). The PAEEG is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the end of taper (at Hour 143.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours after the end of the blinded administration of study treatment or the open-label infusion of SAGE-547, and then continue for the one hour after the end of the 24-hour assessment period (to Hour 169 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547). The duration of the PAEEG will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst or seizure suppression because any seizure activity seen in the 24 hours following the end of the blinded administration of study treatment or the open-label infusion of SAGE-547 that could not be managed using intermittent bolus doses of AEDs.

In practice, most subjects are on continuous EEG monitoring or long periods of intermittent EEG monitoring. However, this protocol does not mandate continuous EEG monitoring and breaks from EEG monitoring to provide relief to the scalp from the irritating effects of the electrodes are advised, particularly in children, according to local practice. If a break in EEG monitoring is mandated by local practice guidelines at a time when one of the protocolled EEG segments is to be collected, the break in EEG monitoring will take precedence, with the reason for missing the EEG reading noted on the eCRF. The EEGs obtained for the study are therefore part of the existing EEG record rather than being obtained de-novo at each timepoint. For timepoints where there might be some ambiguity, such as the TWEEG, the final EEG record is that of the final attempt to wean the last third-line agent, even if earlier attempts to wean that agent took place. In some cases (the TAEED and PAEEG, for instance), the EEG records will overlap, but different cuts are taken to service the different EEG record requirements.

The electronic EEG file will be de-identified, the date and time of the start and stop of the EEG and the subject number will be attached to the file, and the study time point will be indicated (CEEG, QWEEG, BIEEG, TWEEG, TAEED, and PAEEG). The PI will indicate on the eCRF what the EEG shows, as follows:

- For the CEEG, the PI will describe the EEG pattern that determined which path to eligibility the subject was on.
- For the QWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure or success on the qualifying wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst or seizure suppression during the qualifying wean constitutes a failure); the QWEEG will extend to cover the 24 hours after the end of third line agents in order to confirm that the QW was a success.
- For the BIEEG, the PI will note the date and time of the start of the EEG and the pattern seen on the EEG.

- For the TWEEN, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure on the terminal wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst or seizure suppression during the terminal wean).
- For the TAEED, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst or seizure suppression before the end of the SAGE-547 infusion).
- For the PAEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst or seizure suppression in the 24 hours following the end of the SAGE-547 infusion).

A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm the depth of burst or seizure suppression prior to the QW and during the first 12 hours of the blinded study drug infusion, the PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period (average EEG power at the end of Visit 9 of more than two microvolts):

- All subjects will have the CEEG and QWEEN collected and stored, and the CEEG and QWEEN read;
- Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;
- Those subjects randomized who are not administered the open-label study drug will have the QWEEN, BIEEG, TWEEN, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the BIEEG, QWEEN, TWEEN, and PAEEG related to the blinded study drug infusion read;
- Those subjects randomized who later undergo the open-label infusion will have the QWEEN, BIEEG, TWEEN, TAEED and PAEEG related to the blinded study drug infusion and the TWEEN, TAEED, and PAEEG related to the open-label study drug infusion collected and stored, and the BIEEG, QWEEN, TWEEN, and PAEEG related to the blinded study drug infusion read.

All EEG records may be subject to quantitative EEG analysis.

### **11.1.2. Secondary Efficacy**

#### **11.1.2.1. Clinical Global Impression Scale (CGI)**

The clinical global impression scales are often utilized in clinical trials to allow clinicians to integrate several sources of information into a single rating of the subject's condition. Both the CGI-Severity (Question 1, CGI-S) and the CGI-Improvement (Question 2, CGI-I) employ a 7-point Likert scale measuring severity of the disease state in the subject and improvement, respectively. All severity assessments after initiation of SAGE-547 treatment should consider the general state of the subject

over the preceding week. The third question on the scale will not be employed in this trial, and where the scale states “mental illness”, this means “physical illness” in this trial.

The CGI-S will be evaluated at Visit 1 and at the last visit, Visit 12 or 12R. The CGI-I will be evaluated at Visit 12 or 12R.

#### **11.1.2.2. Epilepsy Status**

At Visit 1, the diagnosis of epilepsy will be documented as a no/yes question. If there was a previous diagnosis of epilepsy, further details will be documented, including:

- Date of diagnosis;
- Details of anti-epileptic drugs currently being taken;
- Type of epilepsy;
- Seizure frequency in the past month.

Information about the current (index) episode of status epilepticus will be obtained at Visit 1:

- Date of onset
- Date of failure to respond to first line agent(s) and the name(s) of the agent(s)
- Date of failure to respond to second line agent(s) and the name(s) of the agent(s)
- Any previous treatment with third line agents and the response to those agents (details of the third line agent drugs and previous wean attempts will be recorded on the Third Line Agent Medication CRF)
- The cause of the index episode of status epilepticus
- If the subject was transferred from another hospital or from within the hospital, the reason for the transfer will be recorded (such as for study enrollment, due to lack of medical options at original hospital or unit, due to lack of beds at the original hospital or unit, family request, other)

Previous (non-index) diagnosis of status epilepticus will be documented as a no/yes question. If SE did occur in the past 12 months, further information will be gathered, including:

- SE, RSE, or SRSE diagnosis, whichever was the most severe diagnosis for each episode;
- Cause;
- Treatment, including experimental treatments and need for intubation/ventilation;
- Dates of onset and duration.

At Visit 12 or Visit 12R, the following information will be gathered:

- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of SE up to and including Visit 12 or Visit 12R;
- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of seizures (convulsive and non-convulsive) up to and including Visit 12 or Visit 12R;



- Number of separate episodes of SE after H144 at the end of Visit 8 or Visit 8R (no/yes); if yes,
  - SE, RSE, or SRSE diagnosis;
  - Cause;
  - Treatment, including experimental treatments and need for intubation/ventilation;
  - Dates of onset and duration.

Note that a separate episode of SE is defined as an episode of SE separated from other periods of status epilepticus by at least 24 hours.

- Diagnosis of epilepsy since Visit 11 or Visit 11R will be documented as a no/yes question. If a diagnosis of epilepsy has been made, further details will be documented, including:
  - Status as ongoing or new epilepsy since Visit 11 or Visit 11R after initiation of SAGE-547 treatment;
  - Details of anti-epileptic drugs currently being taken;
  - Type of epilepsy and seizure frequency in the past week.

## 11.2. Safety Assessments

The safety and tolerability of SAGE-547 will be assessed using adverse events, clinical laboratory measures, vital signs, ECG intervals and morphology, and mortality. All safety assessments should be performed per hospital standard of care and will be collected periodically throughout the study according to [Table 1](#), [Table 2](#), and [Table 3](#) (Schedules of Assessments).

### 11.2.1. Adverse Events

AEs will be collected after informed consent has been signed and prior to study-specific screening procedures not considered standard of care, during subject preparation for SAGE-547 administration and through Visit 12 or Visit 12R. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™) coding system (current version). See [Section 14](#) for additional details.

### 11.2.2. Clinical Laboratory Tests

Blood samples will be taken for hematology, and serum chemistry and GFR will be calculated at:

- Visit 1 and then at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.
- Blood samples will be taken at Visit 11 or Visit 11R for serum chemistry (renal panel only).

Urine samples (20 ml) will be taken for urinalysis and urine NAG analysis at:

- Visit 1 and at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.

For adults and children  $\geq 30$  kg, these samples will be analyzed at a central laboratory; hour-to-hour medical decisions will be based on sampling for laboratory testing done outside the protocol as part

of normal standard of care. GFR will be calculated by the central laboratory. For children under 30 kg, results of local laboratory testing undertaken at the protocolled timepoints may be sent to the central laboratory for inclusion in the central study laboratory database; this obviates the need for additional blood sampling for central laboratory testing.

Any out-of-range values will be flagged by the laboratory; the investigator will add a comment about whether the abnormality is clinically significant. Clinical significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

#### **11.2.2.1. Hematology and Serum Chemistry**

Hematology will include complete blood count (CBC) white blood cell count with differential, platelet count and red blood cell (RBC) count, hemoglobin and hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose. In addition triglycerides will be measured in serum chemistry samples (to aid assessment of lipemia in pharmacokinetic samples).

#### **11.2.2.2. Pregnancy Test**

Females of child-bearing potential will be tested for pregnancy by serum pregnancy test at Visit 1. In this study, since an accurate history of menstruation in girls and menopause in older women may not be available at Visit 1, “child-bearing potential” is taken to mean any female aged 10 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy. Female subjects with a positive pregnancy test will be ineligible for study participation.

#### **11.2.2.3. Urinalysis**

Urinalysis will include assessment of protein, blood, leukocytes, glucose, ketones, urobilinogen, pH, and specific gravity.

#### **11.2.3. Vital Signs**

Blood pressure, heart rate, and temperature will be recorded at the following time points relative to the first infusion of study drug, and to the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547:

- Visit 1;
- At 0, +30, +60 minutes (+/-15 minutes) and +2, +4 and +8 hours (+/- 30 minutes) after the start of the infusion;
- At +24, +48, +72, +96, +120, +144, +168, and +192 hours (+/- 2 hours) after the start of the infusion.

#### 11.2.4. Weight and Height

Weight and height will be measured at Visit 1. Weight will also be obtained at V2, within the eight hour window that follows the declaration of the QW failure and prior to the initiation of the blinded infusion loading dose at H0 of V3, and will be used to calculate the infusion rates throughout the entire blinded treatment course. If a subject qualifies for open-label study drug, the infusion rates for the open-label infusion will be calculated using the subject's weight measured prior to dosing during V10.

If it is not possible to obtain an actual weight at the above-referenced time points, permission from the Clinical Monitor must be obtained to use another method to obtain the subject's weight (such as information from the LAR or estimating using an established local protocol).

In addition, a daily weight will be obtained and recorded if this is easily obtained, such as the use of a scale bed.

#### 11.2.5. ECG

For the first 50 subjects randomized in the study, 12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours. If it is not possible to perform ECG immediately after the collection of PK samples up to 160 hours, ECG must be performed within 15 minutes prior to the collection of PK samples up to 160 hours; at other times the allowed time window for ECGs is +/- 2 hours:

- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +128, +136, +144, +152, +160, and +192 hours after the start of the blinded (first) study drug infusion
- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +126, +132, +138, +144, +152, +160, and +192 hours after the start of the open-label (second) study drug

The heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm.

For the subsequent subjects randomized in the study, the following timepoints for ECG will be used:

- pre-dose and at +1, +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the blinded (first) study drug infusion
- pre-dose and at +1, +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the open-label (second) study drug infusion

It is not necessary to collect these ECGs with the PK samples at these timepoints and, apart from the +1h ECG, there is +/- 2 hour time window for these ECGs.

#### 11.2.6. Mortality

Mortality will be recorded on the Visit 12 or Visit 12R case report form. If the subject has died, the following information will be collected:

- Date of death;
- Cause of death.

As accurate as possible cause of death will be collected, which will be further categorized as due to one of the following causes:

- SE;
- complications of long term intubation and third-line agent infusions;
- underlying cause of qualifying SE;
- co-morbidity existing at the time of the qualifying SE;
- new co-morbidity or trauma;
- study drug;
- other (specify).

### 11.2.7. Pharmacogenetic Samples

If a subject's LAR consents to pharmacogenetic sampling, a blood sample for genetic research will be collected at Visit 1 in order to avoid the possible introduction of bias through the exclusion of patients who may withdraw from study due to an AE (a subject population that may be of specific interest for subsequent genetic analysis). If for any reason a sample cannot be taken prior to treatment, a sample can be drawn at any point prior to completion with the restriction that no more than one genetic sample be taken per subject.

The objective of this research is to collect and store blood samples for possible DNA extraction and exploratory research into how genes or specific genetic variation may influence response (i.e. distribution, safety, tolerability, and efficacy) to SAGE-547. Specific genetic variations of interest include but are not limited to: classes of metabolizing enzymes (e.g. Cytochrome P450 supra-family genes), genes encoding enzymes involved in the production and metabolism of allopregnanolone (e.g. AKR1C4 (3 $\alpha$ -hydroxysteroid dehydrogenase)), genes associated with the GABA receptor (e.g. GABRA1-A6, GABRB1-B3, GABRD, GABRE, GABRG1-3) and genes associated with the production and degradation of GABA.

Future research may suggest other genes or gene categories as candidates for influencing not only response to SAGE-547 but also susceptibility to disorders for which SAGE-547 is being evaluated. Thus, the genetic research may involve study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.

#### 11.2.7.1. Biological Sampling and Coding Procedures (Pharmacogenetics)

To ensure patient confidentiality, utmost care will be taken in the coding and storage of pharmacogenetic samples.

*Extraction and coding:* DNA will be extracted from the blood sample and the DNA sample will be assigned a unique number replacing information from sampling tube. The assigned DNA number will be used to identify the sample and its corresponding information within Sage Therapeutics or at any designated contract laboratory for the purpose of sequencing of other DNA specific analysis. No personal details sufficient for individual identification will be available to any person (internal or external to Sage Therapeutics) working with the DNA.

*Genotype/Phenotype Analysis:* Samples and data from genetic analysis will be coded. The link between subject enrollment / randomization code and DNA number will be maintained and stored

in a secure environment with restricted access. The established link will be used to identify relevant DNA samples for analysis, facilitated correlation of genotype results with clinical data, allow regulatory audit, and to trace samples for destruction in case of withdrawal of consent.

#### **11.2.7.2. Retention of Biological Samples for Pharmacogenetic Analysis**

Extracted DNA is a finite research that is destroyed in the process of being analyzed. Primary blood samples from which DNA can be extracted will be stored and used until no further analyses are possible, a maximum storage period of 25 years from time of last subject last visit has been reached, or an individual or LAR withdrawals his/her or their consent.

#### **11.2.8. Other Outcomes**

##### **11.2.8.1. Pharmacokinetic Data**

Formal plasma analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS)). In addition, all samples will be analyzed for important SAGE-547 metabolites (if and when these are identified) and Captisol® concentrations.

##### Plasma Analysis

Plasma will be collected to assay for SAGE-547 concentrations at the following time points relative to the start of each infusion of study drug:

- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion.
- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open-label SAGE-547 study drug infusion.
- All samples will also be analyzed for plasma concentrations of important metabolites of SAGE-547 if and when these are identified.
- All samples from the first 50 subjects randomized will also be analyzed for plasma concentrations of Captisol®.

The plasma samples will be drawn from the arm contralateral to that used for drug administration. Drawing samples from peripheral arterial or venous lines or from a central line is permissible. PK collection times should be adhered to as strictly as possible. The allowed time window for all samples is: pre-dose in the two hours prior to starting the infusion of study drug; samples up to and including 1h, +/- 5 minutes; subsequent samples, +/- 15 minutes. Subject-specific PK kits for sampling including instructions on collection and processing methods, and storage and shipping conditions, will be provided separately. To maintain the blind, all subjects will have samples taken as outlined above: subjects receiving SAGE-547 will have all samples analyzed for all analytes. Subjects on placebo may have samples analyzed to investigate endogenous allopregnanolone and

metabolite concentrations, as well as Captisol<sup>®</sup> concentrations; experience with the plasma concentration data will determine if and which placebo samples are analyzed.

Each blood sample will be 3 ml in volume for adults and children weighing 30 kg or more, and 1 ml in volume for children weighing less than 30 kg. Separate aliquots will be obtained from each sample to service the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum blood draw for PK analysis for a subject having two infusions of study drug will be 99 ml (33 ml for children weighing less than 30 kg).

Plasma PK parameters for SAGE-547 will be calculated where appropriate (e.g.,  $C_{max}$ ,  $C_{min}$ ,  $t_{max}$ ,  $AUC_{last}$ ,  $AUC_{\infty}$ ,  $CL_s$ ). In addition, similar PK parameters will be calculated for Captisol<sup>®</sup>. PK parameters for important metabolites of SAGE-547 may be calculated. An evaluation will be made of the feasibility of adopting a population-PK approach to assess drug-drug-interactions with SAGE-547 as victim of AEDs.

In addition, the Visit 9 sample may be analyzed for plasma concentrations of third-line agents.

#### Other Analysis

If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations. The minimum volume of cerebrospinal fluid for analysis is 100 microlitres.

Full details of all pharmacokinetic analyses will be described in the Pharmacokinetic Analysis Plan.

#### **11.2.8.2. Correlation of QT/QTc Changes and Plasma Concentrations of SAGE-547**

An analysis will be performed to determine whether there is any correlation between changes in QT/QTc interval and plasma concentrations of SAGE-547, in order to investigate any effect that SAGE-547 may have on QT/QTc interval.

#### **11.2.8.3. Pharmacoeconomic Data**

At Visit 12 or Visit 12R, the following information will be collected: number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital. If the subject dies before Visit 12 or Visit 12R, data will be collected up to the date of death. The definition of “hospital” is the institution that the subject was initially treated in. If the subject is transferred to another hospital, that hospital would be the “discharge destination from the hospital” and the “number of days in hospital” would be the number of days in the initial treating hospital.

For those subjects discharged from hospital before Visit 12/12R, the following questions will be asked:

- On what study day was the subject discharged from hospital?
- What type of facility was the subject discharged to (another hospital, a rehabilitation center, a supported care facility, home, other)?
- How many days did the subject stay in this facility?

The following questions will be answered regarding the stay in the ICU and hospital:

- Was the subject still in the ICU at the end of Visit 10/10R?

- If the FOUR Score was  $\geq 12$  at Visit 10/10R and the subject was in the ICU at Visit 10/10R, what was the reason for the subject not being discharged from the ICU (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, other)?
- Was the subject still an in-patient in the hospital at the end of Visit 12/12R?
- If the FOUR Score was  $\geq 15$  at Visit 12/12R and the subject was in the hospital at Visit 12/12R, what was the reason for the subject not being discharged from the hospital (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, unsuitable home circumstances, other)?

#### 11.2.8.4. STESS

The STESS will be assessed during Visit 1 in order to assess the severity of the status epilepticus.

#### 11.2.8.5. FOUR Score

The Full Outline of UnResponsiveness or FOUR Score is designed to assess conscious level and unlike other scores, is suitable for subjects who are intubated. It assesses four domains of neurological function (eye responses, motor responses, brainstem reflexes, and breathing pattern).

The FOUR Score will be collected at the following time points relative to each infusion of study drug (the initial blinded infusion and the second open-label infusion if this is administered):

- baseline, +24, +48, +72, +96, +120, +144, +168, and +192 hours (all +/- 2 hours) after the start of the infusion, and at Visit 11/11R and Visit 12/12R.

#### 11.2.8.6. Glasgow Outcome Scale (GOS)

The GOS is a relatively common assessment scale used to standardize descriptions of the objective degree of recovery from brain injury such as cerebral trauma, or in this case SRSE. It was first used in 1975 ([Jennett and Bond 1975](#)) and allows a prediction of the long-term course of rehabilitation to return to work and everyday life. The scale classifies subjects into 5 groups:

- Death
- Persistent vegetative state
- Severe disability
- Moderate disability
- Good recovery

The GOS will be assessed at Visit 12 or Visit 12R.

#### 11.2.8.7. Supervision Rating Scale (SRS)

The Supervision Rating (SRS) measures the level of supervision that a patient/subject receives from caregivers. The SRS rates level of supervision on a 13-point ordinal scale that can optionally be grouped into five ranked categories (Independent, Overnight Supervision, Part-Time Supervision, Full-Time Indirect Supervision, and Full-Time Direct Supervision). The SRS was designed to be rated by a clinician based on interviews with the subject and an informant who has observed at first hand the level of supervision received by the subject ([Boake 2000](#)). Scoring is a one-step procedure in which the clinician assigns the rating that is closest to the subject's level. Ratings are based on

the level of supervision received, not on how much supervision a subject is judged or predicted to need.

The SRS will be assessed at Visit 1 and Visit 12 or Visit 12R. The Visit 1 assessment will be a retrospective assessment of the supervision required by the subject immediately prior to the admission that included the index episode of status epilepticus.

#### **11.2.8.8. Modified Rankin Scale – 9Q (mRS-9Q)**

The Modified Rankin Scale (mRS) is a commonly used scale to determine disability and functional dependence due to neurological insult such as stroke in adults. The 7-point scale (0 – 6) denotes functional capacity from no symptoms (0) to severe disability (5) and death (6). The Modified Rankin Scale – 9Q is a shortened version consisting of 9 questions that reliably determines the mRS score and was developed to both simplify the assessment and expand the rater base to non- medically trained personnel (Patel, Rao et al. 2012). The assessment is a web-based tool in the public domain with automatic score calculation and error checking found at [www.modifiedrankin.com](http://www.modifiedrankin.com).

The mRS will be assessed at Visit 1 and at Visit 12 or Visit 12R in subjects  $\geq 17$  years of age. The baseline assessment will be a retrospective assessment of the disability and dependence of the subject immediately prior to the admission that included the index episode of status epilepticus.



## 12. STUDY PROCEDURES

The study procedures listed below by study day reflect the required data collection times for this protocol. When a time window is necessary, this is specified below. If no time window is specified, the test may be performed at any time within the specified 24-hour period.

### 12.1. Visit 1 (V2-≤30h)

The baseline period will be up to approximately 84 hours prior to starting blinded study treatment and should include the assessments/procedures listed below and summarized in Table 1 and Table 2 (for open-label treatment), the Schedules of Events.

- Informed consent
- Eligibility checklist
- Verification of inclusion/exclusion criteria.
- Demographic information and medical history obtained by proxy and confirmed by the subject when possible.
- SE and wean history
- Blood will be collected from female subjects 10 years to 55 years for a serum pregnancy test unless they are known to be pre-menstrual or post-menopausal or to have had a hysterectomy.
- Blood and urine samples collected for clinical laboratory testing.
- Pharmacogenetic sample will be collected from consenting/eligible subjects.
- Vital signs
- Height
- Weight
- An ECG reading taken.
- Administration of the STESS.
- Administration of the FOUR Score.
- Administration of SRS.
- Administration of the mRS-9Q assessment.
- Assessment of the CGI scale.
- Evaluation of epilepsy status.
- Administration of continuous IV third-line agents.
- Perform EEG.
- Recording of adverse events.
- Recording of previous and concomitant anti-epileptic drugs.
- Recording of previous and concomitant third-line agents.
- Recording of concomitant pressors.

- Recording of other concomitant medications, procedures, and treatments.

## **12.2. Visit 2 (V3-≤54h)**

- Recording of adverse events.
- Recording of concomitant anti-epileptic drugs.
- Recording of concomitant third-line agents.
- Recording of concomitant pressors.
- Recording of other concomitant medications, procedures, and treatments.
- Wean of continuous third-line agent (QW):
  - If wean is successful, subject is followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (these subjects are Qualifying Wean Success subjects or QWS subjects);
  - If wean is not successful, there is ongoing intravenous administration of at least one continuous IV third-line agent and EEG is performed and the subject is randomized.
- Weight
  - Subject weight will be obtained within the eight-hour period from the declaration of failure of QW and prior to the initiation of the blinded infusion loading dose at H0 of V3. This weight will be the dosing weight used to determine the infusion rate for the entire blinded infusion treatment course.

## **12.3. SAGE-547 Treatment Period**

### **12.3.1. Visit 3/3R (0-24 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs will be recorded at:
  - 0, +30, +60 minutes (+/-15 minutes) and +2, +4, +8 (+/- 30 minutes) and +24 hours (+/- 2 hours) after the start of the infusion
- For the first 50 subjects randomized in the study, ECG readings will be recorded immediately after PK sampling, or within 15 minutes prior to PK sampling, at the following time points:
  - 0 (pre-dose) and at +0.5, +1, +3, +6, +12, and +24 hours after the start of the study drug infusion.
  - Subsequent subjects randomized in the study will have ECG readings recorded at 0 (pre-dose) and +1, +12, and +24 hours after the start of the study drug infusion, it will not be necessary to collect these ECGs with PK samples at these timepoints and, apart from the +1 h ECG, there is +/- 2 hour time window for these ECGs.
- A blood sample for PK analysis should be collected at the following time points (all +/- 15 minutes except where otherwise stated):

- 0 (pre-dose, within two hours of the start of the infusion) and at +0.5, +1 (+/- 5 minutes), +3, +6, +12, and +24 hours after the start of the study drug infusion.
- Completion of the FOUR Score
  - +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the final declaration of QW success)
- Ongoing intravenous administration of a continuous IV third-line agent.
- Study drug administration in loading (Hour 0-1) and maintenance infusions (at completion of Hour 1).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### 12.3.2. Visit 4/4R (25-48 hours)

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +48 hours (+/- 2 hours) after the start of the infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +48 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +48 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +48 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +48 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent.
- Ongoing study drug maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

**12.3.3. Visit 5/5R (49-72 hours)**

- Weight if easily obtained
- Vital signs should be recorded at:
  - +72 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +72 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +72 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +72 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +72 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

**12.3.4. Visit 6/6R (73-96 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +96 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +96 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +96 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.

- A blood sample for PK analysis should be collected:
  - +96 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +96 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Perform EEG.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.5. Visit 7/7R (97-120 hours)**

- Weight if easily obtained
- Vital signs should be recorded at:
  - +120 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +120 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +120 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +120 hours (+/- 15 minutes) after the start of study drug infusion, immediately prior to the end of the maintenance infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +120 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled. Complete wean by 120 hours if at all possible.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).

- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## 12.4. SAGE-547 Taper Period

### 12.4.1. Visit 8/8R (121-144 hours)

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +144 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after each PK sampling, or within 15 minutes prior to PK sampling at the following time points:
  - +128, +136 hours and +144 hours after the start of the blinded study drug infusion
  - +126, +132, +138 hours and +144 hours after the start of the open-label study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +144 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected (+/- 15 minutes unless otherwise stated):
  - +128 (immediately prior to the end of the first taper step), +136 hours (+/- 5 minutes, immediately prior to the end of the second taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of study drug infusion.
  - During the open-label study drug phase of the study PK blood draws at: +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 hours (+/- 5 minutes, immediately prior to the end of the third taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of the study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +144 hours (+/- 2 hours) after the start of the infusion
- Complete wean of third line agents by H144 if not completed by H120.
- Perform EEG.
- Taper of SAGE-547 infusion begins at hour 121.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## **12.5. Follow-up Period**

### **12.5.1. Visit 9/9R (145-168 hours)**

- Vital signs should be recorded at:
  - +168 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at + 152 hours:
  - +152, +160 hours (+/- 2 hours) after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +152 and +160 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +168 hours (+/- 2 hours) after the start of the infusion
- Perform EEG.
- Assessment of the presence of physiologic brain activity using EEG.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.5.2. Visit 10/10R (169-192 hours)**

- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +192 hours (+/- 2 hours) after the start of the infusion
- At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine eligibility for the open-label treatment with the higher dose of study drug. This determination may occur at any point during Visit 10: the higher dose open-label infusion must begin within the Visit 10 window. All patients receiving the higher dose open-label treatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.
- Weight if the subject qualifies for the open-label study drug (Visit 10 only, not Visit 10R).
- Recording of adverse events (QWS subjects also).

- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.3. Visit 11/11R (Visit 3/3R + 14d (±2))**

- Blood samples collected for clinical laboratory testing (renal panel only).
- Completion of the FOUR Score (QWS subjects also).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.4. Visit 12/12R (Visit 3/3R + 21d (±2))**

All assessments also performed for QWS subjects.

- Completion of the FOUR Score.
- Administration of the GOS.
- Administration of the SRS.
- Administration of the mRS-9Q assessment.
- Evaluation of epilepsy status (see [Section 11.1.2.2](#) for details).
- Assessment of the CGI Scale.
- Recording of adverse events.
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications.
- Collection of pharmacoeconomic data.
- Mortality will be assessed throughout the study period.

## **13. STATISTICS**

### **13.1. Statistical Plan**

Complete details for the analysis and reporting of data from this study will be contained in the Statistical Analysis Plan (SAP).

#### **13.1.1. Interim Analysis**

When approximately 50% of subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.



### 13.1.2. Study Populations

The **Safety Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to actual treatment. This analysis population will be used for all safety analyses.

The **Intent to Treat Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to randomized treatment. This analysis population will be used for all efficacy analyses.

The **Modified Intent to Treat Population** is defined as all subjects who:

1. complete their initial course of blinded SAGE-547 or placebo treatment unless the non-completion was due a drug-related adverse event; and
2. have at least one attempt to wean from third-line agents prior to the end of blinded study treatment infusion unless the failure to wean was because seizures were not controlled.

Subjects will be classified according to randomized treatment. This analysis population will be used for sensitivity analyses of the primary endpoint and select secondary efficacy endpoints.

Narratives will be prepared for all subjects who do not complete the infusion of blinded study medication or were not subjected to any wean attempts. Narratives will include details of the cause of SE, the comorbid conditions, the adverse event(s), and reasons for non-completion of the infusion or failure to attempt weaning. This blinded narrative will be reviewed by the medical monitors and the patient adjudicated as MITT eligible or ineligible. Acceptable reasons for defining a subject as MITT ineligible include death or withdrawal of consent due to progression of the underlying cause of SE or comorbid conditions, unless the cause of death or progression of disease were thought by the investigator, sponsor, or DSMB to be related to study drug.

The **Per-Protocol (PP) Population** is defined as a subset of the MITT population but will exclude data from all subjects with significant protocol violations or deviations. Subjects will be classified according to actual treatment received. This data set will be used for sensitivity analyses to examine the robustness of results for the primary and key secondary efficacy endpoints.

The **Pharmacokinetics Population** is defined as all subjects who at least had an infusion of blinded SAGE-547 initiated and have at least one pharmacokinetic sample collected.

The **Pharmacogenetic Population** is defined all subjects who consent to being included in the pharmacogenetic assessment and provide a pharmacogenetic sample.

Summary statistics of all data collected will be presented for subjects who were QW successes.

### 13.1.3. General Aspects

Tabular displays of descriptive statistics will be provided for all variables. Summary tables will include n, mean, mean, standard deviation, minimum and maximum for continuous variable and frequency and percentage for categorical variables.

### 13.1.4. Analysis of Primary Endpoint

The analysis of response to treatment (see Section 11.1.1 for definition of primary endpoint) between SAGE-547 treated subjects and placebo treated subjects will be performed on the ITT population using a Cochran-Mantel-Haenszel (CMH) test with variables for treatment, concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior

to randomization (one vs two or more). The CMH general association statistic and its associated p-value will be presented. The comparison of treatment response rates will be conducted at the 5% level of significance. To confirm the CMH results, a permutation test will also be conducted.

An additional analysis of the primary endpoint will also be performed on the MITT population. In addition sensitivity analyses of the primary endpoint will be performed using the ITT population based on:

- the number of third-line agents (one, two, or three) subjects were administered post-randomization; and
- which third line agent was the subject of the first TW.

As requested by Italian regulators, the primary endpoint will also be summarized by the cause of status epilepticus being or not being an autoimmune disorder as defined by medical history and prior and/or concurrent medication use.

### **13.1.5. Analysis of Secondary Efficacy Endpoints**

Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section ([Section 6](#)). Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. The analysis of the secondary endpoints will also be performed on the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

### **13.1.6. Analysis of Other Endpoints**

Safety and “Other” endpoints will only be summarized by treatment group.

Summaries of safety endpoints will be based on the overall Safety Population.

### **13.1.7. Epilepsy and SRSE Status**

Diagnosis of epilepsy and recurrence of RSE or SRSE will be documented as the percentage of subjects by time point and overall. Kaplan-Meier curves may be plotted if sufficient data are available.

Utilization of AEDs during follow-up and during recurrence will be summarized.

### **13.1.8. Questionnaires**

The data collected from each questionnaire will be interpreted according to the standard methodology for that questionnaire. There will be no adjustment for missing values.

### **13.1.9. Pharmacokinetic Data Analysis**

Details of the pharmacokinetic data analysis will be described in detail in a separate Pharmacokinetic Analysis Plan.

### **13.1.10. Pharmacogenetic Data Analysis**

Any genotype data generated in this study will be stored within a secured database within Sage Therapeutics and / or a third party contracted to work with Sage Therapeutics to analyze the samples. Because the number of subjects agreeing to participate in the genetic research component of the study is unknown, it is not possible to establish, a priori, whether sufficient samples will be obtained to support formal statistical evaluation of data. As a consequence a Pharmacogenetic Analysis Plan will only be prepared where appropriate and the results obtained from any genetic research will be reported in a report separate from the main study CSR.

### **13.1.11. Open-Label Study Drug Subjects**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are treated with SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo.

### **13.1.12. EEG-Responders**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who are classified as EEG-responders/non-responders based on the independent assessment of the PAEEG. Summaries will be derived for the two randomized treatment groups.

### **13.1.13. QT/QTc Assessment**

An analysis of the correlation between changes in QT/QTc intervals and SAGE-547 plasma levels will be performed to investigate if there is a potential effect that SAGE-547 may have on QT/QTc interval. A detailed description of the QT/QTc assessment will be included in the SAP.

### **13.1.14. Quantitative EEG**

The nine EEG records for each subject may be subjected to exploratory quantitative EEG analysis, the details of which will be included in the EEG Analysis Plan. In summary the following comparisons may be made, SAGE-547 versus placebo; the QWEEG versus the TWEEG (main analysis); the CEEG versus PAEEG (subsidiary analysis); and TAEEG versus PAEEG (exploratory analysis).

## **13.2. Determination of Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between treatment groups at a 5% level of significance. Randomization will be stratified by concomitant

pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

### **13.3. Statistical Analysis Plan**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

## **14. ADVERSE EVENTS**

The safety procedures in this study will be detailed in a Safety Management Plan, which will be agreed and signed before the first subject is randomized in the study. [Section 14.1](#) summarizes Investigator responsibilities regarding the identification and documentation of AEs, the classification of AEs for relationship to study drug and severity, and the reporting of AE information to the Sponsor and the IRB.

[Section 14.2](#) summarizes Sponsor/Medical Monitor Responsibilities regarding monitoring of AE data and reporting relevant safety information to FDA.

[Section 14.3](#) lists important AE definitions.

### **14.1. Investigator Responsibilities**

#### **14.1.1. Identification and Documentation of Adverse Events by Investigator**

Subjects will be evaluated and questioned generally (if possible) to identify AEs during the course of the study. AEs will be collected from the signature of the consent form through Visit 12/12R. Adverse events that occur prior to completion of screening will be captured on the Medical History eCRF. Adverse events that occur after completion of screening will be recorded on the Adverse Event eCRF.

All AEs revealed by observation, other diagnostic procedures, or spontaneously reported by the subject and/or in response to an open question from study personnel will be recorded on the Adverse Event Form. Any clinically significant deterioration in laboratory assessments or other clinical findings are considered an AE and must be recorded on the Adverse Event Form, unless otherwise stated. AE information recorded will be entered into the database on an ongoing basis.

AEs with a relationship considered related to study drug (probable, possible) should be followed until the event is resolved or the Investigator determines the event is stable or no longer clinically significant. AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

For SAEs, an electronic Serious Adverse Event eCRF must be completed with as much information as possible and submitted in the time frame described below in [Section 14.1.3](#). When new significant information is obtained as well as when the outcome of an event is known, the electronic SAE eCRF should be updated within 24 hours. If the subject was an outpatient at the time of the SAE and was re-hospitalized due to the SAE, a copy of relevant hospital records (e.g., admission report, laboratory test results, discharge summary, etc.) may be requested to be included as part of the subject medical file.

All SAEs will be followed until resolved or until a stable status has been achieved.

**14.1.2. Adverse Event Classification****14.1.2.1. Relationship to Investigational Drug**

None:	No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state.
Possible:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject, but this is not known for sure.
Probable:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

**14.1.2.2. Severity**

Mild	Discomfort noticed, but no disruption to daily activity.  For subjects that are unconscious, this may be a slight or minor change in a lab result or clinical sign or symptom that does not require immediate corrective action.
Moderate	Discomfort sufficient to reduce or affect normal daily activity, but is not hazardous to health; prescription drug therapy may be employed to treat the AE.  For subjects that are unconscious, this may be a clinically meaningful change that may require immediate corrective action.
Severe	Inability to work or perform normal daily activity and represented a definite hazard to health; prescription drug therapy and/or hospitalization may be employed to treat the AE.  For unconscious subjects, this may be a significant clinical change that requires immediate corrective action.

**14.1.2.3. Action Taken with Investigational Drug**

None	Study medication was continued without change.
Discontinued	Study medication was terminated.
Dose adjusted	Study medication dose/infusion rate was changed and then continued per protocol.
Interrupted	Study medication was interrupted and then continued per protocol.
Unknown	The action taken with regard to study medication is unknown.
Not applicable	Administration of study medication was not ongoing.

**14.1.2.4. Assessment of Outcome**

Ongoing	At the end of the study, the event has not resolved or stabilized.
Ongoing and stable	The event is ongoing but has stabilized and is unlikely to change
Resolved	The event has resolved or the subject recovered without sequelae.
Resolved with sequelae	The event has at least one secondary outcome that may result in permanent disability and/or functional limitation.
Unknown	The status of the event is unknown.
Death	The subject has expired.

**14.1.3. Investigator Reporting to Sponsor and Sponsor Emergency Contact**

All new SAEs that come to the Investigator and/or Sponsor's notice during the course of the study (up to and including the last study visit) must be reported by the Investigator on the designated electronic report form within 24 hours of the point in time when the Investigator becomes aware of the SAE. As additional information becomes available, the designated electronic report form must be updated within 24 hours.

Investigators must report any SAE, whether or not considered drug related. The report must include an assessment of whether there is a reasonable possibility that the drug caused the event.

In a medical emergency (ie, an event that requires immediate attention regarding the treatment of a subject, operation of the clinical study, and/or the use of investigational drug), study site staff will apply appropriate medical intervention according to current standards of care, and contact the Medical Monitor.

**14.1.4. Medical Monitor and Emergency Contact Information**

[REDACTED], MD  
[REDACTED]

In a study related medical emergency situation, when the assigned Medical Monitor cannot be reached by a caller, an on-call Physician can be reached 24 hours per day, 7 days per week via an [REDACTED] Call-Center:

- Telephone: [REDACTED]  
(this is a chargeable telephone number allowing a global reach from both landlines and mobile phones)

- [REDACTED]

On this internet page a list of country-specific toll-free telephone numbers is provided. It should be noted that not all countries globally have access to toll-free numbers as indicated on the “24/7 Medical Help desk” index. Countries without toll-free numbers need to dial the chargeable number as indicated above. Furthermore, toll-free numbers are not available from mobile phones.

#### **14.1.5. SAE Reporting Contact Information**

Contact information and reporting instructions are provided in the Safety Management Plan.

#### **14.1.6. Reporting to Institutional Review Boards (IRBs)**

It is the responsibility of the Investigator to promptly notify the institution’s IRB of all serious and unexpected suspected adverse reactions (see [Section 14.3](#) for definitions).

### **14.2. Sponsor/Medical Monitor Responsibilities**

#### **14.2.1. Monitoring of Adverse Event Data**

The Medical Monitor will review any newly reported adverse events in an ongoing basis. If the aggregate assessment indicates that an event is occurring more frequently than would normally be expected in this population, or as previously observed, and the sponsor believes that the events are causally related to the administration of SAGE-547, the Sponsor will then report that information in an IND safety report.

#### **14.2.2. Data Safety Monitoring Board**

An independent DSMB will monitor the clinical, PK and PD data for safety signals throughout the study and will be asked to assess the placebo response rate at the time of the interim analysis to determine final sample size. In order to perform their monitoring function the DSMB will have access to un-blinded safety data as necessary.

The composition and procedures for the board will be described in a separate DSMB Charter.

#### **14.2.3. Reporting to FDA**

The Sponsor must report in an IND safety report any suspected adverse reaction to study treatment that is both serious and unexpected (21 CFR 312.32(c)(1)(i)). Before submitting an IND safety report, the Sponsor will ensure the event meets all three of the definitions: (1) suspected adverse reaction, (2) serious, (3) unexpected. If the AE does not meet all three of the definitions, it should not be submitted as an IND safety report. The Sponsor should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the adverse event and, therefore, that the event meets the definition of a suspected adverse reaction.

If there is a serious and unexpected suspected adverse reaction, the Sponsor will notify the appropriate regulatory agency(ies) and all appropriate parties on an expedited basis. In addition, Sponsors must submit expedited reports of an increased rate of occurrence or severity of serious suspected adverse reactions over that listed in the protocol or Investigational Brochure.

SUSARs will be unblinded prior to reporting to FDA. Unless it is necessary to unblind for the safety of the patient, the investigator will not be informed of the unblinding of the subject.



Under 21 CFR 312.32, Sponsors should identify in the protocol SAEs that it does not plan to report individually in an expedited manner, because they are known consequences of the disease or otherwise common in the study population. Given the grave condition and prognosis of SRSE being studied, individual occurrences of seizures or seizure activity will not be reported expeditiously in this study. Regardless of which events are reported in an expedited manner, all adverse events will be closely monitored throughout the study.

#### **14.2.4. Reporting to European Regulatory Authorities**

The Sponsor or its designee is responsible for SUSAR notification to the relevant regulatory authorities as outlined in the ICH Guidelines. All investigators participating in the study will also be informed as required by regulations.

Any SUSAR is subject to expedited reporting in the EU. The Sponsor or its designee, will report any single SUSAR to the appropriate National CAs and IECs within 7 days if the SUSAR is life-threatening or fatal (with the relevant follow-up information subsequently communicated within an additional eight days), and within 15 days if the SUSAR is neither life-threatening nor fatal. SUSARs reported will be those that have arisen in the present clinical trial and SUSARs that have arisen in other clinical trials conducted by the Sponsor with the same medicinal product.

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to competent authorities of the concerned Member States and to IEC(s)/IRBs as required by national laws.

### **14.3. Adverse Event Definitions**

#### **14.3.1. Adverse Event**

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

#### **14.3.2. Suspected Adverse Reaction**

Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

#### **14.3.3. Life-Threatening**

An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

#### **14.3.4. Serious**

An AE or suspected adverse reaction is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE – see definition above
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disability
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

#### **14.3.5. Unexpected**

An AE or suspected adverse reaction is considered “unexpected”:

- If it is not listed in the Investigational Brochure or is not listed at the specificity or severity that has been observed, or
- If an Investigational Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigational Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigational Brochure listed only cerebral vascular accidents.

“Unexpected,” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigational Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

#### **14.4. Emergency Identification of Study Medication**

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject’s treatment in the study via the IVRS; this normally requires prior approval by the medical monitor. However, if the subject is at immediate risk and the Investigator believes that immediate knowledge of the study treatment will alter medical management, discussion with the medical monitor may take place after unblinding. The Investigator will not unblind the medical monitor during that discussion. The process of unblinding will ensure that only the investigator is unblinded; the medical monitor, study management team, and data management team will not be made aware of the treatment allocation of an individual subject. All cases of emergency unblinding will be fully documented in a way that does not unblind the medical monitor, study management team, and data management team.

## **15. STUDY ADMINISTRATIVE CONSIDERATIONS**

### **15.1. Quality Control and Quality Assurance**

The Investigators and institutions will permit trial related monitoring, audits, IRB review, and regulatory inspections as requested by FDA, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed informed consent forms, etc.) in addition to case report forms.

Quality assurance and quality control systems with written standard operating procedures (SOPs) will be followed to ensure this trial will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The site's dedicated study monitor will arrange to visit the Investigator at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be identified and resolved. The study monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality assurance officers named by Sage Therapeutics or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements, made by the Sponsor with the Investigator/institution and any other parties involved with the clinical trial, will be in writing in a separate agreement.

### **15.2. Data Handling and Recordkeeping**

#### **15.2.1. Data Handling**

Procedures for data handling (including electronic data) used in this protocol will be documented in a Data Management Plan.

#### **15.2.2. Case Report Form Completion**

eCRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of demographics, study drug administration, study procedures, AEs, questionnaire completion, efficacy assessments and subject status, including survival.

The Investigator will maintain copies of the eCRFs at the study site. For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate eCRF.

### **15.2.3. Retention of Study Records**

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval and until there are no pending or contemplated marketing applications or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to an appropriate person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

### **15.3. Confidentiality**

To maintain subject privacy, all eCRFs, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available trial registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by Sage Therapeutics to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

### **15.4. Publication Policy**

All information concerning SAGE-547 is considered confidential and shall remain the sole property of Sage Therapeutics. The Investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval from Sage Therapeutics. No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between Sage Therapeutics and the Investigator.

### **15.5. Protocol Amendments**

Changes to the conduct of the study should be prepared as a protocol amendment by the Sponsor. Protocol amendments should receive written IRB/IEC approval prior to implementation at the investigative site, except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the trial (eg, change of monitor, telephone numbers). In this case, Sage Therapeutics will amend and implement the protocol change and subsequently notify the regulatory authorities and the Investigative sites who will notify the respective IRB, as appropriate.

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**APPENDIX 1. APPENDIX 1: FOUR SCORE****FOUR score****Full Outline of UnResponsiveness****Eye response**

- E4: eyelids open or opened, tracking, or blinking to command
- E3: eyelids open but not tracking
- E2: eyelids closed but open to loud voice
- E1: eyelids closed but open to pain
- E0: eyelids remain closed with pain

**Motor response**

- M4: thumbs-up, fist or peace sign
- M3: localizing to pain
- M2: flexion response to pain
- M1: extension response to pain
- M0: no response to pain or generalized myoclonus status

**Brainstem reflexes**

- B4: pupil and corneal reflexes present
- B3: one pupil wide and fixed
- B2: pupil or corneal reflexes absent
- B1: pupil and corneal reflexes absent
- B0: absent pupil, corneal and cough reflex

**Respiration pattern**

- R4: not intubated, regular breathing pattern
- R3: not intubated, Cheyne-Stokes breathing pattern
- R2: not intubated, irregular breathing
- R1: breathes above ventilatory rate
- R0: breathes at ventilator rate or apnea

Reference ([Iyer, Hoel et al. 2009](#)).

**APPENDIX 2. GLASGOW OUTCOME SCALE (GOS)****GLASGOW  
OUTCOME  
SCALE**

Patient Name: \_\_\_\_\_  
 Rater Name: \_\_\_\_\_  
 Date: \_\_\_\_\_

*Note:* The scale presented here is based on the original article by Jennett and Bond. It has become common practice in clinical trial administration, however, to use a modified version that places the scores in reverse order (i.e., "good recovery" = 1, "moderate disability" =2, etc.).

Score	Description
1	DEATH
2	PERSISTENT VEGETATIVE STATE Patient exhibits no <i>obvious cortical</i> function.
3	SEVERE DISABILITY (Conscious but disabled). Patient depends upon others for daily support due to mental or physical disability or both.
4	MODERATE DISABILITY (Disabled but independent). Patient is independent as far as daily life is concerned. The disabilities found include varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes.
5	GOOD RECOVERY Resumption of normal activities even though there may be minor neurological or psychological deficits.

**TOTAL (1-5):** \_\_\_\_\_

Reference ([Jennett and Bond 1975](#)).



## APPENDIX 3. SUPERVISION RATING SCALE (SRS)

### SUPERVISION RATING SCALE (SRS)

**Instructions:** Circle the rating that is closest to the amount of supervision that the patient *actually receives*. "Supervision" means that someone is responsible for being with the patient.

<u>Rating</u>	<u>Description</u>
<u>Level 1: INDEPENDENT</u>	
1	The patient lives alone or independently. Other persons can live with the patient, but they cannot take responsibility for supervision (for example, a child or elderly person).
2	The patient is unsupervised overnight. The patient lives with one or more persons who <i>could</i> be responsible for supervision (for example, a spouse or roommate), but they are <i>all</i> sometimes absent overnight.
<u>Level 2: OVERNIGHT SUPERVISION</u>	
3	The patient is only supervised overnight. One or more supervising persons are always present overnight but they are <i>all</i> sometimes absent for the rest of the day.
<u>Level 3: PART-TIME SUPERVISION</u>	
4	The patient is supervised overnight and part-time during waking hours, but is allowed on independent outings. One or more supervising persons are always present overnight and are also present during part of waking hours every day. However, the patient is sometimes allowed to leave the residence without being accompanied by someone who is responsible for supervision.
5	The patient is supervised overnight and part-time during waking hours, but is unsupervised during working hours. Supervising persons are <i>all</i> sometimes absent for enough time for them to work full-time outside the home.
6	The patient is supervised overnight and during most waking hours. Supervising persons are <i>all</i> sometimes absent for periods longer than one hour, but less than the time needed to hold a full-time job away from home.
7	The patient is supervised overnight and during almost all waking hours. Supervising persons are <i>all</i> sometimes absent for periods shorter than one hour.
<u>Level 4: FULL-TIME INDIRECT SUPERVISION</u>	
8	The patient is under full-time indirect supervision. At least one supervising person is <i>always</i> present, but the supervising person does not check on the patient more than once every 30 minutes.
9	Same as #8 plus requires overnight safety precautions (for example, a deadbolt on outside door).
<u>Level 5: FULL-TIME DIRECT SUPERVISION</u>	
10	The patient is under full-time direct supervision. At least one supervising person is always present and the supervising person checks on the patient more than once every thirty minutes.
11	The patient lives in a setting in which the exits are physically controlled by others (for example, a locked ward).
12	Same as #11 plus a supervising person is designated to provide full-time line-of-sight supervision (for example, an escape watch or suicide watch).
13	The patient is in physical restraints.

3/12/93

Corwin Boake, Ph.D., TIRR, 1333 Moursund, Houston, TX 77030-3405, 713/799-6990

## APPENDIX 4. MODIFIED RANKIN SCALE – LEVEL OF FUNCTION SURVEY (mRS-9Q)

1. Do you have any symptoms that are bothering you? (For example, trouble with reading or writing, trouble speaking, problems with vision, numbness, weakness, balance trouble, or problems with swallowing?)	YES <input type="radio"/>	NO <input type="radio"/>
2. Are you able to do the same work as before?	YES <input type="radio"/>	NO <input type="radio"/>
3. Are you able to keep up with your hobbies?	YES <input type="radio"/>	NO <input type="radio"/>
4. Have you maintained your ties to friends and family?	YES <input type="radio"/>	NO <input type="radio"/>
5. Do you need help making a simple meal, doing household chores, or balancing a checkbook?	YES <input type="radio"/>	NO <input type="radio"/>
6. Do you need help with shopping or traveling close to home?	YES <input type="radio"/>	NO <input type="radio"/>
7. Do you need another person to help you walk?	YES <input type="radio"/>	NO <input type="radio"/>
8. Do you need help with eating, going to the toilet, or bathing?	YES <input type="radio"/>	NO <input type="radio"/>
9. Do you stay in bed most of the day and need constant nursing care?	YES <input type="radio"/>	NO <input type="radio"/>

## APPENDIX 5. CLINICAL GLOBAL IMPRESSION (CGI)

### Clinical Global Impression (CGI)

#### 1. Severity of illness

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- |                             |   |
|-----------------------------|---|
| 0 = Not assessed            | 4 = Moderately ill                        |
| 1 = Normal, not at all ill  | 5 = Markedly ill                          |
| 2 = Borderline mentally ill | 6 = Severely ill                          |
| 3 = Mildly ill              | 7 = Among the most extremely ill patients |

#### 2. Global improvement: Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.

Compared to his condition at admission to the project, how much has he changed?

- |                        |                     |
|------------------------|---------------------|
| 0 = Not assessed       | 4 = No change       |
| 1 = Very much improved | 5 = Minimally worse |
| 2 = Much improved      | 6 = Much worse      |
| 3 = Minimally improved | 7 = Very much worse |

#### 3. Efficacy index: Rate this item on the basis of drug effect only.

Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.

EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect		Side effects			
		None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
<b>Marked</b>	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
<b>Moderate</b>	Decided improvement. Partial remission of symptoms	05	06	07	08
<b>Minimal</b>	Slight improvement which doesn't alter status of care of patient	09	10	11	12
<b>Unchanged or worse</b>		13	14	15	16
Not assessed = 00					

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

**APPENDIX 6. STATUS EPILEPTICUS SEVERITY SCORE (STESS)**

Outcome Predictor	Feature	Score
Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type (prior to first treatment)	Simple-partial, complex-parial, absence, myoclonic (complicating idiopathic generalized epilepsy)	0
	Generalized-convulsive	1
	Nonconvulsive status epilepticus in coma	2
Age	< 65 years	0
	≥ 65 years	2
History of previous seizures	Yes	0
	No or unknown	1
Summed Total		

**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY  
TO EVALUATE THE EFFICACY AND SAFETY OF SAGE-547 INJECTION  
IN THE TREATMENT OF SUBJECTS WITH SUPER-REFRACTORY  
STATUS EPILEPTICUS**

**PROTOCOL NUMBER: 547-SSE-301  
ADULT ONLY VERSION**

**IND NUMBER: 117901**

**EudraCT Number: 2015-002142-31**

Product: SAGE-547 Injection (allopregnanolone)

Sponsor Contact: [REDACTED], MD  
Sage Therapeutics  
215 First Street  
Cambridge, MA 02142  
[REDACTED]

Medical Monitor: [REDACTED], MD  
[REDACTED]

Date of Protocol: 09 March 2015  
Date of Amendment One: 27 May 2015  
Date of Amendment Two (Adults Only, 29 February 2016  
Sweden)  
Date of Amendment Three (Adults Only, 22 April 2016  
Sweden [not implemented])  
Date of Amendment Four (Adults Only, 18 August 2016  
Sweden)

**Confidentiality Statement**

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

**PROTOCOL NUMBER: 547-SSE-301**

Sponsor [REDACTED]:

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]  
[REDACTED]

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]  
[REDACTED]

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

CRO [REDACTED]:

[REDACTED]

## 1. SIGNATURE PAGE

Title of Protocol:

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus

Protocol No: 547-SSE-301

### Sponsor Approval

[Redacted Signature]

07 SEP 2016

Date (dd/mmm/yyyy)

[Redacted Signature] MD

Sage Therapeutics

[Redacted Signature]

08 Sept 2016

Date (dd/mmm/yyyy)

[Redacted Signature] MPH

Sage Therapeutics

[Redacted Signature]

07 Sep 2016

Date (dd/mmm/yyyy)

[Redacted Signature] MPH

Sage Therapeutics

[Redacted Signature]

07 SEP 2016

Date (dd/mmm/yyyy)

[Redacted Signature]

Sage Therapeutics

**Investigator Agreement**

By signing this page I attest that I have read and understand the contents of Clinical Protocol 547-SSE-301 and any current amendments. I agree to adhere to the design, conduct, and reporting requirements of the study as stated in the clinical protocol and to my obligations to the Sponsor as described in the protocol and executed contracts between myself, my Institution, and the Sponsor. I also agree to adhere to any subsequent amendments to the clinical protocol.

Investigator's Signature: \_\_\_\_\_

Investigator's Name: \_\_\_\_\_

Institution: \_\_\_\_\_

Date: \_\_\_\_\_



## 2. SYNOPSIS

<b>Name of Sponsor:</b> Sage Therapeutics 215 First Street Cambridge, MA 02142		
<b>Protocol No.</b> 547-SSE-301	<b>Phase:</b> 3	
<b>Name of Investigational Product:</b> SAGE-547 Injection		
<b>Name of Active Ingredient:</b> Allopregnanolone		
<b>Title of the Protocol:</b> A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus		
<b>Dosing Regimen: SAGE-547 or Placebo Dosing Schedule</b>		
<b>Hour</b>	<b>Type and Duration of SAGE-547 Infusions</b>	<b>Dose</b>
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	90 µg/kg/h
H121 – H128	8 hour taper	65 µg/kg/h
H129 – H136	8 hour taper	45 µg/kg/h
H137 – H144	8 hour taper	25 µg/kg/h
<b>Dosing Regimen: SAGE-547 Open-Label Dosing Schedule</b>		
<b>Hour</b>	<b>Type and Duration of SAGE-547 Infusion</b>	<b>Dose</b>
H1	One hour loading infusion	300 µg/kg/h
H2 –H120	119 hour maintenance infusion	150 µg/kg/h
H121 – H126	6 hour taper	125 µg/kg/h
H127 – H132	6 hour taper	95 µg/kg/h
H133 – H138	6 hour taper	65 µg/kg/h
H139 – H144	6 hour taper	35 µg/kg/h
<b>Study Sites</b> Up to 180 sites in the USA, Israel, Europe, and Canada.		
<b>Number of Subjects</b>		

The study will randomize 140 subjects at up to 180 sites.
<b>Study Population</b> <p>Subjects will be aged 18 years or more, in SRSE<sup>1</sup> (as defined in the Inclusion Criteria <a href="#">Section 8.1</a>), and being managed in an intensive care setting.</p>
<b>Duration of Subject Involvement</b> <p>Individual subject participation will be up to 30 days.</p>
<b>Study Design</b> <p>This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.</p> <p>Patients will follow one of three paths to entry to the study. The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst or seizure suppression with a third-line agent. These subjects will be consented for the study after admission to the intensive care unit, before or after any third-line agents are administered for burst or seizure suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their legally authorized representative (LAR) already appointed by the Court for their well-being, and closest relatives. Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours. Once burst or seizure suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.</p> <p>The second path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst or seizure suppression pattern on the EEG. These subjects may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst or seizure suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst or seizure suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst or seizure suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be</p>

<sup>1</sup> In this study, the term Super-Refractory Status Epilepticus or SRSE is equivalent to “Refractory Status Epilepticus (RSE) that has failed standard treatment” and the two terms are used interchangeably.

randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The third path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst or seizure suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These subjects may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR and closest relatives. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 treatment or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within eight hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo).

The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that subjects, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as both the ability to wean the subject off all third-line agents before the end of the infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication infusion, and concurrent signs of physiologic brain activity as determined by EEG. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#) and [Table 2](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo will all subsequently be eligible to be administered SAGE-547 at the higher dose.

## Visit Schedule

The visit schedule and an overview of events at each visit is provided in [Table 1](#), [Table 2](#) and [Table 3](#) Schedule of Assessments.

## **Study Objectives**

### ***Primary objective:***

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult subjects with SRSE, and for the response to endure at least 24 hours after the end of the SAGE-547 or placebo infusion (primary response).

### ***Secondary objectives:***

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in the Clinical Global Impression scale (CGI) between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### ***Safety objectives:***

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

### ***Other objectives:***

1. To evaluate the impact of treatment with a higher dose SAGE-547 infusion;

2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol<sup>®</sup> and identified SAGE-547 metabolite plasma concentrations;
3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;
6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS).

## Endpoints

### *Primary endpoint:*

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### *Secondary endpoints:*

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### *Safety endpoints:*

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;

## 5. Mortality.

**Other endpoints:**

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who are treated with a higher dose of SAGE-547.
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol<sup>®</sup> and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS).

**Inclusion Criteria**

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects 18 years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed zero or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst or seizure suppression pattern; or who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst or seizure suppression pattern.

**Exclusion Criteria**

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone or any excipients in SAGE-547.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy with highly malignant/malignant EEG features ([Westhall, Rosetti et al. 2016](#)).

4. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis but for whatever reason, dialysis that would adequately remove Captisol<sup>®</sup> is not planned;
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. severe hepatic impairment;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the opinion of the investigator, of less than 30 days.
5. Subjects who are being administered more than three third-line agents concomitantly or in whom the qualifying wean cannot be completed within 24 hours, or who are being administered a third-line agent for other indications such as management of raised intra-cranial pressure that would preclude weaning according to this protocol.
6. Subjects with a living will that does not allow heroic measures.
7. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
8. Subjects who have been treated or randomized in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not have received study drug/placebo and then re-enroll).

### **Pharmacogenetic Research**

In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **Statistical Analysis**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

### **Interim Analysis**

When approximately 50% of the subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### **Analysis of Primary Endpoint**

The analysis of response to treatment between SAGE-547 treated subjects and placebo treated subjects will be performed using a Cochran-Mantel-Haenszel test with variables for treatment, concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). In this analysis, a treatment responder is a subject who is successfully

weaned off all third-line agents and blinded study medication prior to the end of study treatment infusion and remains off third-line agents for at least 24 hours following cessation of the blinded study medication, and who has concurrent signs of physiologic brain activity as determined by EEG. The analysis will be based on the ITT Population. The comparison of treatment response rates will be conducted at the 5% level of significance.

### **Analysis of Secondary Efficacy Endpoints**

The primary analysis will be repeated for the MITT population. Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section. Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. Secondary analyses will be repeated for the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from Baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third-line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

Summaries of safety endpoints will be based on the overall Safety Population which is defined as all subjects who at least initiated the infusion with blinded study treatment.

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects are treated with a higher dose of SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo. Summary statistics will be presented for subjects who were QW successes.

### **Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).



**Table 1: Schedule of Assessments for Protocol 547-SSE-301: One Infusion of Study Drug (blinded)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical/SE/Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X	X	X	X	X	X	X	X		X		
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X		X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X		X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X		X	X		X		X		X		
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X			
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>n</sup>											X
Modified Rankin Score (mRS)	X <sup>n</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV 3rd-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>o</sup>				
EEG	X	X				X		X	X			
Randomization		X										
Study Drug Administration <sup>p</sup>			X	X	X	X	X	X				
TW Outcome & Open-label Treatment Decision										X <sup>q</sup>		
Physiologic Brain Activity									X			
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

**Table 2: Schedule of Assessments for Protocol 547-SSE-301: Two Infusions of Study Drug (one blinded, one open-label)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V3R
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	0-24h
Eligibility Checklist	X										S
Informed Consent <sup>a</sup>	X										E
Inclusion/Exclusion Criteria	X										E
Demography <sup>b</sup>	X										
Medical and SE and Wean History <sup>c</sup>	X										T
Height	X										A
Weight <sup>d</sup>	X	X	X	X	X	X	X	X		X	B
Serum Pregnancy Test <sup>e</sup>	X										L
Hematology <sup>f</sup>	X		X	X		X		X		X	E
Serum Chemistry and GFR <sup>f</sup>	X		X	X		X		X		X	
Urinalysis <sup>h</sup>	X		X	X		X		X		X	E
Pharmacogenetic sample	X										X
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X	T
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X	E
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X		N
STESS	X										I
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	O
Glasgow Outcome Score (GOS)											N
Supervision Rating Scale (SRS)	X <sup>n</sup>										
Modified Rankin Score (mRS)	X <sup>n</sup>										
Epilepsy Status	X										N
Clinical Global Impression (CGI)	X										E
Continuous IV Third-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>o</sup>			X
EEG	X	X				X		X	X		T
Randomization		X									
Study Drug Administration <sup>p</sup>			X	X	X	X	X	X			
TW Outcome and Open-label Treatment Decision										X <sup>q</sup>	P
Physiologic Brain Activity									X		
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X	A
Concomitant Anti-Epileptic Drugs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	G
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	E
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X	
Pharmacoeconomic Data											
Mortality											

**Table 2 continued**

	V3R	V4R	V5R	V6R	V7R	V8R	V9R	V10R	V11R	V12R
	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3R+14d (±2d)	V3R+21d (±2d)
Weight <sup>d</sup>	X	X	X	X	X	X				
Serum Pregnancy Test <sup>e</sup>										
Hematology <sup>f</sup>	X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X	X		X		X		X		
Vital Signs <sup>i</sup>	X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>	X	X	X	X	X	X	X			
STESS										
FOUR Score <sup>m</sup>	X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)										X
Supervision Rating Scale (SRS)										X
Modified Rankin Score (mRS)										X
Epilepsy Status										X
Clinical Global Impression Scale (CGI)										X
Continuous IV Third-Line Agent(s)	X	X	Wean	Wean	Wean	Wean <sup>o</sup>				
EEG			X			X	X			
Randomization										
Study Drug Administration <sup>p</sup>	X	X	X	X	X	X				
TW Success and Physiologic Brain Activity							X			
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data										X
Mortality										X

**Table 3: Schedule of Assessments for Protocol 547-SSE-301: Qualifying Wean Successes**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical and SE and Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X											
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X											
Serum Chemistry and GFR <sup>f</sup>	X											
Urinalysis <sup>h</sup>	X											
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X											
ECG <sup>j</sup>	X											
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>n</sup>											X
Modified Rankin Score (mRS)	X <sup>n</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV Third-Line Agent(s)	X	Wean										
EEG	X	X										
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

<sup>a</sup> Written informed consent by proxy (LAR) will be obtained prior to starting any study-related procedures not considered standard of care.

<sup>b</sup> Demographic information will be obtained by proxy and confirmed by the subject when possible.

<sup>c</sup> Medical history will be obtained by proxy and confirmed by the subject when possible. All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Dosing changes with the third-line agent(s) that constitute a wean attempt will be marked as such on the CRF, and the start/stop dates and times of all wean attempts prior to V3 will be recorded, as well as the outcome of the wean attempt.

<sup>d</sup> Weight will be collected at Screening (V1) and prior to administration of the blinded study drug infusion at V2 and the open-label study drug infusion at V10. The weights at V2 and V10 will be used to determine the appropriate infusion rate of the blinded and open-label infusions respectively. If easily obtained (such as via a scale-bed), weight will also be recorded once during each subsequent 24 hour period of the initial study drug infusion period (V3-V8) and second infusion period (V3R-V8R, if applicable).

<sup>e</sup> Serum pregnancy test for females aged 17 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy.

<sup>f</sup> Blood samples will be taken for hematology and serum chemistry and GFR calculation at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will document whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

<sup>g</sup> Blood samples will be taken at V11 or V11R for serum chemistry (renal panel only).

<sup>h</sup> Urine samples will be taken for urinalysis and NAG at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will add a comment about whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

<sup>i</sup> Vital signs will be recorded at the following time points relative to the start of each infusion of study drug: Screening (V1), at 0, 30, 60 minutes ( $\pm 15$  minutes), at 2, 4, and 8 hours ( $\pm 30$  minutes), and at 24, 48, 72, 96, 120, 144, 168, and 192 hours ( $\pm 2$  hours).

<sup>j</sup> For the first 50 subjects randomized in the study, ECG (12-lead) should be performed at Screening (V1) and at the following times relative to the start of study drug infusion. For the blinded (first) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 128, 136, 144, 152, 160, and 192 hours ( $\pm 2$  hours). For the open-label SAGE-547 (second) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 126, 132, 138, 144, 152, 160, and 192 hours ( $\pm 2$  hours). Heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours. Following randomization of the first 50 subjects, subsequent subjects randomized in the study will have ECG collected at the following timepoints: Pre-dose and at 1, 12, 24, 48, 72, 96, 120, 144, and 192 hours after the start of the blinded (first) study drug infusion; and, Pre-dose and at 1, 12, 24, 48, 72, 96, 120, 144, and 192 hours after the start of the open-label (second) study drug infusion. It is not necessary to collect these ECGs with the PK samples at these timepoints and, apart from the 1 h ECG, there is  $\pm 2$  hour time window for these ECGs.

<sup>k</sup> Plasma will be collected to assay for study drug concentrations at the following time points relative to the start of each infusion of study drug: For the blinded (first) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion. For the open-label SAGE-547 (second) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open-label SAGE-547 study drug infusion. Pre-dose samples may be taken within two hours before starting the infusion of study drug; timepoints up to and including 1h will have a time window of  $\pm 5$  minutes; all other timepoints will have a window of  $\pm 15$  minutes.

<sup>m</sup> FOUR Score assessments will be performed at Screening (V1), 24, 48, 72, 96, 120, 144, 168, and 192 hours (all  $\pm 2$  hours) relative to the start of each infusion of study drug, and at V11 or V11R, and at V12 or V12R.

<sup>n</sup> SRS at V1 will be a retrospective assessment of the supervision required by the subject immediately prior to admission that includes the index episode of the SE, and mRS at V1 will be a retrospective assessment of the disability and dependence of the subject immediately prior to admission that includes the index episode of the SE.

<sup>o</sup> Target for complete wean of all continuous IV third-line agents by 144 hours at V8/V8R if not completed by 120 hours at V7/V7R.

<sup>p</sup> Study drug infusion is intended for IV administration only with a dedicated peripheral IV line using Sage-approved IV administration bags and lines.

<sup>q</sup> At V10 only a decision to re-treat at a higher dose of SAGE-547 will be made by the Investigator if the continuous IV third-line agent wean has failed or the third-line agent requires re-introduction during V9. Subjects who become eligible for open-label study drug at a higher dose of SAGE-547 will discontinue the planned visit schedule at V10, then repeat V3 (V3R) and all applicable subsequent visits.

<sup>r</sup> AEs will be collected from the time Informed Consent is obtained and prior to the start of study-specific screening procedures not considered standard of care. Collection of AEs will continue throughout the study from V1 through V12 or V12R.

<sup>s</sup> Subjects may enter the study on AEDs and Pressors and be administered AEDs and Pressors during the study. For all randomized and the first 50 QWS subjects, all Concomitant AEDs and Pressors must be recorded on the CRF with details including date and time of starting/stopping each AED and Pressor, the route of administration, changes in doses, and

frequency of administration. Details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the CRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”. For subsequent QWS subjects, after the detailed information on all concomitant AEDs and Pressors collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant AED and Pressor and the start and stop dates and times) from Visit 3 to Visit 12 will be recorded in the eCRF.

<sup>†</sup> All third-line agents administered since the diagnosis of SE will be recorded on the CRF. For all randomized and the first 50 QWS subjects, details will include the name of the drug, the start/stop dates and times, and, after consent, the doses with start/stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R. For subsequent QWS subjects, after the detailed information on all concomitant third-line agents collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant third-line agent and the start and stop dates and times) from Visit 3 to Visit 12 will be recorded in the eCRF.

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**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
AE	adverse event
AED	anti-epileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the time-concentration curve
AW	additional weans
BDZ	benzodiazepine
BIEEG	blinded infusion electroencephalogram
BUN	blood urea nitrogen
CBC	complete blood count
CEEG	consent electroencephalogram
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
C <sub>max</sub>	maximum plasma concentration
C <sub>min</sub>	minimum plasma concentration
CNS	central nervous system
CRF	case report form
CSR	clinical study report
CYP2C9	cytochrome P450 enzyme involved in drug metabolism
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EEG	electroencephalogram
EIND	Emergency Use Investigational New Drug Application
EP	European Pharmacopeia
ESETT	Established Status Epilepticus Treatment Trial
FDA	Food and Drug Administration
FOUR	Full Outline of UnResponsiveness
GABA	$\gamma$ -aminobutyric acid
GABA <sub>A</sub>	$\gamma$ -aminobutyric acid-gated chloride channel
GCP	Good Clinical Practice

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
GFR	glomerular filtration rate
GOS	Glasgow Outcome Scale
H	hour
HPLC	high performance liquid chromatography
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent to Treat
IV	intravenous
IVRS	Interactive Voice Randomization System
LAR	legally authorized representative
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent to Treat
mRS-9Q	Modified Rankin Score - 9Q
MS/MS	tandem mass spectrometry
nM	nanomolar
NMDA	n-methyl-D-aspartic acid
OW	other weans
PAEEG	primary endpoint electroencephalogram
PD	pharmacodynamics
PK	pharmacokinetic
QOL	quality of life
QW	qualifying wean
QWEEG	qualifying wean electroencephalogram
RBC	red blood cell
RSE	refractory status epilepticus

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
SAE	serious adverse event
SAP	Statistical Analysis Plan
SE	status epilepticus
SOP	standard operating procedure
SRS	Severity Rating Scale
SRSE	Super-refractory status epilepticus
SSRI	Selective serotonin re-uptake inhibitors
STESS	Status Epilepticus Severity Score
SUSAR	Suspected Unexpected Serious Adverse Reactions
SWFI	Sterile Water for Injection
TAEEG	taper electroencephalogram
T <sub>max</sub>	time at maximum plasma concentration
TW	terminal wean
TWEEG	terminal wean electroencephalogram
US	United States
USP	United States Pharmacopeia



### 3. INTRODUCTION AND RATIONALE

#### 3.1. Status Epilepticus

Status epilepticus (SE) is a life-threatening seizure condition in which the brain is in a state of persistent seizure triggered by neuronal hyperexcitability. The Neurocritical Care Society defines SE as one continuous unremitting seizure lasting longer than five minutes or recurrent seizures without regaining consciousness between seizures for greater than five minutes (Brophy, Bell et al. 2012). Common causes of SE include preexisting epilepsy, cerebrovascular disease (in adults), electrolyte and metabolic disturbances, anoxia, encephalopathies, head trauma, high fever (in children, especially in the first year of life) and drug or substance intoxication. SE is associated with substantial morbidity and mortality.

##### 3.1.1. Epidemiology of SE

Geography, sex, age, and race influence the epidemiology of SE, whose incidence has a bimodal distribution, peaking in infants/young children and the elderly (Hauser 1990; DeLorenzo, Pellock et al. 1995; Wu, Shek et al. 2002). The incidence of SE in the elderly population is at least twice that in the general population. Concurrent medical conditions often exist in the elderly population, which can complicate therapy and worsen the prognosis of SE (Chapman, Smith et al. 2001).

The annual incidence of SE in the US is generally quoted to be within the range of 18/100,000 to 61/100,000, based on a 19-year retrospective study in Rochester, Minnesota (Hesdorffer, Logroscino et al. 1998) and a 2-year prospective study in Richmond, Virginia (DeLorenzo, Pellock et al. 1995), respectively. Two studies from Europe give annual incidences of a similar magnitude, ranging between 9.9/100,000 and 15.8/100,000 (Coeytaux, Jallon et al. 2000; Knake, Rosenow et al. 2001). It is thus estimated that in the United States each year there are as many as 150,000 cases of SE (DeLorenzo, Pellock et al. 1995).

#### 3.2. Refractory SE

When a patient begins to seize, the emergency medical technician will administer a first-line intravenous (IV) benzodiazepine (BDZ), such as diazepam, lorazepam or midazolam (Silbergleit, Durkalski et al. 2012), which is done either at the scene of the seizure or in the ambulance. If this is unsuccessful at abating the seizure, additional doses of the first-line therapy will be administered in the emergency room. Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line therapy, which is an IV anti-epileptic drug (AED) such as phenytoin or valproic acid (Novy, Logroscino et al. 2010; Shorvon 2011; Hocker, Britton et al. 2013).

Approximately 20-30% of patients refractory to first-line treatment will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to approximately 70-80% of patients who receive second-line therapy refractory to that therapy.

If a patient's SE continues after administration of BDZs and AEDs, the subject is diagnosed as having refractory status epilepticus (RSE), which must be treated quickly to terminate the seizure activity, maintain the patient's airway, and prevent cerebral damage. RSE patients are immediately admitted to the Intensive Care Unit (ICU) and placed in a medically-induced coma to stop all seizure-related activity. The drugs used to induce coma are continuously-infused IV agents,

commonly propofol, midazolam, or pentobarbital, referred to as third-line agents (Brophy, Bell et al. 2012).

The RSE patient is continually monitored using electroencephalography (EEG) to ensure that seizure and/or burst suppression is achieved. Burst suppression is a pattern of brain waves seen on an EEG, characterized by periods of activity alternating with periods of little or no activity in the brain, informing medical personnel of the effectiveness of the medically-induced coma. The goal of burst suppression is to allow the brain and corresponding neuronal tissue to restore function and reset to normal pre-seizure levels.

### **3.2.1. Epidemiology of RSE**

Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line AED therapy. In turn, approximately 20 – 30% of these patients treated with AEDs will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to 28% of the total estimated SE patient population refractory to second-line therapy. Based on the previously-cited estimated incidence in the US, this means that there are up to 42,000 incident cases of RSE in the USA, annually (DeLorenzo, Pellock et al. 1995).

## **3.3. Super-refractory SE**

After 24 hours of burst or seizure suppression, the patient is weaned off of the third-line therapy. If the weaning is unsuccessful (neuronal activity has not returned to normal), the third-line agent is re-administered or a different third-line agent is started, and the patient is considered to be in super-refractory status epilepticus (SRSE) (Chapman, Smith et al. 2001; Shorvon 2011; Brophy, Bell et al. 2012). SAGE-547 is being developed as an adjunct to third-line therapy in patients in RSE who have failed standard treatment. In this protocol, the term “RSE that has failed standard treatment” is deemed to be equivalent to the term “SRSE” and the two may be used interchangeably.

### **3.3.1. Epidemiology of SRSE**

The incidence of SRSE is very poorly understood, mainly because the diagnostic codes used for SE do not generally differentiate its nature as responding or refractory to treatment. Based on the variable reporting of outcomes data, the incident cases of SRSE could represent between one and two-thirds of the RSE patients (Novy, Logroscino et al. 2010; Ferlisi and Shorvon 2012; Hocker, Britton et al. 2013; Sutter, Marsch et al. 2013). More detailed epidemiology studies are needed to better elucidate the proportion of RSE patients whose condition becomes super-refractory. A recent review of ICU discharge data in the USA suggests an annual incidence of approximately 35,000, based on patients who required at least three days in the ICU for SE [Sage data on file].

### **3.3.2. Outcomes of SRSE**

SE has varying degrees of mortality depending on the underlying etiologies. Table 4 outlines the acute mortality in patients with SE by etiology (Neligan and Shorvon 2010). The mortality rate of SRSE is estimated to be 30% to 50% using current standard of care.

The causes of death from SE (and therefore SRSE) are heterogeneous, resulting from neuronal cell death, complications of underlying medical conditions, or adverse effects of the current standard treatments. Prognosis worsens and mortality increases with longer duration of SE, i.e. with SE that develops into RSE or SRSE (Neligan and Shorvon 2010), and with longer duration of

medically-induced coma ([Ferlisi and Shorvon 2012](#)). There is an obvious unmet medical need to improve upon the current standard of care treatment regimens.

Morbidity is high and survivors have outcomes ranging from poor function to vegetative state ([Shorvon 2011](#)). Approximately one third of patients with RSE and SRSE will recover, but with chronic neurologic or other deficits ([Neligan and Shorvon 2010](#); [Hocker, Britton et al. 2013](#)). In all, it is estimated that less than 25-30% of all SRSE patients have a favorable functional outcome.

**Table 4: Approximate Mortality of Status Epilepticus in Different Etiologies**

Underlying Etiology	Associated Acute Mortality in Patients with SE (%)
Drug reduction/withdrawal, poor AED compliance, or low AED levels	0-10
Cerebrovascular Disease	20-60
Metabolic Disorders	10-35
Acute CNS Infection	0-30
Anoxia	60-100
Alcohol Abuse	0-10
Head Trauma	0-25
Drug Overdose/Toxicity	10-25
Brain Tumors	0-20
Cryptogenic/Idiopathic	5-20

### 3.3.3. Unmet Medical Need in Super-refractory Status Epilepticus

Treatment approaches for SRSE consist of diagnosis and treatment of underlying medical conditions, adding and changing anti-seizure drugs, and repeated attempts at weaning from IV anesthetic agents. Treatment of SRSE has three aims:

- to prevent excitotoxicity, which begins within 24 hours of SE onset;
- to prevent cerebral damage by initiating neuroprotective burst or seizure suppression;
- to prevent the complications of extended periods of anesthesia or unconsciousness ([Shorvon 2011](#)).

Currently, there are no therapies that have been specifically approved for RSE or SRSE. The primary drugs used to induce coma are continuously infused IV anesthetics such as propofol, midazolam, or pentobarbital/thiopental, known as third-line agents. Use of these drugs to control SRSE has only been studied in small retrospective reviews or small prospective studies without controls ([Hocker, Britton et al. 2013](#)) therefore there is no agreement on which drug is optimal nor on an optimal dosing regimen for the treatments that are used.

The most common adverse effect of the third-line agents is hemodynamic instability; in addition, they are not universally effective, with breakthrough seizures and withdrawal seizures requiring dose adjustments and changes in third-line agent(s). The drug thought to be most effective in SRSE, pentobarbital, is also associated with the most toxic adverse effect profile, comprising

decreased blood pressure and cardiorespiratory collapse (Claassen, Hirsch et al. 2002). The ability to wean patients successfully off the third-line agents as quickly as possible is therefore paramount, and an adjunct to SRSE treatment that enhances the success of the third-line agents and supports their successful weaning in a short timeframe would be an important addition to the therapeutic armamentarium. Preliminary clinical data show that SAGE-547 has been a successful adjunct to third-line therapy in this regard.

### 3.4. SAGE-547 Injection

Allopregnanolone is an endogenous, naturally occurring neuroactive steroid formed in the corpus luteum of the ovary, adrenal cortex and central nervous system (CNS) (Holzbauer, Birmingham et al. 1985; Paul and Purdy 1992; Ottander, Poromaa et al. 2005). It is a metabolite of progesterone created by the actions of 5- $\alpha$  reductase and 3- $\alpha$  hydroxy-steroid dehydrogenase. Allopregnanolone is a potent positive allosteric modulator of both synaptic and extra-synaptic GABA<sub>A</sub> receptors.

SAGE-547 Injection (allopregnanolone aqueous formulation in Captisol<sup>®</sup>) is being developed for the treatment of patients in RSE who have not responded to standard treatment. SAGE-547 Injection is a solution of 5 mg/mL allopregnanolone in Sterile Water for Injection (SWFI), USP and 250 mg/mL betadex sulfobutyl-ether sodium, NF. It is further diluted with Sterile Water for Injection, USP (SWFI) in IV bags to achieve an allopregnanolone concentration of approximately 1.67 mg/mL in an approximately isotonic solution and will be administered intravenously.

#### 3.4.1. Scientific Rationale for SAGE-547 in SRSE

Ineffective recruitment of inhibitory neurotransmission, together with excessive neuronal excitation, likely plays a role in the initiation and propagation of the electrical disturbance occurring in SE. GABA ( $\gamma$ -aminobutyric acid), the major inhibitory neurotransmitter in the central nervous system (CNS), is released from GABAergic neurons and binds to several types of GABA receptors (GABA<sub>A</sub>, GABA<sub>B</sub>, and GABA<sub>C</sub>) on target neurons. GABA<sub>A</sub> receptors are macromolecular proteins that form a chloride ion channel complex and contain specific binding sites for GABA and a number of allosteric regulators, including barbiturates, benzodiazepines, and some anesthetic agents. GABA receptor-mediated inhibition contributes significantly to the normal termination of a seizure (Kapur and Macdonald 1997). SAGE-547 is a positive allosteric modulator of the GABA<sub>A</sub> receptor.

The importance of terminating seizure activity as soon as possible is underpinned by a growing body of evidence from research and clinical observation that SE becomes more difficult to control as its duration increases. It has been postulated that this occurs due to a mechanistic shift from inadequate GABAergic inhibitory receptor-mediated transmission to excessive N-methyl-D-aspartic acid (NMDA) excitatory receptor-mediated transmission (Kapur and Macdonald 1997). As prolonged epileptiform bursting results in a reduction of GABA<sub>A</sub>-mediated synaptic inhibition, antiepileptic treatments which rely on enhancing intrasynaptic GABA<sub>A</sub> neurotransmission become less effective the longer SE continues.

Furthermore, the constitutive process of synaptic GABA<sub>A</sub> receptor internalization is accelerated by the increased neuronal activity associated with seizures. These findings suggest that the rate of GABA<sub>A</sub> receptor internalization is regulated by neuronal activity, and its acceleration contributes to the reduction of inhibitory transmission observed during prolonged seizures (Kapur and Macdonald 1997). Of note is that SAGE-547 binds to extrasynaptic as well as intrasynaptic GABA<sub>A</sub> receptors;

extrasynaptic receptors remain active with ongoing seizure activity, resulting in a putative mode of action for SAGE-547 in SRSE.

Status epilepticus induces cerebral damage that includes neuronal cell necrosis, gliosis, and network reorganization. The major cause of cell death in cerebral damage is excitotoxicity, which is initiated by glutaminergic receptor over-activation, causing calcium to flood the cell, thereby leading to apoptosis and necrosis. This process is initiated within a few hours of the start of seizure activity, and provides the medical imperative to terminate SE as quickly as possible. To prevent the consequences of the excitotoxicity cascade, it is recommended that anesthesia be initiated within 1-2 hours of onset of seizures at doses designed to induce EEG suppression patterns (Shorvon and Ferlisi 2011).

### **3.4.2. SAGE-547 Clinical Program in the Treatment of SRSE**

The current SAGE-547 development program includes:

- a completed Phase 2 open-label trial, Study 547-SSE-201;
- this proposed Phase 3 randomized, double-blind, placebo-controlled trial, Study 547-SSE-301;
- an ongoing open-label, expanded access protocol, Study 547-SSE-302;
- a number of EINDs for SAGE-547 in patients with SRSE.

The designs of these studies are all similar, with a five to six day infusion of SAGE-547 (or placebo), during which time attempts are made to wean the subject off all third-line agents. In the Phase 3 studies, those subjects who cannot be weaned off third-line agents while being administered SAGE-547 (or placebo) may be eligible for a second open-label infusion of SAGE-547 at a higher dose. Follow up of subjects is for 21 – 30 days after the first infusion of study medication.

### **3.4.3. Data from the SAGE-547 Development Program**

The data from 30 subjects included in the on-going clinical evaluation of SAGE-547 for the treatment of adults and children with SRSE clearly offers preliminary evidence that SAGE-547 could provide substantial and clinically significant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate. These subjects comprise 20 from the ongoing Phase 2 trial (71% success rate in 12/17 evaluable subjects) and 10 subjects who received EIND treatments (78% success rate in 7/9 evaluable subjects).

Successful therapy of SRSE has been defined as “the SE is completely controlled by the therapy, without breakthrough of withdrawal seizures, or discontinuation due to side effects or death during therapy,” (Ferlisi and Shorvon 2012). By this definition, which is in accord with the efficacy assessments used in the overall clinical evaluation of SAGE-547, 19 of the 26 (73%) subjects with SRSE who completed the SAGE-547 infusion were treatment successes. As data collection is ongoing, this information is preliminary and subject to change upon further monitoring.

Published reports on RSE and SRSE have stated mortality rate ranges from 35% to 65%. The underlying etiologies of SE in the 547-SAGE-201 study and EINDs are heterogeneous, and each one conveys a different risk of mortality and longer term morbidity. However, the death rate in subjects who have received SAGE-547, 6 out of 30 (20%) subjects, appears to be lower than the published rates. None of the deaths were considered related to SAGE-547: brain tumor, organophosphate toxicity, respiratory failure, respiratory arrest due to ventilator support withdrawal, and breast cancer.

In the Phase 2 study, 20 SAEs (15 non-fatal) have been reported in 13 (65%) subjects, and of these 3 events in 2 subjects (10%) were considered by the investigator to be related to SAGE-547: pulmonary emboli and tracheostomy dehiscence/infection. The Sponsor did not consider these events to be related to SAGE-547, rather to the underlying disease states. Four of the 20 subjects (20%) experienced AEs considered possibly related to SAGE-547 by the investigator, namely moderate myopathy and severe pulmonary emboli in 1 subject, moderate tracheostomy dehiscence and tracheostomy infection in 1 subject, moderate thrombocytosis in 1 subject and moderate BUN, ALT and AST elevation in 1 subject.

Review of the most current safety data from 547-SAGE-201 reveals that there were changes in serum chemistry, hematology, and urinalysis during the study, but that none of those changes were assessed as related to SAGE-547. There were also no SAGE-547-related changes to vital signs.

Despite the heterogeneity in the underlying causes of SE, the ages of the subject, comorbidities, which normally complicate the treatment of SE, and the fact that all subjects had failed current standard of care treatment, a large majority of subjects had a successful therapy outcome, with discontinuation of all third-line agents and resolution of SE.

Refer to the Investigational Brochure for further information on the pre-clinical and clinical data supporting the use of SAGE-547 in SRSE.

### **3.5. Study Rationale - SAGE-547 in SRSE**

#### **3.5.1. Justification for the Control Group**

Although SAGE-547 has demonstrated extremely promising activity in subjects with SRSE, both in the Phase 2 study and during the EINDs, these have been open-label investigations with no control data for comparison. Generally in the literature there are few data describing the success rates of wean attempts of third-line agents, and few comparative data on the effectiveness of the three main third-line agents, propofol, pentobarbital/thiopental, and midazolam.

Several options for a control group in Study 547-SSE-301 were considered:

- No control group was thought to be unacceptable since there are no reliable published data on success rates in this population that could be used for broad comparisons;
- An active control was considered but found to be impractical since none of the third-line agents are approved for their use in SRSE, no standardized dosing regimens or treatment guidelines have been adopted for the management of SRSE, and clinicians were unlikely to agree which of the available third-line agents would be reserved for the active control arm;
- Historical controls were considered but abandoned because of the practical difficulties of obtaining high quality data, the lack of ability to prospectively match cases, and a suspicion that clinical practice in the standard of care of SRSE is evolving, mandating the use of prospective, concurrent control data;
- Comparison to standard of care alone was considered as a feasible design. However, in a field where no widely adopted treatment guidelines exist, there was a concern that knowledge of the treatment group (SAGE-547 plus standard of care versus standard of care alone) would alter the behavior of the investigators such that they could be more aggressive with weaning in the SAGE-547 group;



- Placebo control is not without its challenges since the preliminary efficacy data for SAGE-547 show that the compound exerts central pharmacological effects and is associated with positive outcomes in around 70% of patients. There is therefore a potential ethical concern about administering placebo to desperately ill patients who have often exhausted all treatment options for SRSE. This concern has been addressed in two ways: firstly all patients receive current standard of care; secondly, all subjects who fail to be weaned from their third-line agents at the end of the blinded infusion of study drug will be administered open-label SAGE-547 without un-blinding their initial treatment allocation, so treatment with the investigational product is not denied, but delayed about a week in the setting of ongoing receipt of full current standard of care.

It was therefore decided that a blinded, placebo-controlled design was appropriate for Study 547-SSE-301.

### **3.5.2. Justification for the Dose Regimen**

The standard dose regimen has been studied in 19 subjects in the 547-SSE-201 Phase 2 trial; the average peak plasma concentration of SAGE-547 at the end of the loading dose was approximately 144 ng/ml. The average plasma concentration during the maintenance infusion was approximately 70 ng/ml. At these concentrations, there were no clear safety signals although two-thirds of subjects experienced an SAE and there were four deaths, all related to the underlying comorbid conditions. The standard dosing regimen was associated with an approximate 70% successful treatment outcome. For these reasons, the standard dosing regimen has been adopted for the initial SAGE-547 infusion to be compared in a blinded fashion to placebo.

In the 547-SSE-201 trial, three subjects have thus far received the higher dose regimen. This dose regimen has also been well tolerated. The average peak plasma concentrations at the end of the loading dose for both dosing regimens will be in the same range, as the loading dose is the same for both regimens. The average plasma concentrations observed during the higher maintenance dose are 102 ng/ml (n=2). The rationale for adopting the higher dose regimen as the open-label infusion of SAGE-547 for subjects who are retreated in this 547-SSE-301 trial is that those who fail on the standard SAGE-547 dose regimen are afforded the opportunity to have access to a higher dose. The justification to also administer the higher dose regimen to failures on placebo is that the regimen has thus far been well tolerated, and this methodology preserves the blind for the initial infusion.

A five-day dosing regimen with SAGE-547 was investigated in the Phase 2 study, 547-SSE-201. There were some cases when weaning off all third-line agents was not possible within 48 hours, but weaning was completed after the end of the infusion of SAGE-547. For this reason, the duration of dosing with SAGE-547 has been increased from 120 hours (five days) in Phase 2 to 144 hours (six days) in this Phase 3 study.

### **3.5.3. Rationale for Genetic Testing Sub-study**

Sage Therapeutics intends to perform genetic research in the SAGE-547 development program in order to explore how genetic variations may affect the metabolism and activity of SAGE-547. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials, and, possibly, to genetically-guided treatment strategies for optimizing decision making with respect to individual benefit:risk. Participation of subjects in genetic research as part of the overall clinical study is optional.

### **3.6. Benefit-Risk Evaluation of the Present Study**

Previous reports of human administration of exogenous allopregnanolone indicate that for exposures in men and women up to 150 nM, the most commonly reported AEs were sedation (recorded as sleepiness or tiredness), feelings of intoxication (like alcohol), flushing, and mild headache (Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007). No SAEs were reported (Navarro, Kaddouz et al. 2003; Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007; Kask, Backstrom et al. 2008; Kask, Backstrom et al. 2009; Timby, Hedstrom et al. 2011a). In view of the reduced consciousness and sedation of study subjects at entry into this protocol, none of these previously-reported events are likely to impact subjects in this study.

To date, in the SAGE-547 Phase 2 study and the EIND subjects, a majority of subjects demonstrated a successful therapy outcome (>70%). The majority in the clinical trial (65%) have also experienced SAEs, but none has been considered related to SAGE-547 by the Sponsor (SAEs in 2 subjects (10%) were considered possibly related by Investigator). Five deaths have been reported in 30 subjects (20%), all related to the underlying cause of SRSE and not related to SAGE-547 – this is in the context of published mortality rates between 35% and 65%. These preliminary data suggest that SAGE-547 has the potential to provide clinically relevant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate.

The underlying etiologies of SE are heterogeneous, and each one conveys a different risk of mortality. Subjects who survive SRSE still have a high risk of severe morbidity (Neligan and Shorvon 2010). The subjects treated with SAGE-547 in Study 547-SSE-201, are heterogeneous in factors such as age and etiology of SE, factors that usually complicate treatment and can increase morbidity and mortality. Even with this heterogeneity, the preliminary efficacy and safety data for SAGE-547 are very encouraging, and the mortality rate suggests that the risk to benefit assessment of this treatment rests on the side of benefit.

## **4. ETHICS**

### **4.1. Institutional Review Board or Independent Ethics Committee**

This protocol will be reviewed and approved by the Institutional Review Board (IRB) where the study is conducted. The IRB will meet all FDA requirements governing IRBs (CFR, Title 21, Part 56).

### **4.2. Ethical Conduct of the Study**

The Sponsor, the Medical Monitor, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable ICH and GCP guidelines, and must also conduct the study in accordance with local regulations.

### **4.3. Subject Information and Informed Consent**

Subjects prospectively enrolled in this study will be unable to give consent. Therefore, consent will be given by proxy by a legally authorized representative (LAR) already appointed by the Court for their well-being, and closest relatives. According to Swedish Medicinal Products Act (Läkemedelslagen 1992:859), consent will be obtained by both the LAR and the closest relatives of the patients. Only patients with a previously appointed LAR by the Court will be included in the



study, providing also the closest relatives consent to the study. Written informed consent is required for each subject prior to any testing under this protocol not considered standard of care, including screening tests and evaluations. Should a subject gain the ability to sufficiently comprehend the situation and consent during the course of the study, written informed consent or verbal assent will be documented as required or recommended by the institution's IRB.

The form of consent to be obtained will depend on the condition of the subject as determined by the Principal Investigator. The informed consent form (ICF), as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50.

It is the responsibility of the Investigator to obtain consent and to provide the subject's LAR and closest relatives with a copy of the signed and dated informed consent form. The informed consent form for subject participation must also be available as part of the subject file for review by the site's dedicated study monitor or any authorized auditor of the Sponsor or regulatory authorities.

All ICFs used in this study must be approved by the appropriate IRB and by the Sponsor. The ICF must not be altered without the prior agreement of the relevant IRB and the Sponsor.

#### **4.4. Ethical and Regulatory Considerations for Pharmacogenetic Sub-study**

##### **4.4.1. Informed Consent for Pharmacogenetics**

The genetic component of this study is optional and subjects may participate in other components of the main study without having to agree to participate in the genetic component. If subject chooses to participate in the genetic component of the study, the subject or LAR and closest relatives must sign and date a specific consent form for the genetic component of the study in addition to the main study consent form. The principal investigator(s) is responsible for ensuring that consent is freely given and that the subject understands that they may discontinue from the genetic aspect of the study independent of their decision to remain within or withdrawal from the main study.

##### **4.4.2. Subject Data Protection Relative to Pharmacogenomics**

Sage Therapeutics will not provide individual genotype results to subjects, their family members, their general physician, their employer or any insurance company unless required to do so by law. While extra precautions will be taken to preserve confidentiality and to prevent genetic data from being linked to an individual's identity outside of a restricted access site, in certain exceptional situations (e.g. in case of a medical emergency or as a consequence of a specific regulatory need), certain individuals may see both genetic data and the personal identifiers of a subject; however in all cases a subject's medical information and genetic files will remain physically separated.

## **5. STUDY OBJECTIVES**

### **5.1. Primary Objective**

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult subjects with SRSE, and for the response to endure at least 24 hours after cessation of the SAGE-547 or placebo infusion (primary response).

## 5.2. Secondary Objectives

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in Clinical Global Impression Scale between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

## 5.3. Safety Objectives

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

## 5.4. Other Objectives

1. To evaluate the impact of retreatment with a higher dose of SAGE-547 infusion;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;

6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS).

## **6. ENDPOINTS**

### **6.1. Primary Endpoint**

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### **6.2. Secondary Endpoints**

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) and to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### **6.3. Safety Endpoints**

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.

### **6.4. Other Endpoints**

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who are treated with a higher dose of SAGE-547;

2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS).

## 7. INVESTIGATIONAL PLAN

### 7.1. Overview of Study Design

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

[Figure 1](#) provides an overview of the study design and [Figure 2](#) gives the details of treatment and follow-up on the active treatment arm. Patients will follow one of three paths to entry to the study. The first path is for patients who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst or seizure suppression with a third-line agent. These patients will be consented for the study after admission to the intensive care unit, before or after any third-line agents are administered for burst or seizure suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their LAR and closest relatives. Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours. Once burst or seizure suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned during the QW will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst or seizure suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The second path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst or seizure suppression pattern on the EEG. These patients may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst or seizure suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst or seizure suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst or seizure suppression has been achieved, the third-line agent or agents will

be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst or seizure suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The third path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst or seizure suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These patients may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR and closest relatives. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst or seizure suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within eight hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third line agent wean attempts prior to randomization (one vs two or more).

The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

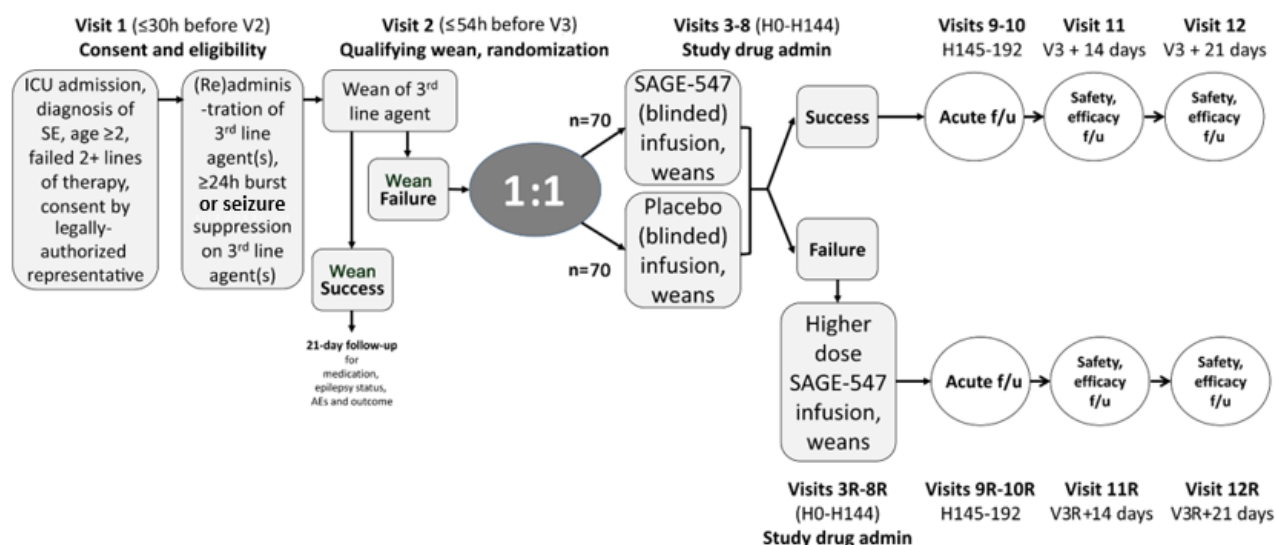
For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as the ability to wean the subject off all third-line agents before the end of the first infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication. Subjects must also have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) at the end of the primary endpoint assessment period as determined by EEG in order to be deemed a success. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#), [Table 2](#) and [Table 3](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion may be eligible to receive an open-label infusion of SAGE-547 at a dose higher than

that administered in the blinded part of the study. Eligibility for the open-label treatment must be confirmed in writing by the medical monitor prior to the open-label infusion starting. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo may all subsequently be eligible to be administered SAGE-547 at the higher dose.

**Figure 1: Study Design**



## 7.2. Trial Conduct

This study will be conducted according to the principles of the World Medical Association Declaration of Helsinki and most recent amendment, and in compliance with the protocol approved by the IRBs/Independent Ethics Committees (IECs), and in accordance with ICH Guidelines on GCP standards.

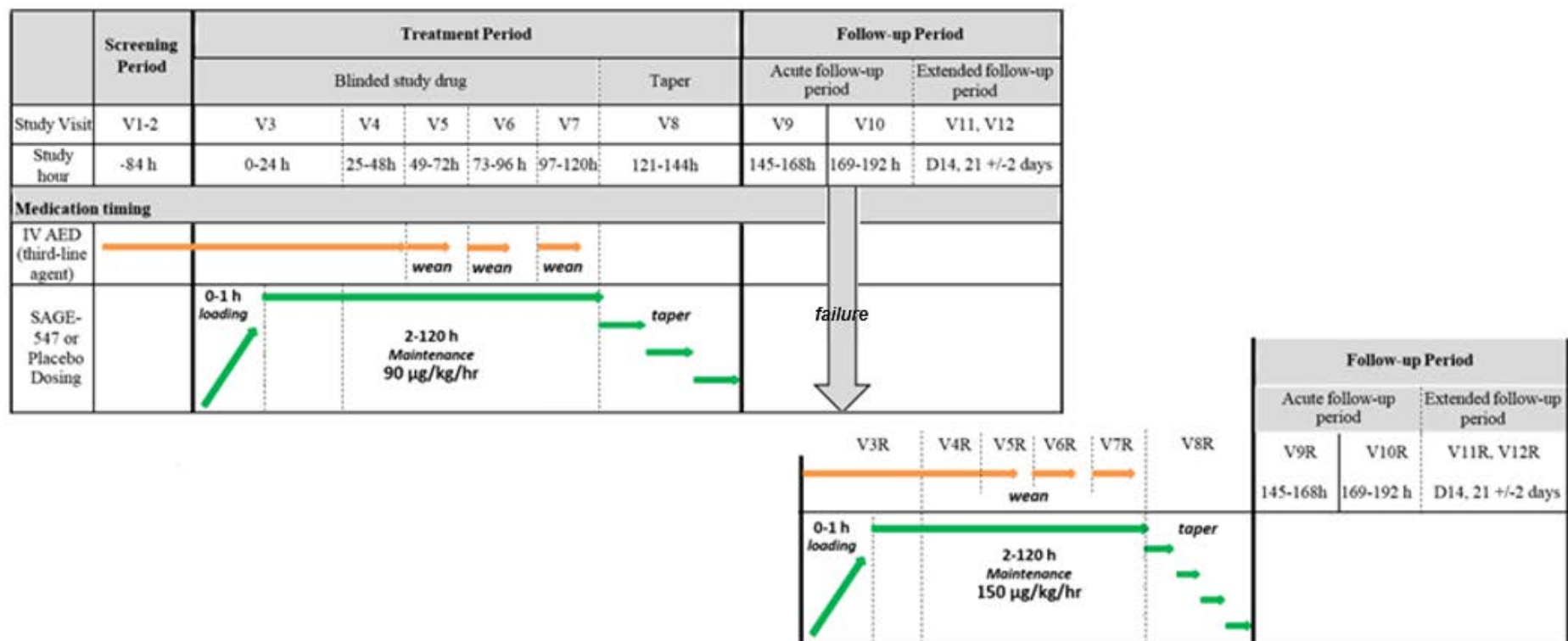
## 7.3. Blinding and Randomization

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo). Details of the dynamic randomization process will be included in the SAP.

The randomized portion of the study will be blinded, with the two treatment products (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

The second infusion of SAGE-547 will be administered on an open-label basis to subjects who meet the criteria for open-label treatment.

### Figure 2: Details of Treatment Administration and Follow-up



## 8. SELECTION AND WITHDRAWAL OF SUBJECTS

The study will randomize 140 patients at up to 180 sites. All subjects deemed eligible to enroll must have written Medical Monitor approval on a case-by-case basis prior to undertaking the qualifying wean.

### 8.1. Inclusion Criteria

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects 18 years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; *or* who have previously failed zero or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst or seizure suppression pattern; *or* who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst or seizure suppression pattern.

### 8.2. Exclusion Criteria

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy with highly malignant/malignant EEG features ([Westhall, Rosetti et al. 2016](#)).
4. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis but for whatever reason, dialysis that would adequately remove Captisol® is not planned;
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. severe hepatic impairment;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the experience of the investigator, is less than 30 days.
5. Subjects who are being administered more than three third-line agents concomitantly or for whom the qualifying wean cannot be completed within 24 hours or who are being



administered a third-line agent for indications such as raised intra-cranial pressure that would preclude weaning according to this protocol.

6. Subjects with a living will that does not allow heroic measure.
7. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
8. Subjects who have been treated or randomized in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not have received study drug/placebo and then re-enroll).

### **8.3. Selection and Consent of Subjects for Pharmacogenetic Substudy**

All subjects will be asked to participate in pharmacogenetic research; however, participation in research is voluntary and a subject can decide to decline his/her participation without penalty or loss of benefit. Participation or lack thereof will not be a cause for exclusion from any aspect of the main study. In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **8.4. Subject Withdrawal / Study Termination**

#### **8.4.1. Withdrawal/Discontinuation of Individual Subjects**

The reasons for study drug discontinuation and/or subject withdrawal from the study must be recorded in the subject's electronic case report form (eCRF). The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject has been discontinued/withdrawn due to an AE.

##### **8.4.1.1. Withdrawal from the Study**

Subjects or their LAR may withdraw subjects from the study at any time for any reason without compromising the subject's medical care. The Investigator will also withdraw subjects upon the request of Sage Therapeutics or upon termination of the study.

Subjects who withdraw from the study prior to Visit 10 (or 10R) should complete the procedures scheduled for the day of study drug taper (Hour 121-144; Visit8/8R) on the day of their withdrawal, including the SAGE-547 taper schedule, with the addition of the mortality assessment from Visit 12/12R. Subjects who withdraw from the study after Visit 10/10R should undergo study procedures as outlined for Visit 12/12R on the day of their withdrawal. In all cases, the reason for subject withdrawal will be recorded in the eCRF.

Withdrawal of subjects for any reason should be discussed with the Medical Monitor.

##### **8.4.1.2. Discontinuation of Study Drug**

If it is necessary to discontinue the study drug earlier than planned, subjects should continue to be followed per protocol to capture safety and efficacy assessments for the duration of the study period.

The investigator may withdraw the subject from the study drug for the following reasons:

- Upon subject's or LAR's request
- The subject or LAR is unwilling or unable to adhere to the protocol-specified visits
- The subject experiences an intolerable adverse event
- During the course of the study, the subject develops symptoms or conditions listed in the exclusion criteria.
- Other medical reason, at the discretion of the Investigator and/or the Medical Monitor

Subjects who discontinue the study due to an AE considered related to study drug should be followed until the event is resolved, considered stable, or the Investigator determines the event is no longer clinically significant. Study drug discontinuation due to AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

#### **8.4.2. Study Termination**

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of AEs or other findings suggesting unacceptable risk to subjects, administrative or operational reasons. In the event of study termination, Sage Therapeutics will provide written notification to the Investigator. Investigational sites must promptly notify their IRB and initiate withdrawal procedures for participating subjects.

## **9. INVESTIGATIONAL PRODUCT**

### **9.1. Identity of Investigational Product**

SAGE-547 Injection (allopregnanolone)

### **9.2. Clinical Supplies**

#### **9.2.1. SAGE-547**

Adequate supplies of SAGE-547 Injection and materials for intravenous administration will be provided to each site.

SAGE-547 Injection is a clear, colorless sterile solution of allopregnanolone intended for intravenous injection. SAGE-547 Injection is an aqueous solution of 5 mg/mL allopregnanolone in 250 mg/mL Captisol® (betadex sulfobutyl-ether sodium, NF). It is presented either un-buffered or buffered with 10 mM citrate at a pH of 6.0 in either 20 mL or 50 mL vials. SAGE-547 is further diluted according to the Pharmacy Manual to achieve an approximately isotonic solution and will be administered intravenously.

No preservatives are included in the drug product, which is intended to be used as a single-use vial. All inactive components (excipients) used in the formulation are compendial grade and conform to current USP/EP, and include sodium citrate, citric acid and betadex sulfobutyl-ether sodium (Captisol®).

#### **9.2.2. Placebo**

Placebo will be identical to SAGE-547 and presented in identical vials. Placebo will be manufactured in a similar way to SAGE-547 and comprises all excipients but no SAGE-547.

### 9.2.3. Blinding

The vials of SAGE-547 and placebo will be identical in every way so that they are indistinguishable by the pharmacist, investigator, anyone treating or managing the patient, the monitors, and the sponsor. In this way the first infusion of study drug administered to each patient will be double-blind.

For the blinded study drug infusions, subject-specific dosing kits will be provided. These dosing kits will be pre-labelled with kit number for the first blinded infusion. For the second-infusion, open-label kits will be provided, which will require subject assignment by the pharmacy for reconciliation purposes. The study kits must be stored under refrigerated conditions (2-8 °C). IV administration bags and lines may be provided for the blinded and open-label infusions. Refer to the Pharmacy Manual for additional details.

The label for the SAGE-547 Injection vials will include standard product identification information according to the Code of Federal Regulations, 21CFR 312.6. All study labels will also contain the following statement:

Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use.

### 9.3. Preparation of SAGE-547 or Placebo Injection for Dosing

The Pharmacy will be responsible for preparing the blinded and open-label study drug for subject dosing. The prepared admixture will be assigned a room temperature (20-25 °C) storage shelf life of 30 hours from time of compounding.

SAGE-547, which is hypertonic, will require dilution with SWFI to achieve an approximately isotonic solution according to the instructions provided in the Pharmacy Manual. Exactly the same procedures will be used to prepare the placebo admixture, so that all site staff remain blinded as to treatment allocation for the first infusion of study drug. SAGE-547 Injection is not intended to be administered to patients undiluted.

Refer to the Pharmacy Manual for specific instructions regarding infusion preparation.

### 9.4. Administration and Accountability

The Pharmacy will maintain accurate records of all investigational product supplies. Accurate records will be kept regarding the volume of SAGE-547 Injection or placebo used for each IV preparation, as well as the required infusion rate or rates, and the date and time of preparation. Reasons for departure from the expected dosing regimen must also be recorded. To satisfy regulatory requirements regarding drug accountability, all study medication will be reconciled in full. Refer to the Pharmacy Manual for additional details.

## 10. TREATMENT OF SUBJECTS

### 10.1. Dosing Schedule (Blinded Infusions)

SAGE-547 Injection or placebo will be administered according to the dosing schedules in [Table 5](#). The infusion rates to accomplish these µg/kg/h doses will be calculated according to the weight of the subject obtained within the eight-hour window that follows the declaration of the QW failure at V2 and prior to dosing at V3. The infusion rates will be applied to blinded study drug for the first infusion of study medication.

**Table 5: SAGE-547 or Placebo Dosing Schedule**

Hour	Type and Duration of Study Drug Infusion	Description
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	90 µg/kg/h
H121 – H128	8 hour taper	65 µg/kg/h
H129 – H136	8 hour taper	45 µg/kg/h
H137 – H144	8 hour taper	25 µg/kg/h

## 10.2. Dosing Schedule (Open-Label Infusions)

Those subjects that qualify for the open-label study drug will be administered SAGE-547 Injection will be re-administered according to the dosing schedule in Table 6. The dose will be administered on a µg/kg/h basis, and the subject's weight measured prior to dosing during V10 will be used to calculate the doses. These infusion rates will be applied to SAGE-547 treatment for the open-label second infusions of study medication.

**Table 6: SAGE-547 Open-Label Dosing Schedule**

Hour	Type and Duration of SAGE-547 Infusion	Description
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	150 µg/kg/h
H121 – H126	6 hour taper	125 µg/kg/h
H127 – H132	6 hour taper	95 µg/kg/h
H133 – H138	6 hour taper	65 µg/kg/h
H139 – H144	6 hour taper	35 µg/kg/h

## 10.3. Route of Administration

SAGE-547 Injection is intended for IV administration only. The compatibility of SAGE-547 with other drugs is unknown, and the product should be administered via a dedicated peripheral IV line using any Sage-supplied study-specific IV administration bags and lines. In order to preserve blinding, these instructions also apply to the blinded placebo infusions.

## 10.4. Treatment Period

The treatment period with double-blind SAGE-547 or placebo is six 24-hour periods (144 hours), which may encompass 6-7 calendar days. The open-label study drug treatment period is of identical duration.

## 10.5. Concomitant Medications, Procedures and Treatments

Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. For all randomized and the first 50 qualifying wean success (QWS) subjects, detailed information on all concomitant medications (concomitant AEDs, third-line agents, pressors, and other concomitant medications), procedures, and treatments should

be documented throughout the study from Screening through Visit 12/12R, as described below, and recorded on the eCRF. For subsequent QWS subjects, after the detailed information on all concomitant AEDs, pressors, third-line agents, procedures, and treatments collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant AED or pressor, third-line agent, procedure, and/or treatment, and the start and stop dates and times) from Visit 3 through Visit 12 will be recorded in the eCRF. For subsequent QWS subjects, after the detailed information on all concomitant medications collected during the screening period (Visits 1 and 2) has been recorded, only minimal information, to include the name of the concomitant medications and indication only will be recorded from Visit 3 through Visit 12.

SAGE-547 has demonstrated inhibitory effects on cytochrome P450 isoenzyme 2C9 (CYP2C9). Therefore, AEDs such as phenytoin and phenobarbital that are primarily metabolized by CYP2C9 should be closely monitored during SAGE-547 administration to ensure target exposures are maintained. A list of drugs which are inhibitors/inducers of CYP2C9 (as well as CYP2C8, CYP2C19, and CYP3A4) is provided in Appendix 7. In the absence of formal drug-drug interaction studies of SAGE-547, Investigators should ensure that co-administration is performed with caution.

#### **10.5.1. Concomitant AEDs**

Subjects may enter the study on AEDs, and be administered AEDs during the study. All of these must be recorded on the eCRF with details including date and time of starting and stopping each AED, the route of administration, changes in doses, and frequency of administration. In addition, details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the eCRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.

#### **10.5.2. Concomitant Third-Line Agents**

All third-line agents (as defined in [Section 8](#)) administered since the diagnosis of SE will be recorded on the eCRF, whatever path the patient took for entry into the study. Details will include the name of the drug, the start and stop dates and times, and, after consent, the doses with start and stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

In addition, those changes in dose that constitute a wean attempt will be marked as such on the eCRF. In this way the start and stop dates and times of all wean attempts (see [Section 11](#) for definitions) will be recorded, as will the type of wean (QW, OW, or TW) and the outcome of the wean attempt (successful, failed and dose of this third-line agent increased or failed and this third-line agent stopped and another third-line agent started). Those wean attempts that occur after the TW up to and including Visit 12/12R will be marked “AW”.

Some third-line agents (such as propofol) are also used to induce sedation to facilitate a subject’s ability to tolerate the ventilator. For subjects requiring such sedation, propofol is the preferred agent unless there are contraindications. The eCRF will make clear from the indication for the third-line agent when it is being used for burst or seizure suppression and when it is being used as ventilator support or for another purpose. The investigator will add a note to the eCRF to justify that the doses used are appropriate for sedation and not for seizure or burst suppression. The doses used for ventilator support and other similar uses are usually much lower than those used for seizure or burst suppression, and use of these third-line agents for these other purposes does not constitute a wean failure under this protocol.

### **10.5.3. Concomitant Pressors**

The start and stop dates and times of all pressors will be recorded as well as the start and stop dates and times of all dose changes.

### **10.5.4. Other Concomitant Medications**

All other concomitant medications must be recorded on the eCRF with details including date and time of starting and stopping, the route of administration, dose, and frequency of administration.

## **11. STUDY ASSESSMENTS**

### **11.1. Efficacy Assessments**

#### **11.1.1. Primary Efficacy**

Success or failure will be determined, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo infusion and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the blinded (first) infusion of SAGE-547 or placebo. In addition, subjects must have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) to be deemed to be successes. All subjects who fail to complete their infusion of randomized treatment or do not have at least one attempt during study treatment to wean off all third-line agents will be considered as “failures” for the primary endpoint.

##### **11.1.1.1. Weaning**

Third-line agents are anesthetic agents that are administered in order to reach a seizure or burst suppression EEG pattern. For the purposes of this study, third-line agents are defined as continuous intravenous infusions of pentobarbital/thiopental, midazolam, propofol, and ketamine at maintenance doses alone or in combination sufficient to produce a burst or seizure suppression pattern on the EEG. The following are considered to be minimum maintenance doses of these agents that may be expected alone or in combination to achieve EEG burst suppression. If subjects are on lower doses than these and are not in EEG burst suppression for the first 12 hours of the blinded study drug infusion, they will be considered to be protocol violators and will exit the study.

- Pentobarbital: 1 mg/kg/hour
- Thiopental: 3mg/kg/hour
- Midazolam: 0.1 mg/kg/hour
- Propofol: 3 mg/kg/hour
- Ketamine 1.2 mg/kg/hour

The timing and nature of the third-line agent weans will be guided by the Clinical Standardization Guidelines for the study, and the clinical judgment of the investigator, and will always be primarily done in the best medical interests of the subject. Advice about weaning may be sought from the Clinical Standardization Team, a group of fellow investigators with experience of performing clinical trials in subjects with SRSE. The Clinical Standardization Team will be able to discuss EEGs in real time related to key study timepoints (terminal wean and the period after the end of the

blinded study drug infusion if the terminal wean was successful) in a timely manner in order to provide advice about compliance with the Clinical Standardization Guidelines.

The following guidance for weaning applies to all weans of third-line agents undertaken during the study. Continued determined efforts to liberate subjects from sedation must be undertaken for the entire duration of the blinded study drug infusion. Each failed wean from third-line agents should be followed by a 6-24 hour period of suppression and then another wean attempt, with further optimization of the AED regimen.

Weans include the qualifying wean (QW); the terminal wean (TW), which is the wean of the third-line agent if the subject is on only one third-line agent or the wean of the last third-line agent if the subject is on more than one third-line agent; the other weans (OW), which are the weans of the third-line agents other than the TW if the subject is on more than one third-line agent. The guidance also applies to additional weans (AW), which are the weans from third-line agents that take place after the TW for the first blinded study drug infusion or the second open-label study drug infusion.

### **QW Guidance**

- Wean to be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace that third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Investigators should allow 24 hours to lapse after the end of a “successful” qualifying wean before finally declaring the QW a success. If a third-line agent needs to be re-instituted within that 24 hours, the QW is a failure, and the subject may then be randomized in the study.

### **OW Guidance**

- First OW should not begin before H49 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- If the subject is on two third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the TW. However the OW may be completed over a shorter or longer time period and may overlap if clinically indicated with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- If the subject is on three third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the wean of the second agent. The second agent should be weaned over 24 hours and that wean completed before starting the TW. However the OWs may be completed over a shorter or longer time period and may overlap if clinically indicated with each other and with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the

dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.

- All OWs should be completed before H96 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **TW Guidance**

- The TW is defined as the wean of the last third-line agent.
- If the subject is on one third-line agent, the TW should not begin before H49 and should begin no later than H97 after starting administration of study drug or starting the open-label infusion of SAGE-547. If the subject has had one or more OWs, the TW should ideally begin as soon as the last OW is complete but in any case not later than H97 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- The TW must be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace this third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Every effort must be made to complete the TW before H120 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547, but the TW must be complete before H144 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **AW Guidance**

- AWs will take place when medically indicated in the opinion of the investigator.
- Ideally the AW should take place over 24 hours, but completion may be over a shorter or longer time period than this. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.

#### **11.1.1.2. EEG**

Electroencephalographs (EEGs) that are representative of the intermittent or continuous EEG being used to support key investigator decisions will be collected at the following time points:

- A 24-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst or seizure suppression for the second path to eligibility, and a variable pattern for the third path to eligibility. This EEG also aims to capture the burst or seizure suppression pattern during the 24 hours that precede the QW. If the CEEG does not capture the 24 hours that precede the QW, additional EEG data collected as standard of care prior to the CEEG and prior to the



QW may be collected to assess the depth of burst or seizure suppression in the 24 hour period prior to the QW.

- EEG will be performed to cover the qualifying wean (QWEEG). EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for up to 24 hours after the end of the QW. The duration of the QWEEG will be up to 48.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s), the decision to re-institute a third-line agent(s) at doses intended to induce burst or seizure suppression, and the decision that the QW is a success.
- EEG will be performed from three hours prior to the start of the blinded infusion to 12 hours after the start of the blinded infusion. This will be called the BIEEG. The intent of this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG and to assess the depth of burst suppression in the first 12 hours of blinded study drug infusion.
- EEG will be performed to cover the final or terminal wean of third-line agent (TWEEG). The TW is the wean of the final third-line agent during the blinded administration of study drug or the open-label infusion of SAGE-547; if the subject was on one third-line agent, the TW is the wean of that agent. If the subject was on three third-line agents, the TW is the wean of the third and final agent. EEG recording will start 30 minutes prior to the start of the TW, continue for up to 24 hours during the TW, and then continue for the one hour after the end of the TW. The duration of the TWEEG will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the final third-line agent or the decision to re-institute a third-line agent at doses intended to induce burst or seizure suppression because any seizure activity could not be managed using intermittent bolus doses of AEDs.
- EEG will be performed during the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 (TAEEG). The TAEEG is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the start of the taper (at Hour 119.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours during the taper, and then continue for the one hour after the end of the taper (to Hour 145 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547). The duration of the TAEEG will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst or seizure suppression because any seizure activity seen during the taper could not be managed using intermittent bolus doses of AEDs.
- EEG will be obtained to cover the end of the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 and the ensuing 24-hour period, during which the primary endpoint is assessed (PAEEG). The PAEEG is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the end of taper (at Hour 143.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours after the end of the blinded administration of study treatment or the open-label infusion of SAGE-547, and then continue for the one hour after the end of the 24-hour assessment period (to Hour 169 after starting the blinded administration of study

treatment or after starting the open-label infusion of SAGE-547). The duration of the PAEEG will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst or seizure suppression because any seizure activity seen in the 24 hours following the end of the blinded administration of study treatment or the open-label infusion of SAGE-547 that could not be managed using intermittent bolus doses of AEDs.

In practice, most subjects are on continuous EEG monitoring or long periods of intermittent EEG monitoring. However, this protocol does not mandate continuous EEG monitoring and breaks from EEG monitoring to provide relief to the scalp from the irritating effects of the electrodes are advised, according to local practice. If a break in EEG monitoring is mandated by local practice guidelines at a time when one of the protocolled EEG segments is to be collected, the break in EEG monitoring will take precedence, with the reason for missing the EEG reading noted on the eCRF. The EEGs obtained for the study are therefore part of the existing EEG record rather than being obtained de-novo at each timepoint. For timepoints where there might be some ambiguity, such as the TWEEG, the final EEG record is that of the final attempt to wean the last third-line agent, even if earlier attempts to wean that agent took place. In some cases (the TAEED and PAEEG, for instance), the EEG records will overlap, but different cuts are taken to service the different EEG record requirements.

The electronic EEG file will be de-identified, the date and time of the start and stop of the EEG and the subject number will be attached to the file, and the study time point will be indicated (CEEG, QWEEG, BIEEG, TWEEG, TAEED, and PAEEG). The PI will indicate on the eCRF what the EEG shows, as follows:

- For the CEEG, the PI will describe the EEG pattern that determined which path to eligibility the subject was on.
- For the QWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure or success on the qualifying wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst or seizure suppression during the qualifying wean constitutes a failure); the QWEEG will extend to cover the 24 hours after the end of third line agents in order to confirm that the QW was a success.
- For the BIEEG, the PI will note the date and time of the start of the EEG and the pattern seen on the EEG.
- For the TWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure on the terminal wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst or seizure suppression during the terminal wean).
- For the TAEED, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst or seizure suppression before the end of the SAGE-547 infusion).
- For the PAEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary

endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst or seizure suppression in the 24 hours following the end of the SAGE-547 infusion).

A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm the depth of burst or seizure suppression prior to the QW and during the first 12 hours of the blinded study drug infusion, the PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period (average EEG power at the end of Visit 9 of more than two microvolts):

- All subjects will have the CEEG and QWEEG collected and stored, and the CEEG and QWEEG read;
- Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;
- Those subjects randomized who are not administered the open-label study drug will have the QWEEG, BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the BIEEG, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read;
- Those subjects randomized who later undergo the open-label infusion will have the QWEEG, BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion and the TWEEG, TAEED, and PAEEG related to the open-label study drug infusion collected and stored, and the BIEEG, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read.

All EEG records may be subject to quantitative EEG analysis.

### **11.1.2. Secondary Efficacy**

#### **11.1.2.1. Clinical Global Impression Scale (CGI)**

The clinical global impression scales are often utilized in clinical trials to allow clinicians to integrate several sources of information into a single rating of the subject's condition. Both the CGI-Severity (Question 1, CGI-S) and the CGI-Improvement (Question 2, CGI-I) employ a 7-point Likert scale measuring severity of the disease state in the subject and improvement, respectively. All severity assessments after initiation of SAGE-547 treatment should consider the general state of the subject over the preceding week. The third question on the scale will not be employed in this trial, and where the scale states "mental illness", this means "physical illness" in this trial.

The CGI-S will be evaluated at Visit 1 and at the last visit, Visit 12 or 12R. The CGI-I will be evaluated at Visit 12 or 12R.

#### **11.1.2.2. Epilepsy Status**

At Visit 1, the diagnosis of epilepsy will be documented as a no/yes question. If there was a previous diagnosis of epilepsy, further details will be documented, including:

- Date of diagnosis;
- Details of anti-epileptic drugs currently being taken;

- Type of epilepsy;
- Seizure frequency in the past month.

Information about the current (index) episode of status epilepticus will be obtained at Visit 1:

- Date of onset
- Date of failure to respond to first line agent(s) and the name(s) of the agent(s)
- Date of failure to respond to second line agent(s) and the name(s) of the agent(s)
- Any previous treatment with third line agents and the response to those agents (details of the third line agent drugs and previous wean attempts will be recorded on the Third Line Agent Medication CRF)
- The cause of the index episode of status epilepticus
- If the subject was transferred from another hospital or from within the hospital, the reason for the transfer will be recorded (such as for study enrollment, due to lack of medical options at original hospital or unit, due to lack of beds at the original hospital or unit, family request, other)

Previous (non-index) diagnosis of status epilepticus will be documented as a no/yes question. If SE did occur in the past 12 months, further information will be gathered, including:

- SE, RSE, or SRSE diagnosis, whichever was the most severe diagnosis for each episode;
- Cause;
- Treatment, including experimental treatments and need for intubation/ventilation;
- Dates of onset and duration.

At Visit 12 or Visit 12R, the following information will be gathered:

- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of SE up to and including Visit 12 or Visit 12R;
- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of seizures (convulsive and non-convulsive) up to and including Visit 12 or Visit 12R;
- Number of separate episodes of SE after H144 at the end of Visit 8 or Visit 8R (no/yes); if yes,
  - SE, RSE, or SRSE diagnosis;
  - Cause;
  - Treatment, including experimental treatments and need for intubation/ventilation;
  - Dates of onset and duration.

Note that a separate episode of SE is defined as an episode of SE separated from other periods of status epilepticus by at least 24 hours.

- Diagnosis of epilepsy since Visit 11 or Visit 11R will be documented as a no/yes question. If a diagnosis of epilepsy has been made, further details will be documented, including:

- Status as ongoing or new epilepsy since Visit 11 or Visit 11R after initiation of SAGE-547 treatment;
- Details of anti-epileptic drugs currently being taken;
- Type of epilepsy and seizure frequency in the past week.

## 11.2. Safety Assessments

The safety and tolerability of SAGE-547 will be assessed using adverse events, clinical laboratory measures, vital signs, ECG intervals and morphology, and mortality. All safety assessments should be performed per hospital standard of care and will be collected periodically throughout the study according to [Table 1](#), [Table 2](#), and [Table 3](#) (Schedules of Assessments).

### 11.2.1. Adverse Events

AEs will be collected after informed consent has been signed and prior to study-specific screening procedures not considered standard of care, during subject preparation for SAGE-547 administration and through Visit 12 or Visit 12R. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™) coding system (current version). See [Section 14](#) for additional details.

### 11.2.2. Clinical Laboratory Tests

Blood samples will be taken for hematology, and serum chemistry and GFR will be calculated at:

- Visit 1 and then at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.
- Blood samples will be taken at Visit 11 or Visit 11R for serum chemistry (renal panel only).

Urine samples (20 ml) will be taken for urinalysis and urine NAG analysis at:

- Visit 1 and at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.

These samples will be analyzed at a central laboratory; hour-to-hour medical decisions will be based on sampling for laboratory testing done outside the protocol as part of normal standard of care. GFR will be calculated by the central laboratory.

Any out-of-range values will be flagged by the laboratory; the investigator will add a comment about whether the abnormality is clinically significant. Clinical significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

#### 11.2.2.1. Hematology and Serum Chemistry

Hematology will include complete blood count (CBC) white blood cell count with differential, platelet count and red blood cell (RBC) count, hemoglobin and hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatine kinase,

lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose. In addition triglycerides will be measured in serum chemistry samples (to aid assessment of lipemia in pharmacokinetic samples).

#### **11.2.2.2. Pregnancy Test**

Females of child-bearing potential will be tested for pregnancy by serum pregnancy test at Visit 1. In this study, since an accurate history of menstruation in girls and menopause in older women may not be available at Visit 1, “child-bearing potential” is taken to mean any female aged 18 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy. Female subjects with a positive pregnancy test will be ineligible for study participation.

#### **11.2.2.3. Urinalysis**

Urinalysis will include assessment of protein, blood, leukocytes, glucose, ketones, urobilinogen, pH, and specific gravity.

#### **11.2.3. Vital Signs**

Blood pressure, heart rate, and temperature will be recorded at the following time points relative to the first infusion of study drug, and to the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547:

- Visit 1;
- At 0, +30, +60 minutes (+/-15 minutes) and +2, +4 and +8 hours (+/- 30 minutes) after the start of the infusion;
- At +24, +48, +72, +96, +120, +144, +168, and +192 hours (+/- 2 hours) after the start of the infusion.

#### **11.2.4. Weight and Height**

Weight and height will be measured at Visit 1. Weight will also be obtained at V2, within the eight hour window that follows the declaration of the QW failure and prior to the initiation of the blinded infusion loading dose at H0 of V3, and will be used to calculate the infusion rates throughout the entire blinded treatment course. If a subject qualifies for open-label study drug, the infusion rates for the open-label infusion will be calculated using the subject’s weight measured prior to dosing during V10.

If it is not possible to obtain the actual weight at the above-referenced timepoints, permission from the Clinical Monitor must be obtained to use another method to obtain the subject’s weight (such as information from the LAR or estimating using an established local protocol).

In addition, a daily weight will be obtained and recorded if this is easily obtained, such as the use of a scale bed.

#### **11.2.5. ECG**

For the first 50 subjects randomized in the study, 12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours. If it is not possible to

perform ECG immediately after the collection of PK samples up to 160 hours, ECG must be performed within 15 minutes prior to the collection of PK samples up to 160 hours; at other times the allowed time window for ECGs is +/- 2 hours:

- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +128, +136, +144, +152, +160, and +192 hours after the start of the blinded (first) study drug infusion
- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +126, +132, +138, +144, +152, +160, and +192 hours after the start of the open-label (second) study drug

The heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm.

For the subsequent subjects randomized in the study, the following timepoints for ECG will be used:

- pre-dose and at +1, +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the blinded (first) study drug infusion
- pre-dose and at +1, +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the open-label (second) study drug infusion

It is not necessary to collect these ECGs with the PK samples at these timepoints and, apart from the +1h ECG, there is +/- 2 hour time window for these ECGs.

#### **11.2.6. Mortality**

Mortality will be recorded on the Visit 12 or Visit 12R case report form. If the subject has died, the following information will be collected:

- Date of death;
- Cause of death.

As accurate as possible cause of death will be collected, which will be further categorized as due to one of the following causes:

- SE;
- complications of long term intubation and third-line agent infusions;
- underlying cause of qualifying SE;
- co-morbidity existing at the time of the qualifying SE;
- new co-morbidity or trauma;
- study drug;
- other (specify).

#### **11.2.7. Pharmacogenetic Samples**

If a subject's LAR and closest relatives consent to pharmacogenetic sampling, a blood sample for genetic research will be collected at Visit 1 in order to avoid the possible introduction of bias through the exclusion of patients who may withdraw from study due to an AE (a subject population that may be of specific interest for subsequent genetic analysis). If for any reason a sample cannot be taken prior to treatment, a sample can be drawn at any point prior to completion with the restriction that no more than one genetic sample be taken per subject.

The objective of this research is to collect and store blood samples for possible DNA extraction and exploratory research into how genes or specific genetic variation may influence response (i.e. distribution, safety, tolerability, and efficacy) to SAGE-547. Specific genetic variations of interest include but are not limited to: classes of metabolizing enzymes (e.g. Cytochrome P450 supra-family genes), genes encoding enzymes involved in the production and metabolism of allopregnanolone (e.g. AKR1C4 (3 $\alpha$ -hydroxysteroid dehydrogenase)), genes associated with the GABA receptor (e.g. GABRA1-A6, GABRB1-B3, GABRD, GABRE, GABRG1-3) and genes associated with the production and degradation of GABA.

Future research may suggest other genes or gene categories as candidates for influencing not only response to SAGE-547 but also susceptibility to disorders for which SAGE-547 is being evaluated. Thus, the genetic research may involve study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.

#### **11.2.7.1. Biological Sampling and Coding Procedures (Pharmacogenetics)**

To ensure patient confidentiality, utmost care will be taken in the coding and storage of pharmacogenetic samples.

*Extraction and coding:* DNA will be extracted from the blood sample and the DNA sample will be assigned a unique number replacing information from sampling tube. The assigned DNA number will be used to identify the sample and its corresponding information within Sage Therapeutics or at any designated contract laboratory for the purpose of sequencing of other DNA specific analysis. No personal details sufficient for individual identification will be available to any person (internal or external to Sage Therapeutics) working with the DNA.

*Genotype/Phenotype Analysis:* Samples and data from genetic analysis will be coded. The link between subject enrollment / randomization code and DNA number will be maintained and stored in a secure environment with restricted access. The established link will be used to identify relevant DNA samples for analysis, facilitated correlation of genotype results with clinical data, allow regulatory audit, and to trace samples for destruction in case of withdrawal of consent.

#### **11.2.7.2. Retention of Biological Samples for Pharmacogenetic Analysis**

Extracted DNA is a finite research that is destroyed in the process of being analyzed. Primary blood samples from which DNA can be extracted will be stored and used until no further analyses are possible, a maximum storage period of 25 years from time of last subject last visit has been reached, or an individual or LAR withdraws his/her or their consent.

### **11.2.8. Other Outcomes**

#### **11.2.8.1. Pharmacokinetic Data**

Formal plasma analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS)). In addition, all samples will be analyzed for important SAGE-547 metabolites (if and when these are identified) and Captisol<sup>®</sup> concentrations.

#### Plasma Analysis

Plasma will be collected to assay for SAGE-547 concentrations at the following time points relative to the start of each infusion of study drug:



- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion.
- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open-label SAGE-547 study drug infusion.
- All samples will also be analyzed for plasma concentrations of important metabolites of SAGE-547 if and when these are identified.
- All samples from the first 50 subjects randomized will also be analyzed for plasma concentrations of Captisol<sup>®</sup>.

The plasma samples will be drawn from the arm contralateral to that used for drug administration. Drawing samples from peripheral arterial or venous lines or from a central line is permissible. PK collection times should be adhered to as strictly as possible. The allowed time window for all samples is: pre-dose in the two hours prior to starting the infusion of study drug; samples up to and including 1h, +/- 5 minutes; subsequent samples, +/- 15 minutes. Subject-specific PK kits for sampling including instructions on collection and processing methods, and storage and shipping conditions, will be provided separately. To maintain the blind, all subjects will have samples taken as outlined above: subjects receiving SAGE-547 will have all samples analyzed for all analytes. Subjects on placebo may have samples analyzed to investigate endogenous allopregnanolone and metabolite concentrations, as well as Captisol<sup>®</sup> concentrations; experience with the plasma concentration data will determine if and which placebo samples are analyzed.

Each blood sample will be 3 ml in volume for subjects weighing 30 kg or more, and 1 ml in volume for subjects weighing less than 30 kg. Separate aliquots will be obtained from each sample to service the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum blood draw for PK analysis for a subject having two infusions of study drug will be 99 ml (33 ml for subjects weighing less than 30 kg).

Plasma PK parameters for SAGE-547 will be calculated where appropriate (e.g.,  $C_{max}$ ,  $C_{min}$ ,  $t_{max}$ ,  $AUC_{last}$ ,  $AUC_{\infty}$ ,  $CL_s$ ). In addition, similar PK parameters will be calculated for Captisol<sup>®</sup>. PK parameters for important metabolites of SAGE-547 may be calculated. An evaluation will be made of the feasibility of adopting a population-PK approach to assess drug-drug-interactions with SAGE-547 as victim of AEDs.

In addition, the Visit 9 sample may be analyzed for plasma concentrations of third-line agents.

#### Other Analysis

If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR and closest relatives will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations. The minimum volume of cerebrospinal fluid for analysis is 100 microlitres.

Full details of all pharmacokinetic analyses will be described in the Pharmacokinetic Analysis Plan.

**11.2.8.2. Correlation of QT/QTc Changes and Plasma Concentrations of SAGE-547**

An analysis will be performed to determine whether there is any correlation between changes in QT/QTc interval and plasma concentrations of SAGE-547, in order to investigate any effect that SAGE-547 may have on QT/QTc interval.

**11.2.8.3. Pharmacoeconomic Data**

At Visit 12 or Visit 12R, the following information will be collected: number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital. If the subject dies before Visit 12 or Visit 12R, data will be collected up to the date of death. The definition of “hospital” is the institution that the subject was initially treated in. If the subject is transferred to another hospital, that hospital would be the “discharge destination from the hospital” and the “number of days in hospital” would be the number of days in the initial treating hospital.

For those subjects discharged from hospital before Visit 12/12R, the following questions will be asked:

- On what study day was the subject discharged from hospital?
- What type of facility was the subject discharged to (another hospital, a rehabilitation center, a supported care facility, home, other)?
- How many days did the subject stay in this facility?

The following questions will be answered regarding the stay in the ICU and hospital:

- Was the subject still in the ICU at the end of Visit 10/10R?
- If the FOUR Score was  $\geq 12$  at Visit 10/10R and the subject was in the ICU at Visit 10/10R, what was the reason for the subject not being discharged from the ICU (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, other)?
- Was the subject still an in-patient in the hospital at the end of Visit 12/12R?
- If the FOUR Score was  $\geq 15$  at Visit 12/12R and the subject was in the hospital at Visit 12/12R, what was the reason for the subject not being discharged from the hospital (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, unsuitable home circumstances, other)?

**11.2.8.4. STESS**

The STESS will be assessed during Visit 1 in order to assess the severity of the status epilepticus.

**11.2.8.5. FOUR Score**

The Full Outline of UnResponsiveness or FOUR Score is designed to assess conscious level and unlike other scores, is suitable for subjects who are intubated. It assesses four domains of neurological function (eye responses, motor responses, brainstem reflexes, and breathing pattern).

The FOUR Score will be collected at the following time points relative to each infusion of study drug (the initial blinded infusion and the second open-label infusion if this is administered):

- baseline, +24, +48, +72, +96, +120, +144, +168, and +192 hours (all +/- 2 hours) after the start of the infusion, and at Visit 11/11R and Visit 12/12R.

#### **11.2.8.6. Glasgow Outcome Scale (GOS)**

The GOS is a relatively common assessment scale used to standardize descriptions of the objective degree of recovery from brain injury such as cerebral trauma, or in this case SRSE. It was first used in 1975 ([Jennett and Bond 1975](#)) and allows a prediction of the long-term course of rehabilitation to return to work and everyday life. The scale classifies subjects into 5 groups:

- Death
- Persistent vegetative state
- Severe disability
- Moderate disability
- Good recovery

The GOS will be assessed at Visit 12 or Visit 12R.

#### **11.2.8.7. Supervision Rating Scale (SRS)**

The Supervision Rating (SRS) measures the level of supervision that a patient/subject receives from caregivers. The SRS rates level of supervision on a 13-point ordinal scale that can optionally be grouped into five ranked categories (Independent, Overnight Supervision, Part-Time Supervision, Full-Time Indirect Supervision, and Full-Time Direct Supervision). The SRS was designed to be rated by a clinician based on interviews with the subject and an informant who has observed at first hand the level of supervision received by the subject ([Boake 2000](#)). Scoring is a one-step procedure in which the clinician assigns the rating that is closest to the subject's level. Ratings are based on the level of supervision received, not on how much supervision a subject is judged or predicted to need.

The SRS will be assessed at Visit 1 and Visit 12 or Visit 12R. The Visit 1 assessment will be a retrospective assessment of the supervision required by the subject immediately prior to the admission that included the index episode of status epilepticus.

#### **11.2.8.8. Modified Rankin Scale – 9Q (mRS-9Q)**

The Modified Rankin Scale (mRS) is a commonly used scale to determine disability and functional dependence due to neurological insult such as stroke in adults. The 7-point scale (0 – 6) denotes functional capacity from no symptoms (0) to severe disability (5) and death (6). The Modified Rankin Scale – 9Q is a shortened version consisting of 9 questions that reliably determines the mRS score and was developed to both simplify the assessment and expand the rater base to non- medically trained personnel ([Patel, Rao et al. 2012](#)). The assessment is a web-based tool in the public domain with automatic score calculation and error checking found at [www.modifiedrankin.com](http://www.modifiedrankin.com).

The mRS will be assessed at Visit 1 and at Visit 12 or Visit 12R. The baseline assessment will be a retrospective assessment of the disability and dependence of the subject immediately prior to the admission that included the index episode of status epilepticus.

## 12. STUDY PROCEDURES

The study procedures listed below by study day reflect the required data collection times for this protocol. When a time window is necessary, this is specified below. If no time window is specified, the test may be performed at any time within the specified 24-hour period.

### 12.1. Visit 1 (V2-≤30h)

The baseline period will be up to approximately 84 hours prior to starting blinded study treatment and should include the assessments/procedures listed below and summarized in [Table 1 and Table 2 \(for open-label treatment\)](#), the Schedules of Events.

- Informed consent
- Eligibility checklist
- Verification of inclusion/exclusion criteria.
- Demographic information and medical history obtained by proxy and confirmed by the subject when possible.
- SE and wean history
- Blood will be collected from female subjects 18 years to 55 years for a serum pregnancy test unless they are known to be pre-menstrual or post-menopausal or to have had a hysterectomy.
- Blood and urine samples collected for clinical laboratory testing.
- Pharmacogenetic sample will be collected from consenting/eligible subjects.
- Vital signs
- Height
- Weight
- An ECG reading taken.
- Administration of the STESS.
- Administration of the FOUR Score.
- Administration of SRS.
- Administration of the mRS-9Q assessment.
- Assessment of the CGI scale.
- Evaluation of epilepsy status.
- Administration of continuous IV third-line agents.
- Perform EEG.
- Recording of adverse events.
- Recording of previous and concomitant anti-epileptic drugs.
- Recording of previous and concomitant third-line agents.
- Recording of concomitant pressors.

- Recording of other concomitant medications, procedures, and treatments.

## **12.2. Visit 2 (V3-≤54h)**

- Recording of adverse events.
- Recording of concomitant anti-epileptic drugs.
- Recording of concomitant third-line agents.
- Recording of concomitant pressors.
- Recording of other concomitant medications, procedures, and treatments.
- Wean of continuous third-line agent (QW):
  - If wean is successful, subject is followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (these subjects are Qualifying Wean Success subjects or QWS subjects);
  - If wean is not successful, there is ongoing intravenous administration of at least one continuous IV third-line agent and EEG is performed and the subject is randomized.
- Weight
  - Subject weight will be obtained within the eight-hour period from the declaration of failure of QW and prior to the initiation of the blinded infusion loading dose at H0 of V3. This weight will be the dosing weight used to determine the infusion rate for the entire blinded infusion treatment course.

## **12.3. SAGE-547 Treatment Period**

### **12.3.1. Visit 3/3R (0-24 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs will be recorded at:
  - 0, +30, +60 minutes (+/-15 minutes) and +2, +4, +8 (+/- 30 minutes) and +24 hours (+/- 2 hours) after the start of the infusion
- For the first 50 subjects randomized in the study, ECG readings will be recorded immediately after PK sampling, or within 15 minutes prior to PK sampling, at the following time points:
  - 0 (pre-dose) and at +0.5, +1, +3, +6, +12, and +24 hours after the start of the blinded study drug infusion.
  - Subsequent subjects randomized in the study will have ECG readings recorded at 0 (pre-dose) and +1, +12, and +24 hours after the start of the study drug infusion, it will not be necessary to collect these ECGs with PK samples at these timepoints and, apart from the +1 h ECG, there is +/- 2 hour time window for these ECGs
- A blood sample for PK analysis should be collected at the following time points (all +/- 15 minutes except where otherwise stated):

0 (pre-dose, within two hours of the start of the infusion) and at +0.5, +1 (+/- 5 minutes), +3, +6, +12, and +24 hours after the start of the study drug infusion.

- Completion of the FOUR Score
  - +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the final declaration of QW success)
- Ongoing intravenous administration of a continuous IV third-line agent.
- Study drug administration in loading (Hour 0-1) and maintenance infusions (at completion of Hour 1).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.2. Visit 4/4R (25-48 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +48 hours (+/- 2 hours) after the start of the infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +48 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +48 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +48 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +48 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent.
- Ongoing study drug maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.3. Visit 5/5R (49-72 hours)**

- Weight if easily obtained

- Vital signs should be recorded at:
  - +72 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +72 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +72 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +72 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +72 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.4. Visit 6/6R (73-96 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +96 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +96 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +96 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +96 hours (+/- 15 minutes) after the start of study drug infusion.

- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +96 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Perform EEG.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.5. Visit 7/7R (97-120 hours)**

- Weight if easily obtained
- Vital signs should be recorded at:
  - +120 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +120 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +120 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +120 hours (+/- 15 minutes) after the start of study drug infusion, immediately prior to the end of the maintenance infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +120 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled. Complete wean by 120 hours if at all possible.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).



## 12.4. SAGE-547 Taper Period

### 12.4.1. Visit 8/8R (121-144 hours)

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +144 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after each PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +128, +136 hours and +144 hours after the start of the blinded study drug infusion
  - +126, +132, +138 hours and +144 hours after the start of the open-label study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +144 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected (+/- 15 minutes unless otherwise stated):
  - +128 (immediately prior to the end of the first taper step), +136 hours (+/- 5 minutes, immediately prior to the end of the second taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of study drug infusion.
  - During the open-label study drug phase of the study PK blood draws at: +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 hours (+/- 5 minutes, immediately prior to the end of the third taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of the study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +144 hours (+/- 2 hours) after the start of the infusion
- Complete wean of third line agents by H144 if not completed by H120.
- Perform EEG.
- Taper of SAGE-547 infusion begins at hour 121.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## **12.5. Follow-up Period**

### **12.5.1. Visit 9/9R (145-168 hours)**

- Vital signs should be recorded at:
  - +168 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +152, +160 hours (+/- 2 hours) after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +152 and +160 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +168 hours (+/- 2 hours) after the start of the infusion
- Perform EEG.
- Assessment of the presence of physiologic brain activity using EEG.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.5.2. Visit 10/10R (169-192 hours)**

- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +192 hours (+/- 2 hours) after the start of the infusion
- At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine eligibility for the open-label treatment with the higher dose of study drug. This determination may occur at any point during Visit 10: the higher dose open-label infusion must begin within the Visit 10 window. All patients receiving the higher dose open-label treatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.
- Weight if the subject qualifies for the open-label study drug (Visit 10 only, not Visit 10R).
- Recording of adverse events (QWS subjects also).

- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.3. Visit 11/11R (Visit 3/3R + 14d (±2))**

- Blood samples collected for clinical laboratory testing (renal panel only).
- Completion of the FOUR Score (QWS subjects also).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.4. Visit 12/12R (Visit 3/3R + 21d (±2))**

All assessments also performed for QWS subjects.

- Completion of the FOUR Score.
- Administration of the GOS.
- Administration of the SRS.
- Administration of the mRS-9Q assessment.
- Evaluation of epilepsy status (see [Section 11.1.2.2](#) for details).
- Assessment of the CGI Scale.
- Recording of adverse events.
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications.
- Collection of pharmacoeconomic data.
- Mortality will be assessed throughout the study period.

## **13. STATISTICS**

### **13.1. Statistical Plan**

Complete details for the analysis and reporting of data from this study will be contained in the Statistical Analysis Plan (SAP).

#### **13.1.1. Interim Analysis**

When approximately 50% of subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### 13.1.2. Study Populations

The **Safety Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to actual treatment. This analysis population will be used for all safety analyses.

The **Intent to Treat Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to randomized treatment. This analysis population will be used for all efficacy analyses.

The **Modified Intent to Treat Population** is defined as all subjects who:

1. complete their initial course of blinded SAGE-547 or placebo treatment unless the non-completion was due a drug-related adverse event; and
2. have at least one attempt to wean from third-line agents prior to the end of blinded study treatment infusion unless the failure to wean was because seizures were not controlled.

Subjects will be classified according to randomized treatment. This analysis population will be used for sensitivity analyses of the primary endpoint and select secondary efficacy endpoints.

Narratives will be prepared for all subjects who do not complete the infusion of blinded study medication or were not subjected to any wean attempts. Narratives will include details of the cause of SE, the comorbid conditions, the adverse event(s), and reasons for non-completion of the infusion or failure to attempt weaning. This blinded narrative will be reviewed by the medical monitors and the patient adjudicated as MITT eligible or ineligible. Acceptable reasons for defining a subject as MITT ineligible include death or withdrawal of consent due to progression of the underlying cause of SE or comorbid conditions, unless the cause of death or progression of disease were thought by the investigator, sponsor, or DSMB to be related to study drug.

The **Per-Protocol (PP) Population** is defined as a subset of the MITT population but will exclude data from all subjects with significant protocol violations or deviations. Subjects will be classified according to actual treatment received. This data set will be used for sensitivity analyses to examine the robustness of results for the primary and key secondary efficacy endpoints.

The **Pharmacokinetics Population** is defined as all subjects who at least had an infusion of blinded SAGE-547 initiated and have at least one pharmacokinetic sample collected.

The **Pharmacogenetic Population** is defined all subjects who consent to being included in the pharmacogenetic assessment and provide a pharmacogenetic sample.

Summary statistics of all data collected will be presented for subjects who were QW successes.

### 13.1.3. General Aspects

Tabular displays of descriptive statistics will be provided for all variables. Summary tables will include n, mean, mean, standard deviation, minimum and maximum for continuous variable and frequency and percentage for categorical variables.

### 13.1.4. Analysis of Primary Endpoint

The analysis of response to treatment (see Section 11.1.1 for definition of primary endpoint) between SAGE-547 treated subjects and placebo treated subjects will be performed on the ITT population using a Cochran-Mantel-Haenszel (CMH) test with variables for treatment, concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior

to randomization (one vs two or more). The CMH general association statistic and its associated p-value will be presented. The comparison of treatment response rates will be conducted at the 5% level of significance. To confirm the CMH results, a permutation test will also be conducted.

An additional analysis of the primary endpoint will also be performed on the MITT population. In addition sensitivity analyses of the primary endpoint will be performed using the ITT population based on:

- the number of third-line agents (one, two, or three) subjects were administered post-randomization; and
- which third line agent was the subject of the first TW.

### **13.1.5. Analysis of Secondary Efficacy Endpoints**

Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section ([Section 6](#)). Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. The analysis of the secondary endpoints will also be performed on the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

### **13.1.6. Analysis of Other Endpoints**

Safety and “Other” endpoints will only be summarized by treatment group.

Summaries of safety endpoints will be based on the overall Safety Population.

### **13.1.7. Epilepsy and SRSE Status**

Diagnosis of epilepsy and recurrence of RSE or SRSE will be documented as the percentage of subjects by time point and overall. Kaplan-Meier curves may be plotted if sufficient data are available.

Utilization of AEDs during follow-up and during recurrence will be summarized.

### **13.1.8. Questionnaires**

The data collected from each questionnaire will be interpreted according to the standard methodology for that questionnaire. There will be no adjustment for missing values.

### **13.1.9. Pharmacokinetic Data Analysis**

Details of the pharmacokinetic data analysis will be described in detail in a separate Pharmacokinetic Analysis Plan.

### **13.1.10. Pharmacogenetic Data Analysis**

Any genotype data generated in this study will be stored within a secured database within Sage Therapeutics and / or a third party contracted to work with Sage Therapeutics to analyze the samples. Because the number of subjects agreeing to participate in the genetic research component of the study is unknown, it is not possible to establish, a priori, whether sufficient samples will be obtained to support formal statistical evaluation of data. As a consequence a Pharmacogenetic Analysis Plan will only be prepared where appropriate and the results obtained from any genetic research will be reported in a report separate from the main study CSR.

### **13.1.11. Open-Label Study Drug Subjects**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are treated with SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo.

### **13.1.12. EEG-Responders**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who are classified as EEG-responders/non-responders based on the independent assessment of the PAEEG. Summaries will be derived for the two randomized treatment groups.

### **13.1.13. QT/QTc Assessment**

An analysis of the correlation between changes in QT/QTc intervals and SAGE-547 plasma levels will be performed to investigate if there is a potential effect that SAGE-547 may have on QT/QTc interval. A detailed description of the QT/QTc assessment will be included in the SAP.

### **13.1.14. Quantitative EEG**

The nine EEG records for each subject may be subjected to exploratory quantitative EEG analysis, the details of which will be included in the EEG Analysis Plan. In summary the following comparisons may be made, SAGE-547 versus placebo: the QWEEG versus the TWEEG (main analysis); the CEEG versus PAEEG (subsidiary analysis); and TAEEG versus PAEEG (exploratory analysis).

## **13.2. Determination of Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between treatment groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

### **13.3. Statistical Analysis Plan**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

## **14. ADVERSE EVENTS**

The safety procedures in this study will be detailed in a Safety Management Plan, which will be agreed and signed before the first subject is randomized in the study. [Section 14.1](#) summarizes Investigator responsibilities regarding the identification and documentation of AEs, the classification of AEs for relationship to study drug and severity, and the reporting of AE information to the Sponsor and the IRB.

[Section 14.2](#) summarizes Sponsor/Medical Monitor Responsibilities regarding monitoring of AE data and reporting relevant safety information to FDA.

[Section 14.3](#) lists important AE definitions.

### **14.1. Investigator Responsibilities**

#### **14.1.1. Identification and Documentation of Adverse Events by Investigator**

Subjects will be evaluated and questioned generally (if possible) to identify AEs during the course of the study. AEs will be collected from the signature of the consent form through Visit 12/12R. Adverse events that occur prior to completion of screening will be captured on the Medical History eCRF. Adverse events that occur after completion of screening will be recorded on the Adverse Event eCRF.

All AEs revealed by observation, other diagnostic procedures, or spontaneously reported by the subject and/or in response to an open question from study personnel will be recorded on the Adverse Event Form. Any clinically significant deterioration in laboratory assessments or other clinical findings are considered an AE and must be recorded on the Adverse Event Form, unless otherwise stated. AE information recorded will be entered into the database on an ongoing basis.

AEs with a relationship considered related to study drug (probable, possible) should be followed until the event is resolved or the Investigator determines the event is stable or no longer clinically significant. AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

For SAEs, an electronic Serious Adverse Event eCRF must be completed with as much information as possible and submitted in the time frame described below in [Section 14.1.3](#). When new significant information is obtained as well as when the outcome of an event is known, the electronic SAE eCRF should be updated within 24 hours. If the subject was an outpatient at the time of the SAE and was re-hospitalized due to the SAE, a copy of relevant hospital records (e.g., admission report, laboratory test results, discharge summary, etc.) may be requested to be included as part of the subject medical file.

All SAEs will be followed until resolved or until a stable status has been achieved.



**14.1.2. Adverse Event Classification****14.1.2.1. Relationship to Investigational Drug**

None:	No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state.
Possible:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject, but this is not known for sure.
Probable:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

**14.1.2.2. Severity**

Mild	Discomfort noticed, but no disruption to daily activity.  For subjects that are unconscious, this may be a slight or minor change in a lab result or clinical sign or symptom that does not require immediate corrective action.
Moderate	Discomfort sufficient to reduce or affect normal daily activity, but is not hazardous to health; prescription drug therapy may be employed to treat the AE.  For subjects that are unconscious, this may be a clinically meaningful change that may require immediate corrective action.
Severe	Inability to work or perform normal daily activity and represented a definite hazard to health; prescription drug therapy and/or hospitalization may be employed to treat the AE.  For unconscious subjects, this may be a significant clinical change that requires immediate corrective action.

**14.1.2.3. Action Taken with Investigational Drug**

None	Study medication was continued without change.
Discontinued	Study medication was terminated.
Dose adjusted	Study medication dose/infusion rate was changed and then continued per protocol.
Interrupted	Study medication was interrupted and then continued per protocol.
Unknown	The action taken with regard to study medication is unknown.
Not applicable	Administration of study medication was not ongoing.

**14.1.2.4. Assessment of Outcome**

Ongoing	At the end of the study, the event has not resolved or stabilized.
Ongoing and stable	The event is ongoing but has stabilized and is unlikely to change
Resolved	The event has resolved or the subject recovered without sequelae.
Resolved with sequelae	The event has at least one secondary outcome that may result in permanent disability and/or functional limitation.
Unknown	The status of the event is unknown.
Death	The subject has expired.

**14.1.3. Investigator Reporting to Sponsor and Sponsor Emergency Contact**

All new SAEs that come to the Investigator and/or Sponsor's notice during the course of the study (up to and including the last study visit) must be reported by the Investigator on the designated electronic report form within 24 hours of the point in time when the Investigator becomes aware of the SAE. As additional information becomes available, the designated electronic report form must be updated within 24 hours.

Investigators must report any SAE, whether or not considered drug related. The report must include an assessment of whether there is a reasonable possibility that the drug caused the event.

In a medical emergency (ie, an event that requires immediate attention regarding the treatment of a subject, operation of the clinical study, and/or the use of investigational drug), study site staff will apply appropriate medical intervention according to current standards of care, and contact the Medical Monitor.

**14.1.4. Medical Monitor and Emergency Contact Information**

[REDACTED], MD  
[REDACTED]

In a study related medical emergency situation, when the assigned Medical Monitor cannot be reached by a caller, an on-call Physician can be reached 24 hours per day, 7 days per week via an [REDACTED] Call-Center:

- Telephone: [REDACTED]  
(this is a chargeable telephone number allowing a global reach from both landlines and mobile phones)

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On this internet page a list of country-specific toll-free telephone numbers is provided. It should be noted that not all countries globally have access to toll-free numbers as indicated on the “24/7 Medical Help desk” index. Countries without toll-free numbers need to dial the chargeable number as indicated above. Furthermore, toll-free numbers are not available from mobile phones.

#### **14.1.5. SAE Reporting Contact Information**

Contact information and reporting instructions are provided in the Safety Management Plan.

#### **14.1.6. Reporting to Institutional Review Boards (IRBs)**

It is the responsibility of the Investigator to promptly notify the institution’s IRB of all serious and unexpected suspected adverse reactions (see [Section 14.3](#) for definitions).

### **14.2. Sponsor/Medical Monitor Responsibilities**

#### **14.2.1. Monitoring of Adverse Event Data**

The Medical Monitor will review any newly reported adverse events in an ongoing basis. If the aggregate assessment indicates that an event is occurring more frequently than would normally be expected in this population, or as previously observed, and the sponsor believes that the events are causally related to the administration of SAGE-547, the Sponsor will then report that information in an IND safety report.

#### **14.2.2. Data Safety Monitoring Board**

An independent DSMB will monitor the clinical, PK and PD data for safety signals throughout the study and will be asked to assess the placebo response rate at the time of the interim analysis to determine final sample size. In order to perform their monitoring function the DSMB will have access to un-blinded safety data as necessary.

The composition and procedures for the board will be described in a separate DSMB Charter.

#### **14.2.3. Reporting to FDA**

The Sponsor must report in an IND safety report any suspected adverse reaction to study treatment that is both serious and unexpected (21 CFR 312.32(c)(1)(i)). Before submitting an IND safety report, the Sponsor will ensure the event meets all three of the definitions: (1) suspected adverse reaction, (2) serious, (3) unexpected. If the AE does not meet all three of the definitions, it should not be submitted as an IND safety report. The Sponsor should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the adverse event and, therefore, that the event meets the definition of a suspected adverse reaction.

If there is a serious and unexpected suspected adverse reaction, the Sponsor will notify the appropriate regulatory agency(ies) and all appropriate parties on an expedited basis. In addition, Sponsors must submit expedited reports of an increased rate of occurrence or severity of serious suspected adverse reactions over that listed in the protocol or Investigational Brochure.

SUSARs will be unblinded prior to reporting to FDA. Unless it is necessary to unblind for the safety of the patient, the investigator will not be informed of the unblinding of the subject.

Under 21 CFR 312.32, Sponsors should identify in the protocol SAEs that it does not plan to report individually in an expedited manner, because they are known consequences of the disease or otherwise common in the study population. Given the grave condition and prognosis of SRSE being studied, individual occurrences of seizures or seizure activity will not be reported expeditiously in this study. Regardless of which events are reported in an expedited manner, all adverse events will be closely monitored throughout the study.

#### **14.2.4. Reporting to European Regulatory Authorities**

The Sponsor or its designee is responsible for SUSAR notification to the relevant regulatory authorities as outlined in the ICH Guidelines. All investigators participating in the study will also be informed as required by regulations.

Any SUSAR is subject to expedited reporting in the EU. The Sponsor or its designee, will report any single SUSAR to the appropriate National CAs and IECs within 7 days if the SUSAR is life-threatening or fatal (with the relevant follow-up information subsequently communicated within an additional eight days), and within 15 days if the SUSAR is neither life-threatening nor fatal. SUSARs reported will be those that have arisen in the present clinical trial and SUSARs that have arisen in other clinical trials conducted by the Sponsor with the same medicinal product.

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to competent authorities of the concerned Member States and to IEC(s)/IRBs as required by national laws.

### **14.3. Adverse Event Definitions**

#### **14.3.1. Adverse Event**

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

#### **14.3.2. Suspected Adverse Reaction**

Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

#### **14.3.3. Life-Threatening**

An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

#### **14.3.4. Serious**

An AE or suspected adverse reaction is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE – see definition above
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disability
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

#### **14.3.5. Unexpected**

An AE or suspected adverse reaction is considered “unexpected”:

- If it is not listed in the Investigational Brochure or is not listed at the specificity or severity that has been observed, or
- If an Investigational Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigational Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigational Brochure listed only cerebral vascular accidents.

“Unexpected,” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigational Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

#### **14.4. Emergency Identification of Study Medication**

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject’s treatment in the study via the IVRS; this normally requires prior approval by the medical monitor. However, if the subject is at immediate risk and the Investigator believes that immediate knowledge of the study treatment will alter medical management, discussion with the medical monitor may take place after unblinding. The Investigator will not unblind the medical monitor during that discussion. The process of unblinding will ensure that only the investigator is unblinded; the medical monitor, study management team, and data management team will not be made aware of the treatment allocation of an individual subject. All

cases of emergency unblinding will be fully documented in a way that does not unblind the medical monitor, study management team, and data management team.

## **15. STUDY ADMINISTRATIVE CONSIDERATIONS**

### **15.1. Quality Control and Quality Assurance**

The Investigators and institutions will permit trial related monitoring, audits, IRB review, and regulatory inspections as requested by FDA, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed informed consent forms, etc.) in addition to case report forms.

Quality assurance and quality control systems with written standard operating procedures (SOPs) will be followed to ensure this trial will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The site's dedicated study monitor will arrange to visit the Investigator at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be identified and resolved. The study monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality assurance officers named by Sage Therapeutics or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements, made by the Sponsor with the Investigator/institution and any other parties involved with the clinical trial, will be in writing in a separate agreement.

### **15.2. Data Handling and Recordkeeping**

#### **15.2.1. Data Handling**

Procedures for data handling (including electronic data) used in this protocol will be documented in a Data Management Plan.

#### **15.2.2. Case Report Form Completion**

eCRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of demographics, study drug administration, study procedures, AEs, questionnaire completion, efficacy assessments and subject status, including survival.

The Investigator will maintain copies of the eCRFs at the study site. For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate eCRF.

### **15.2.3. Retention of Study Records**

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval and until there are no pending or contemplated marketing applications or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to an appropriate person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

## **15.3. Confidentiality**

To maintain subject privacy, all eCRFs, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available trial registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by Sage Therapeutics to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

## **15.4. Publication Policy**

All information concerning SAGE-547 is considered confidential and shall remain the sole property of Sage Therapeutics. The Investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval from Sage Therapeutics. No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between Sage Therapeutics and the Investigator.

## **15.5. Protocol Amendments**

Changes to the conduct of the study should be prepared as a protocol amendment by the Sponsor. Protocol amendments should receive written IRB/IEC approval prior to implementation at the investigative site, except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the trial (eg, change of monitor, telephone numbers). In this case, Sage Therapeutics will amend and implement the protocol change

and subsequently notify the regulatory authorities and the Investigative sites who will notify the respective IRB, as appropriate.



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**APPENDIX 1. APPENDIX 1: FOUR SCORE****FOUR score****Full Outline of UnResponsiveness****Eye response**

- E4: eyelids open or opened, tracking, or blinking to command
- E3: eyelids open but not tracking
- E2: eyelids closed but open to loud voice
- E1: eyelids closed but open to pain
- E0: eyelids remain closed with pain

**Motor response**

- M4: thumbs-up, fist or peace sign
- M3: localizing to pain
- M2: flexion response to pain
- M1: extension response to pain
- M0: no response to pain or generalized myoclonus status

**Brainstem reflexes**

- B4: pupil and corneal reflexes present
- B3: one pupil wide and fixed
- B2: pupil or corneal reflexes absent
- B1: pupil and corneal reflexes absent
- B0: absent pupil, corneal and cough reflex

**Respiration pattern**

- R4: not intubated, regular breathing pattern
- R3: not intubated, Cheyne-Stokes breathing pattern
- R2: not intubated, irregular breathing
- R1: breathes above ventilatory rate
- R0: breathes at ventilator rate or apnea

Reference ([Iyer, Hoel et al. 2009](#)).

**APPENDIX 2. GLASGOW OUTCOME SCALE (GOS)****GLASGOW  
OUTCOME  
SCALE**

Patient Name: \_\_\_\_\_  
 Rater Name: \_\_\_\_\_  
 Date: \_\_\_\_\_

*Note:* The scale presented here is based on the original article by Jennett and Bond. It has become common practice in clinical trial administration, however, to use a modified version that places the scores in reverse order (i.e., "good recovery" = 1, "moderate disability" =2, etc.).

Score	Description
1	DEATH
2	PERSISTENT VEGETATIVE STATE Patient exhibits no <i>obvious cortical</i> function.
3	SEVERE DISABILITY (Conscious but disabled). Patient depends upon others for daily support due to mental or physical disability or both.
4	MODERATE DISABILITY (Disabled but independent). Patient is independent as far as daily life is concerned. The disabilities found include varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes.
5	GOOD RECOVERY Resumption of normal activities even though there may be minor neurological or psychological deficits.

**TOTAL (1-5):** \_\_\_\_\_

Reference ([Jennett and Bond 1975](#)).

## APPENDIX 3. SUPERVISION RATING SCALE (SRS)

### SUPERVISION RATING SCALE (SRS)

**Instructions:** Circle the rating that is closest to the amount of supervision that the patient *actually receives*. "Supervision" means that someone is responsible for being with the patient.

<u>Rating</u>	<u>Description</u>
<b>Level 1: INDEPENDENT</b>	
1	The patient lives alone or independently. Other persons can live with the patient, but they cannot take responsibility for supervision (for example, a child or elderly person).
2	The patient is unsupervised overnight. The patient lives with one or more persons who <i>could</i> be responsible for supervision (for example, a spouse or roommate), but they are <i>all</i> sometimes absent overnight.
<b>Level 2: OVERNIGHT SUPERVISION</b>	
3	The patient is only supervised overnight. One or more supervising persons are always present overnight but they are <i>all</i> sometimes absent for the rest of the day.
<b>Level 3: PART-TIME SUPERVISION</b>	
4	The patient is supervised overnight and part-time during waking hours, but is allowed on independent outings. One or more supervising persons are always present overnight and are also present during part of waking hours every day. However, the patient is sometimes allowed to leave the residence without being accompanied by someone who is responsible for supervision.
5	The patient is supervised overnight and part-time during waking hours, but is unsupervised during working hours. Supervising persons are <i>all</i> sometimes absent for enough time for them to work full-time outside the home.
6	The patient is supervised overnight and during most waking hours. Supervising persons are <i>all</i> sometimes absent for periods longer than one hour, but less than the time needed to hold a full-time job away from home.
7	The patient is supervised overnight and during almost all waking hours. Supervising persons are <i>all</i> sometimes absent for periods shorter than one hour.
<b>Level 4: FULL-TIME INDIRECT SUPERVISION</b>	
8	The patient is under full-time indirect supervision. At least one supervising person is <i>always</i> present, but the supervising person does not check on the patient more than once every 30 minutes.
9	Same as #8 plus requires overnight safety precautions (for example, a deadbolt on outside door).
<b>Level 5: FULL-TIME DIRECT SUPERVISION</b>	
10	The patient is under full-time direct supervision. At least one supervising person is always present and the supervising person checks on the patient more than once every thirty minutes.
11	The patient lives in a setting in which the exits are physically controlled by others (for example, a locked ward).
12	Same as #11 plus a supervising person is designated to provide full-time line-of-sight supervision (for example, an escape watch or suicide watch).
13	The patient is in physical restraints.

3/12/93

Corwin Boake, Ph.D., TIRR, 1333 Moursund, Houston, TX 77030-3405, 713/799-6990

## APPENDIX 4. MODIFIED RANKIN SCALE – LEVEL OF FUNCTION SURVEY (mRS-9Q)

1. Do you have any symptoms that are bothering you? (For example, trouble with reading or writing, trouble speaking, problems with vision, numbness, weakness, balance trouble, or problems with swallowing?)	YES	<input type="radio"/>	NO	<input type="radio"/>
2. Are you able to do the same work as before?	YES	<input type="radio"/>	NO	<input type="radio"/>
3. Are you able to keep up with your hobbies?	YES	<input type="radio"/>	NO	<input type="radio"/>
4. Have you maintained your ties to friends and family?	YES	<input type="radio"/>	NO	<input type="radio"/>
5. Do you need help making a simple meal, doing household chores, or balancing a checkbook?	YES	<input type="radio"/>	NO	<input type="radio"/>
6. Do you need help with shopping or traveling close to home?	YES	<input type="radio"/>	NO	<input type="radio"/>
7. Do you need another person to help you walk?	YES	<input type="radio"/>	NO	<input type="radio"/>
8. Do you need help with eating, going to the toilet, or bathing?	YES	<input type="radio"/>	NO	<input type="radio"/>
9. Do you stay in bed most of the day and need constant nursing care?	YES	<input type="radio"/>	NO	<input type="radio"/>

## APPENDIX 5. CLINICAL GLOBAL IMPRESSION (CGI)

### Clinical Global Impression (CGI)

#### 1. Severity of illness

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- |                             |   |
|-----------------------------|---|
| 0 = Not assessed            | 4 = Moderately ill                        |
| 1 = Normal, not at all ill  | 5 = Markedly ill                          |
| 2 = Borderline mentally ill | 6 = Severely ill                          |
| 3 = Mildly ill              | 7 = Among the most extremely ill patients |

#### 2. Global improvement: Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.

Compared to his condition at admission to the project, how much has he changed?

- |                        |                     |
|------------------------|---------------------|
| 0 = Not assessed       | 4 = No change       |
| 1 = Very much improved | 5 = Minimally worse |
| 2 = Much improved      | 6 = Much worse      |
| 3 = Minimally improved | 7 = Very much worse |

#### 3. Efficacy index: Rate this item on the basis of drug effect only.

Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.

EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect		Side effects			
		None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
<b>Marked</b>	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
<b>Moderate</b>	Decided improvement. Partial remission of symptoms	05	06	07	08
<b>Minimal</b>	Slight improvement which doesn't alter status of care of patient	09	10	11	12
<b>Unchanged or worse</b>		13	14	15	16

Not assessed = 00

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

**APPENDIX 6. STATUS EPILEPTICUS SEVERITY SCORE (STESS)**

Outcome Predictor	Feature	Score
Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type (prior to first treatment)	Simple-partial, complex-parial, absence, myoclonic (complicating idiopathic generalized epilepsy)	0
	Generalized-convulsive	1
	Nonconvulsive status epilepticus in coma	2
Age	< 65 years	0
	≥ 65 years	2
History of previous seizures	Yes	0
	No or unknown	1
Summed Total		



**APPENDIX 7. LIST OF INHIBITORS/INDUCERS AT SELECTED CYPS**

Although there exists no universally accepted list of cytochrome P450 inhibitors categorized according to potency, Indiana University does maintain a table of clinically relevant cytochrome P450 inhibitors which does provide a potency classification (*Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). "/clinpharm/ddis/clinical-table/" Accessed 22FEB2016*). According to this resource, the medications that should be administered cautiously with SAGE-547 are:

- gemfibrozil (CYP2C8)
- fluconazole (CYP2C9)
- indinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, and nefazodone (CYP3A4).

**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY  
TO EVALUATE THE EFFICACY AND SAFETY OF SAGE-547 INJECTION  
IN THE TREATMENT OF SUBJECTS WITH SUPER-REFRACTORY  
STATUS EPILEPTICUS**

**PROTOCOL NUMBER: 547-SSE-301**

**IND NUMBER: 117901**

**EudraCT Number: 2015-002142-31**

Product: SAGE-547 Injection (allopregnanolone)

Sponsor Contact: [REDACTED], MD

Sage Therapeutics  
215 First Street  
Cambridge, MA 02142

Medical Monitor: [REDACTED], MD

Date of Protocol: 09 March 2015

Date of Amendment One 27 May 2015

Date of Amendment Two (Adults Only) 17 November 2015

Date of Amendment Two (Adults Only, Germany Specific) 05 July 2016

Date of Amendment Three (Adults Only, Germany Specific [not implemented]) 22 April 2016

Date of Amendment Four (Adults Only, Germany Specific) 12 September 2016

**Confidentiality Statement**

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

**PROTOCOL NUMBER: 547-SSE-301**

Sponsor [REDACTED]:

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

CRO [REDACTED]:

[REDACTED]

## 1. SIGNATURE PAGE

Title of Protocol:

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus

Protocol No: 547-SSE-301

### Sponsor Approval

[Redacted Signature]

13 SEP 2016

[Redacted Signature] MD

Date (dd/mmm/yyyy)

Sage Therapeutics

[Redacted Signature]

13 Sep 2016

Date (dd/mmm/yyyy)

[Redacted Signature]

Sage Therapeutics

[Redacted Signature]

13 Sep 2016

Date (dd/mmm/yyyy)

[Redacted Signature] MPH

Sage

[Redacted Signature]

14 SEP 2016

Date (dd/mmm/yyyy)

[Redacted Signature]

Sage Therapeutics

**Investigator Agreement**

By signing this page I attest that I have read and understand the contents of Clinical Protocol 547-SSE-301 and any current amendments. I agree to adhere to the design, conduct, and reporting requirements of the study as stated in the clinical protocol and to my obligations to the Sponsor as described in the protocol and executed contracts between myself, my Institution, and the Sponsor. I also agree to adhere to any subsequent amendments to the clinical protocol.

Investigator's Signature: \_\_\_\_\_

Investigator's Name: \_\_\_\_\_

Institution: \_\_\_\_\_

Date: \_\_\_\_\_

## 2. SYNOPSIS

<b>Name of Sponsor:</b> Sage Therapeutics 215 First Street Cambridge, MA 02142																							
<b>Protocol No.</b> 547-SSE-301	<b>Phase:</b> 3																						
<b>Name of Investigational Product:</b> SAGE-547 Injection																							
<b>Name of Active Ingredient:</b> Allopregnanolone																							
<b>Title of the Protocol:</b> A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus																							
<b>Dosing Regimen: SAGE-547 or Placebo Dosing Schedule</b> <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 10px;"> <thead> <tr> <th style="width: 20%;">Hour</th> <th style="width: 40%;">Type and Duration of SAGE-547 Infusions</th> <th style="width: 40%;">Dose</th> </tr> </thead> <tbody> <tr> <td>H1</td> <td>One hour loading Infusion</td> <td>300 µg/kg/h</td> </tr> <tr> <td>H2 – H120</td> <td>119 hour maintenance infusion</td> <td>90 µg/kg/h</td> </tr> <tr> <td>H121 – H128</td> <td>8 hour taper</td> <td>65 µg/kg/h</td> </tr> <tr> <td>H129 – H136</td> <td>8 hour taper</td> <td>45 µg/kg/h</td> </tr> <tr> <td>H137 – H144</td> <td>8 hour taper</td> <td>25 µg/kg/h</td> </tr> </tbody> </table>			Hour	Type and Duration of SAGE-547 Infusions	Dose	H1	One hour loading Infusion	300 µg/kg/h	H2 – H120	119 hour maintenance infusion	90 µg/kg/h	H121 – H128	8 hour taper	65 µg/kg/h	H129 – H136	8 hour taper	45 µg/kg/h	H137 – H144	8 hour taper	25 µg/kg/h			
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<b>Study Sites</b> Up to 180 sites in the USA, Israel, Europe, and Canada.																							

<p><b>Number of Subjects</b></p> <p>The study will randomize 140 subjects at up to 180 sites.</p>
<p><b>Study Population</b></p> <p>Subjects will be aged 18 years or more, in SRSE<sup>1</sup> (as defined in the Inclusion Criteria <a href="#">Section 8.1</a>), and being managed in an intensive care setting.</p>
<p><b>Duration of Subject Involvement</b></p> <p>Individual subject participation will be up to 30 days.</p>
<p><b>Study Design</b></p> <p>This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.</p> <p>Patients will follow one of three paths to entry to the study. The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst or seizure suppression with a third-line agent. These subjects will be consented for the study after admission to the intensive care unit, but before or after any third-line agents are administered for burst or seizure suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their legally authorized representative (LAR). Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours. Once burst or seizure suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.</p> <p>The second path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst or seizure suppression pattern on the EEG. These subjects may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst or seizure suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst or seizure suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to</p>

<sup>1</sup> In this study, the term Super-Refractory Status Epilepticus or SRSE is equivalent to “Refractory Status Epilepticus (RSE) that has failed standard treatment” and the two terms are used interchangeably.

concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The third path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst or seizure suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These subjects may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 treatment or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within eight hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo).

The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that subjects, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as both the ability to wean the subject off all third-line agents before the end of the infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication infusion, and concurrent signs of physiologic brain activity as determined by EEG. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#) and [Table 2](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo will all subsequently be eligible to be administered SAGE-547 at the higher dose.

## Visit Schedule



The visit schedule and an overview of events at each visit is provided in [Table 1](#), [Table 2](#) and [Table 3](#) Schedule of Assessments.

## **Study Objectives**

### ***Primary objective:***

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult subjects with SRSE, and for the response to endure at least 24 hours after the end of the SAGE-547 or placebo infusion (primary response).

### ***Secondary objectives:***

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in the Clinical Global Impression scale (CGI) between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### ***Safety objectives:***

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

### ***Other objectives:***

1. To evaluate the impact of treatment with a higher dose SAGE-547 infusion;

2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;
6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS).

## Endpoints

### *Primary endpoint:*

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### *Secondary endpoints:*

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### *Safety endpoints:*

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;

## 5. Mortality.

**Other endpoints:**

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who are treated with a higher dose of SAGE-547.
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol<sup>®</sup> and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS).

**Inclusion Criteria**

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects 18 years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed zero, one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst or seizure suppression pattern; or who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst or seizure suppression pattern.

**Exclusion Criteria**

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone or any excipients in SAGE-547.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy with highly malignant/malignant EEG features ([Westhall, Rosetti et al. 2016](#)).

4. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis but for whatever reason, dialysis that would adequately remove Captisol<sup>®</sup> is not planned;
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the opinion of the investigator, of less than 30 days.
5. Subjects who are being administered more than three third-line agents concomitantly or in whom the qualifying wean cannot be completed within 24 hours, or who are being administered a third-line agent for other indications such as management of raised intra-cranial pressure that would preclude weaning according to this protocol.
6. Subjects with a living will that does not allow heroic measures.
7. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
8. Subjects who have been treated or randomized in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not have received study drug/placebo and then re-enroll).

### **Pharmacogenetic Research**

In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **Statistical Analysis**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

### **Interim Analysis**

When approximately 50% of the subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### **Analysis of Primary Endpoint**

The analysis of response to treatment between SAGE-547 treated subjects and placebo treated subjects will be performed using a Cochran-Mantel-Haenszel test with variables for treatment, concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). In this analysis, a treatment responder is a subject who is successfully

weaned off all third-line agents and blinded study medication prior to the end of study treatment infusion and remains off third-line agents for at least 24 hours following cessation of the blinded study medication, and who has concurrent signs of physiologic brain activity as determined by EEG. The analysis will be based on the ITT Population. The comparison of treatment response rates will be conducted at the 5% level of significance.

### **Analysis of Secondary Efficacy Endpoints**

The primary analysis will be repeated for the MITT population. Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section. Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. Secondary analyses will be repeated for the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from Baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third-line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

Summaries of safety endpoints will be based on the overall Safety Population which is defined as all subjects who at least initiated the infusion with blinded study treatment.

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who are treated with a higher dose of SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo. Summary statistics will be presented for subjects who were QW successes.

### **Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

**Table 1: Schedule of Assessments for Protocol 547-SSE-301: One Infusion of Study Drug (blinded)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical/SE/Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X	X	X	X	X	X	X	X		X		
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X		X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X		X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X		X	X		X		X		X		
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X			
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>n</sup>											X
Modified Rankin Score (mRS)	X <sup>n</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV 3rd-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>o</sup>				
EEG	X	X				X		X	X			
Randomization		X										
Study Drug Administration <sup>p</sup>			X	X	X	X	X	X				
TW Outcome & Open-Label Treatment Decision										X <sup>q</sup>		
Physiologic Brain Activity									X			
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

**Table 2: Schedule of Assessments for Protocol 547-SSE-301: Two Infusions of Study Drug (one blinded, one open-label)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V3R
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	0-24h
Eligibility Checklist	X										S
Informed Consent <sup>a</sup>	X										E
Inclusion/Exclusion Criteria	X										E
Demography <sup>b</sup>	X										
Medical and SE and Wean History <sup>c</sup>	X										T
Height	X										A
Weight <sup>d</sup>	X	X	X	X	X	X	X	X		X	B
Serum Pregnancy Test <sup>e</sup>	X										L
Hematology <sup>f</sup>	X		X	X		X		X		X	E
Serum Chemistry and GFR <sup>f</sup>	X		X	X		X		X		X	
Urinalysis <sup>h</sup>	X		X	X		X		X		X	E
Pharmacogenetic sample	X										X
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X	T
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X	E
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X		N
STESS	X										I
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	O
Glasgow Outcome Score (GOS)											N
Supervision Rating Scale (SRS)	X <sup>n</sup>										
Modified Rankin Score (mRS)	X <sup>n</sup>										
Epilepsy Status	X										N
Clinical Global Impression (CGI)	X										E
Continuous IV Third-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>o</sup>			X
EEG	X	X				X		X	X		T
Randomization		X									
Study Drug Administration <sup>p</sup>			X	X	X	X	X	X			
TW Outcome and Open-Label Treatment Decision										X <sup>q</sup>	P
Physiologic Brain Activity									X		
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X	A
Concomitant Anti-Epileptic Drugs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	G
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	E
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X	
Pharmacoeconomic Data											
Mortality											

**Table 2 continued**

	V3R	V4R	V5R	V6R	V7R	V8R	V9R	V10R	V11R	V12R
	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3R+14d (±2d)	V3R+21d (±2d)
Weight <sup>d</sup>	X	X	X	X	X	X				
Serum Pregnancy Test <sup>e</sup>										
Hematology <sup>f</sup>	X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X	X		X		X		X		
Vital Signs <sup>i</sup>	X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>	X	X	X	X	X	X	X			
STESS										
FOUR Score <sup>m</sup>	X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)										X
Supervision Rating Scale (SRS)										X
Modified Rankin Score (mRS)										X
Epilepsy Status										X
Clinical Global Impression Scale (CGI)										X
Continuous IV Third-Line Agent(s)	X	X	Wean	Wean	Wean	Wean <sup>o</sup>				
EEG			X			X	X			
Randomization										
Study Drug Administration <sup>p</sup>	X	X	X	X	X	X				
TW Success and Physiologic Brain Activity							X			
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data										X
Mortality										X



**Table 3: Schedule of Assessments for Protocol 547-SSE-301: Qualifying Wean Successes**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical and SE and Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X											
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X											
Serum Chemistry and GFR <sup>f</sup>	X											
Urinalysis <sup>h</sup>	X											
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X											
ECG <sup>j</sup>	X											
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>n</sup>											X
Modified Rankin Score (mRS)	X <sup>n</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV Third-Line Agent(s)	X	Wean										
EEG	X	X										
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

<sup>a</sup> Written informed consent by proxy (LAR) will be obtained prior to starting any study-related procedures not considered standard of care.

<sup>b</sup> Demographic information will be obtained by proxy and confirmed by the subject when possible.

<sup>c</sup> Medical history will be obtained by proxy and confirmed by the subject when possible. All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Dosing changes with the third-line agent(s) that constitute a wean attempt will be marked as such on the CRF, and the start/stop dates and times of all wean attempts prior to V3 will be recorded, as well as the outcome of the wean attempt.

<sup>d</sup> Weight will be collected at Screening (V1) and prior to administration of the blinded study drug infusion at V2 and the open-label study drug infusion at V10. The weights at V2 and V10 will be used to determine the appropriate infusion rate of the blinded and open-label infusions respectively. If easily obtained (such as via a scale-bed), weight will also be recorded once during each subsequent 24 hour period of the initial study drug infusion period (V3-V8) and second infusion period (V3R-V8R, if applicable).

<sup>e</sup> Serum pregnancy test for females aged 18 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy.

<sup>f</sup> Blood samples will be taken for hematology and serum chemistry and GFR calculation at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will document whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

<sup>g</sup> Blood samples will be taken at V11 or V11R for serum chemistry (renal panel only).

<sup>h</sup> Urine samples will be taken for urinalysis and NAG at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will add a comment about whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

<sup>i</sup> Vital signs will be recorded at the following time points relative to the start of each infusion of study drug: Screening (V1), at 0, 30, 60 minutes ( $\pm 15$  minutes), at 2, 4, and 8 hours ( $\pm 30$  minutes), and at 24, 48, 72, 96, 120, 144, 168, and 192 hours ( $\pm 2$  hours).

<sup>j</sup> For the first 50 subjects randomized in the study, ECG (12-lead) should be performed at Screening (V1) and at the following times relative to the start of study drug infusion. For the blinded (first) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 128, 136, 144, 152, 160, and 192 hours ( $\pm 2$  hours). For the open-label SAGE-547 (second) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 126, 132, 138, 144, 152, 160, and 192 hours ( $\pm 2$  hours). Heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours. If it is not possible to perform ECG immediately after PK sampling up to 160 hours, ECG must be performed within 15 minutes prior to PK sampling up to 160 hours. Following randomization of the first 50 subjects, subsequent subjects randomized in the study will have ECG collected at the following timepoints: Pre-dose and at 1, 12, 24, 48, 72, 96, 120, 144, and 192 hours after the start of the blinded (first) study drug infusion; and, Pre-dose and at 1, 12, 24, 48, 72, 96, 120, 144, and 192 hours after the start of the open-label (second) study drug infusion. It is not necessary for to collect these ECGs with the PK samples at these timepoints and, apart from the 1 h ECG, there is  $\pm 2$  hour time window for these ECGs.

<sup>k</sup> Plasma will be collected to assay for study drug concentrations at the following time points relative to the start of each infusion of study drug: For the blinded (first) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion. For the open-label SAGE-547 (second) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open-label SAGE-547 study drug infusion. Pre-dose samples may be taken within two hours before starting the infusion of study drug; timepoints up to and including 1h will have a time window of  $\pm 5$  minutes; all other timepoints will have a window of  $\pm 15$  minutes.

<sup>m</sup> FOUR Score assessments will be performed at Screening (V1), 24, 48, 72, 96, 120, 144, 168, and 192 hours (all  $\pm 2$  hours) relative to the start of each infusion of study drug, and at V11 or V11R, and at V12 or V12R.

<sup>n</sup> SRS at V1 will be a retrospective assessment of the supervision required by the subject immediately prior to admission that includes the index episode of the SE, and mRS at V1 will be a retrospective assessment of the disability and dependence of the subject immediately prior to admission that includes the index episode of the SE.

<sup>o</sup> Target for complete wean of all continuous IV third-line agents by 144 hours at V8/V8R if not completed by 120 hours at V7/V7R.

<sup>p</sup> Study drug infusion is intended for IV administration only with a dedicated peripheral IV line using Sage-approved IV administration bags and lines.

<sup>q</sup> At V10 only a decision to re-treat at a higher dose of SAGE-547 will be made by the Investigator if the continuous IV third-line agent wean has failed or the third-line agent requires re-introduction during V9. Subjects who become eligible for open-label study drug at a higher dose of SAGE-547 will discontinue the planned visit schedule at V10, then repeat V3 (V3R) and all applicable subsequent visits.

<sup>r</sup> AEs will be collected from the time Informed Consent is obtained and prior to the start of study-specific screening procedures not considered standard of care. Collection of AEs will continue throughout the study from V1 through V12 or V12R.

<sup>s</sup> Subjects may enter the study on AEDs and Pressors and be administered AEDs and Pressors during the study. For all randomized and the first 50 QWS subjects, all Concomitant AEDs and Pressors must be recorded on the CRF with details including date and time of starting/stopping each AED and Pressor, the route of administration, changes in doses, and

frequency of administration. Details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the CRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”. For subsequent QWS subjects, after the detailed information on all concomitant AEDs and Pressors collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant AED and Pressor and the start and stop dates and times) from Visit 3 to Visit 12 will be recorded in the eCRF.

<sup>†</sup> All third-line agents administered since the diagnosis of SE will be recorded on the CRF. For all randomized and the first 50 QWS subjects, details will include the name of the drug, the start/stop dates and times, and, after consent, the doses with start/stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R. For subsequent QWS subjects, after the detailed information on all concomitant third-line agents collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant third-line agent and the start and stop dates and times) from Visit 3 to Visit 12 will be recorded in the eCRF.

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**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
AE	adverse event
AED	anti-epileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the time-concentration curve
AW	additional weans
BDZ	benzodiazepine
BIEEG	blinded infusion electroencephalogram
BUN	blood urea nitrogen
CBC	complete blood count
CEEG	consent electroencephalogram
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
C <sub>max</sub>	maximum plasma concentration
C <sub>min</sub>	minimum plasma concentration
CNS	central nervous system
CRF	case report form
CSR	clinical study report
CYP2C9	cytochrome P450 enzyme involved in drug metabolism
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EEG	electroencephalogram
EIND	Emergency Use Investigational New Drug Application
EP	European Pharmacopeia
ESETT	Established Status Epilepticus Treatment Trial
FDA	Food and Drug Administration
FOUR	Full Outline of UnResponsiveness
GABA	$\gamma$ -aminobutyric acid
GABA <sub>A</sub>	$\gamma$ -aminobutyric acid-gated chloride channel
GCP	Good Clinical Practice

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
GFR	glomerular filtration rate
GOS	Glasgow Outcome Scale
H	hour
HPLC	high performance liquid chromatography
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent to Treat
IV	intravenous
IVRS	Interactive Voice Randomization System
LAR	legally authorized representative
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent to Treat
mRS-9Q	Modified Rankin Score - 9Q
MS/MS	tandem mass spectrometry
nM	nanomolar
NMDA	n-methyl-D-aspartic acid
OW	other weans
PAEEG	primary endpoint electroencephalogram
PD	pharmacodynamics
PK	pharmacokinetic
QOL	quality of life
QW	qualifying wean
QWEEG	qualifying wean electroencephalogram
RBC	red blood cell
RSE	refractory status epilepticus

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
SAE	serious adverse event
SAP	Statistical Analysis Plan
SE	status epilepticus
SOP	standard operating procedure
SRS	Severity Rating Scale
SRSE	Super-refractory status epilepticus
SSRI	Selective serotonin re-uptake inhibitors
STESS	Status Epilepticus Severity Score
SUSAR	Suspected Unexpected Serious Adverse Reactions
SWFI	Sterile Water for Injection
TAEEG	taper electroencephalogram
T <sub>max</sub>	time at maximum plasma concentration
TW	terminal wean
TWEEG	terminal wean electroencephalogram
US	United States
USP	United States Pharmacopeia

### 3. INTRODUCTION AND RATIONALE

#### 3.1. Status Epilepticus

Status epilepticus (SE) is a life-threatening seizure condition in which the brain is in a state of persistent seizure triggered by neuronal hyperexcitability. The Neurocritical Care Society defines SE as one continuous unremitting seizure lasting longer than five minutes or recurrent seizures without regaining consciousness between seizures for greater than five minutes (Brophy, Bell et al. 2012). Common causes of SE include preexisting epilepsy, cerebrovascular disease (in adults), electrolyte and metabolic disturbances, anoxia, encephalopathies, head trauma, high fever (in children, especially in the first year of life) and drug or substance intoxication. SE is associated with substantial morbidity and mortality.

##### 3.1.1. Epidemiology of SE

Geography, sex, age, and race influence the epidemiology of SE, whose incidence has a bimodal distribution, peaking in infants/young children and the elderly (Hauser 1990; DeLorenzo, Pellock et al. 1995; Wu, Shek et al. 2002). The incidence of SE in the elderly population is at least twice that in the general population. Concurrent medical conditions often exist in the elderly population, which can complicate therapy and worsen the prognosis of SE (Chapman, Smith et al. 2001).

The annual incidence of SE in the US is generally quoted to be within the range of 18/100,000 to 61/100,000, based on a 19-year retrospective study in Rochester, Minnesota (Hesdorffer, Logroscino et al. 1998) and a 2-year prospective study in Richmond, Virginia (DeLorenzo, Pellock et al. 1995), respectively. Two studies from Europe give annual incidences of a similar magnitude, ranging between 9.9/100,000 and 15.8/100,000 (Coeytaux, Jallon et al. 2000; Knake, Rosenow et al. 2001). It is thus estimated that in the United States each year there are as many as 150,000 cases of SE (DeLorenzo, Pellock et al. 1995).

#### 3.2. Refractory SE

When a patient begins to seize, the emergency medical technician will administer a first-line intravenous (IV) benzodiazepine (BDZ), such as diazepam, lorazepam or midazolam (Silbergleit, Durkalski et al. 2012), which is done either at the scene of the seizure or in the ambulance. If this is unsuccessful at abating the seizure, additional doses of the first-line therapy will be administered in the emergency room. Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line therapy, which is an IV anti-epileptic drug (AED) such as phenytoin or valproic acid (Novy, Logroscino et al. 2010; Shorvon 2011; Hocker, Britton et al. 2013).

Approximately 20-30% of patients refractory to first-line treatment will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to approximately 70-80% of patients who receive second-line therapy refractory to that therapy.

If a patient's SE continues after administration of BDZs and AEDs, the subject is diagnosed as having refractory status epilepticus (RSE), which must be treated quickly to terminate the seizure activity, maintain the patient's airway, and prevent cerebral damage. RSE patients are immediately admitted to the Intensive Care Unit (ICU) and placed in a medically-induced coma to stop all seizure-related activity. The drugs used to induce coma are continuously-infused IV agents,

commonly propofol, midazolam, or pentobarbital, referred to as third-line agents (Brophy, Bell et al. 2012).

The RSE patient is continually monitored using electroencephalography (EEG) to ensure that seizure and/or burst suppression is achieved. Burst suppression is a pattern of brain waves seen on an EEG, characterized by periods of activity alternating with periods of little or no activity in the brain, informing medical personnel of the effectiveness of the medically-induced coma. The goal of burst suppression is to allow the brain and corresponding neuronal tissue to restore function and reset to normal pre-seizure levels.

### **3.2.1. Epidemiology of RSE**

Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line AED therapy. In turn, approximately 20 – 30% of these patients treated with AEDs will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to 28% of the total estimated SE patient population refractory to second-line therapy. Based on the previously-cited estimated incidence in the US, this means that there are up to 42,000 incident cases of RSE in the USA, annually (DeLorenzo, Pellock et al. 1995).

## **3.3. Super-refractory SE**

After 24 hours of burst or seizure suppression, the patient is weaned off of the third-line therapy. If the weaning is unsuccessful (neuronal activity has not returned to normal), the third-line agent is re-administered or a different third-line agent is started, and the patient is considered to be in super-refractory status epilepticus (SRSE) (Chapman, Smith et al. 2001; Shorvon 2011; Brophy, Bell et al. 2012). SAGE-547 is being developed as an adjunct to third-line therapy in patients in RSE who have failed standard treatment. In this protocol, the term “RSE that has failed standard treatment” is deemed to be equivalent to the term “SRSE” and the two may be used interchangeably.

### **3.3.1. Epidemiology of SRSE**

The incidence of SRSE is very poorly understood, mainly because the diagnostic codes used for SE do not generally differentiate its nature as responding or refractory to treatment. Based on the variable reporting of outcomes data, the incident cases of SRSE could represent between one and two-thirds of the RSE patients (Novy, Logroscino et al. 2010; Ferlisi and Shorvon 2012; Hocker, Britton et al. 2013; Sutter, Marsch et al. 2013). More detailed epidemiology studies are needed to better elucidate the proportion of RSE patients whose condition becomes super-refractory. A recent review of ICU discharge data in the USA suggests an annual incidence of approximately 35,000, based on patients who required at least three days in the ICU for SE [Sage data on file].

### **3.3.2. Outcomes of SRSE**

SE has varying degrees of mortality depending on the underlying etiologies. Table 4 outlines the acute mortality in patients with SE by etiology (Neligan and Shorvon 2010). The mortality rate of SRSE is estimated to be 30% to 50% using current standard of care.

The causes of death from SE (and therefore SRSE) are heterogeneous, resulting from neuronal cell death, complications of underlying medical conditions, or adverse effects of the current standard treatments. Prognosis worsens and mortality increases with longer duration of SE, i.e. with SE that develops into RSE or SRSE (Neligan and Shorvon 2010), and with longer duration of

medically-induced coma ([Ferlisi and Shorvon 2012](#)). There is an obvious unmet medical need to improve upon the current standard of care treatment regimens.

Morbidity is high and survivors have outcomes ranging from poor function to vegetative state ([Shorvon 2011](#)). Approximately one third of patients with RSE and SRSE will recover, but with chronic neurologic or other deficits ([Neligan and Shorvon 2010](#); [Hocker, Britton et al. 2013](#)). In all, it is estimated that less than 25-30% of all SRSE patients have a favorable functional outcome.

**Table 4: Approximate Mortality of Status Epilepticus in Different Etiologies**

Underlying Etiology	Associated Acute Mortality in Patients with SE (%)
Drug reduction/withdrawal, poor AED compliance, or low AED levels	0-10
Cerebrovascular Disease	20-60
Metabolic Disorders	10-35
Acute CNS Infection	0-30
Anoxia	60-100
Alcohol Abuse	0-10
Head Trauma	0-25
Drug Overdose/Toxicity	10-25
Brain Tumors	0-20
Cryptogenic/Idiopathic	5-20

### 3.3.3. Unmet Medical Need in Super-refractory Status Epilepticus

Treatment approaches for SRSE consist of diagnosis and treatment of underlying medical conditions, adding and changing anti-seizure drugs, and repeated attempts at weaning from IV anesthetic agents. Treatment of SRSE has three aims:

- to prevent excitotoxicity, which begins within 24 hours of SE onset;
- to prevent cerebral damage by initiating neuroprotective burst or seizure suppression;
- to prevent the complications of extended periods of anesthesia or unconsciousness ([Shorvon 2011](#)).

Currently, there are no therapies that have been specifically approved for RSE or SRSE. The primary drugs used to induce coma are continuously infused IV anesthetics such as propofol, midazolam, or pentobarbital/thiopental, known as third-line agents. Use of these drugs to control SRSE has only been studied in small retrospective reviews or small prospective studies without controls ([Hocker, Britton et al. 2013](#)) therefore there is no agreement on which drug is optimal nor on an optimal dosing regimen for the treatments that are used.

The most common adverse effect of the third-line agents is hemodynamic instability; in addition, they are not universally effective, with breakthrough seizures and withdrawal seizures requiring dose adjustments and changes in third-line agent(s). The drug thought to be most effective in SRSE, pentobarbital, is also associated with the most toxic adverse effect profile, comprising



decreased blood pressure and cardiorespiratory collapse (Claassen, Hirsch et al. 2002). The ability to wean patients successfully off the third-line agents as quickly as possible is therefore paramount, and an adjunct to SRSE treatment that enhances the success of the third-line agents and supports their successful weaning in a short timeframe would be an important addition to the therapeutic armamentarium. Preliminary clinical data show that SAGE-547 has been a successful adjunct to third-line therapy in this regard.

### 3.4. SAGE-547 Injection

Allopregnanolone is an endogenous, naturally occurring neuroactive steroid formed in the corpus luteum of the ovary, adrenal cortex and central nervous system (CNS) (Holzbauer, Birmingham et al. 1985; Paul and Purdy 1992; Ottander, Poromaa et al. 2005). It is a metabolite of progesterone created by the actions of 5- $\alpha$  reductase and 3- $\alpha$  hydroxy-steroid dehydrogenase. Allopregnanolone is a potent positive allosteric modulator of both synaptic and extra-synaptic GABA<sub>A</sub> receptors.

SAGE-547 Injection (allopregnanolone aqueous formulation in Captisol<sup>®</sup>) is being developed for the treatment of patients in RSE who have not responded to standard treatment. SAGE-547 Injection is a solution of 5 mg/mL allopregnanolone in Sterile Water for Injection (SWFI), USP and 250 mg/mL betadex sulfobutyl-ether sodium, NF. It is further diluted with Sterile Water for Injection, USP (SWFI) in IV bags to achieve an allopregnanolone concentration of approximately 1.67 mg/mL in an approximately isotonic solution and will be administered intravenously.

#### 3.4.1. Scientific Rationale for SAGE-547 in SRSE

Ineffective recruitment of inhibitory neurotransmission, together with excessive neuronal excitation, likely plays a role in the initiation and propagation of the electrical disturbance occurring in SE. GABA ( $\gamma$ -aminobutyric acid), the major inhibitory neurotransmitter in the central nervous system (CNS), is released from GABAergic neurons and binds to several types of GABA receptors (GABA<sub>A</sub>, GABA<sub>B</sub>, and GABA<sub>C</sub>) on target neurons. GABA<sub>A</sub> receptors are macromolecular proteins that form a chloride ion channel complex and contain specific binding sites for GABA and a number of allosteric regulators, including barbiturates, benzodiazepines, and some anesthetic agents. GABA receptor-mediated inhibition contributes significantly to the normal termination of a seizure (Kapur and Macdonald 1997). SAGE-547 is a positive allosteric modulator of the GABA<sub>A</sub> receptor.

The importance of terminating seizure activity as soon as possible is underpinned by a growing body of evidence from research and clinical observation that SE becomes more difficult to control as its duration increases. It has been postulated that this occurs due to a mechanistic shift from inadequate GABAergic inhibitory receptor-mediated transmission to excessive N-methyl-D-aspartic acid (NMDA) excitatory receptor-mediated transmission (Kapur and Macdonald 1997). As prolonged epileptiform bursting results in a reduction of GABA<sub>A</sub>-mediated synaptic inhibition, antiepileptic treatments which rely on enhancing intrasynaptic GABA<sub>A</sub> neurotransmission become less effective the longer SE continues.

Furthermore, the constitutive process of synaptic GABA<sub>A</sub> receptor internalization is accelerated by the increased neuronal activity associated with seizures. These findings suggest that the rate of GABA<sub>A</sub> receptor internalization is regulated by neuronal activity, and its acceleration contributes to the reduction of inhibitory transmission observed during prolonged seizures (Kapur and Macdonald 1997). Of note is that SAGE-547 binds to extrasynaptic as well as intrasynaptic GABA<sub>A</sub> receptors;

extrasynaptic receptors remain active with ongoing seizure activity, resulting in a putative mode of action for SAGE-547 in SRSE.

Status epilepticus induces cerebral damage that includes neuronal cell necrosis, gliosis, and network reorganization. The major cause of cell death in cerebral damage is excitotoxicity, which is initiated by glutaminergic receptor over-activation, causing calcium to flood the cell, thereby leading to apoptosis and necrosis. This process is initiated within a few hours of the start of seizure activity, and provides the medical imperative to terminate SE as quickly as possible. To prevent the consequences of the excitotoxicity cascade, it is recommended that anesthesia be initiated within 1-2 hours of onset of seizures at doses designed to induce EEG suppression patterns (Shorvon and Ferlisi 2011).

### **3.4.2. SAGE-547 Clinical Program in the Treatment of SRSE**

The current SAGE-547 development program includes:

- a completed Phase 2 open-label trial, Study 547-SSE-201;
- this proposed Phase 3 randomized, double-blind, placebo-controlled trial, Study 547-SSE-301;
- an ongoing open-label, expanded access protocol, Study 547-SSE-302;
- a number of EINDs for SAGE-547 in patients with SRSE.

The designs of these studies are all similar, with a five to six day infusion of SAGE-547 (or placebo), during which time attempts are made to wean the subject off all third-line agents. In the Phase 3 studies, those subjects who cannot be weaned off third-line agents while being administered SAGE-547 (or placebo) may be eligible for a second open-label infusion of SAGE-547 at a higher dose. Follow up of subjects is for 21 – 30 days after the first infusion of study medication.

### **3.4.3. Data from the SAGE-547 Development Program**

The data from 30 subjects included in the on-going clinical evaluation of SAGE-547 for the treatment of adults and children with SRSE clearly offers preliminary evidence that SAGE-547 could provide substantial and clinically significant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate. These subjects comprise 20 from the ongoing Phase 2 trial (71% success rate in 12/17 evaluable subjects) and 10 subjects who received EIND treatments (78% success rate in 7/9 evaluable subjects).

Successful therapy of SRSE has been defined as “the SE is completely controlled by the therapy, without breakthrough of withdrawal seizures, or discontinuation due to side effects or death during therapy,” (Ferlisi and Shorvon 2012). By this definition, which is in accord with the efficacy assessments used in the overall clinical evaluation of SAGE-547, 19 of the 26 (73%) subjects with SRSE who completed the SAGE-547 infusion were treatment successes. As data collection is ongoing, this information is preliminary and subject to change upon further monitoring.

Published reports on RSE and SRSE have stated mortality rate ranges from 35% to 65%. The underlying etiologies of SE in the 547-SAGE-201 study and EINDs are heterogeneous, and each one conveys a different risk of mortality and longer term morbidity. However, the death rate in subjects who have received SAGE-547, 6 out of 30 (20%) subjects, appears to be lower than the published rates. None of the deaths were considered related to SAGE-547: brain tumor, organophosphate toxicity, respiratory failure, respiratory arrest due to ventilator support withdrawal, and breast cancer.

In the Phase 2 study, 20 SAEs (15 non-fatal) have been reported in 13 (65%) subjects, and of these 3 events in 2 subjects (10%) were considered by the investigator to be related to SAGE-547: pulmonary emboli and tracheostomy dehiscence/infection. The Sponsor did not consider these events to be related to SAGE-547, rather to the underlying disease states. Four of the 20 subjects (20%) experienced AEs considered possibly related to SAGE-547 by the investigator, namely moderate myopathy and severe pulmonary emboli in 1 subject, moderate tracheostomy dehiscence and tracheostomy infection in 1 subject, moderate thrombocytosis in 1 subject and moderate BUN, ALT and AST elevation in 1 subject.

Review of the most current safety data from 547-SAGE-201 reveals that there were changes in serum chemistry, hematology, and urinalysis during the study, but that none of those changes were assessed as related to SAGE-547. There were also no SAGE-547-related changes to vital signs.

Despite the heterogeneity in the underlying causes of SE, the ages of the subject, comorbidities, which normally complicate the treatment of SE, and the fact that all subjects had failed current standard of care treatment, a large majority of subjects had a successful therapy outcome, with discontinuation of all third-line agents and resolution of SE.

Refer to the Investigational Brochure for further information on the pre-clinical and clinical data supporting the use of SAGE-547 in SRSE.

### **3.5. Study Rationale - SAGE-547 in SRSE**

#### **3.5.1. Justification for the Control Group**

Although SAGE-547 has demonstrated extremely promising activity in subjects with SRSE, both in the Phase 2 study and during the EINDs, these have been open-label investigations with no control data for comparison. Generally in the literature there are few data describing the success rates of wean attempts of third-line agents, and few comparative data on the effectiveness of the three main third-line agents, propofol, pentobarbital/thiopental, and midazolam.

Several options for a control group in Study 547-SSE-301 were considered:

- No control group was thought to be unacceptable since there are no reliable published data on success rates in this population that could be used for broad comparisons;
- An active control was considered but found to be impractical since none of the third-line agents are approved for their use in SRSE, no standardized dosing regimens or treatment guidelines have been adopted for the management of SRSE, and clinicians were unlikely to agree which of the available third-line agents would be reserved for the active control arm;
- Historical controls were considered but abandoned because of the practical difficulties of obtaining high quality data, the lack of ability to prospectively match cases, and a suspicion that clinical practice in the standard of care of SRSE is evolving, mandating the use of prospective, concurrent control data;
- Comparison to standard of care alone was considered as a feasible design. However, in a field where no widely adopted treatment guidelines exist, there was a concern that knowledge of the treatment group (SAGE-547 plus standard of care versus standard of care alone) would alter the behavior of the investigators such that they could be more aggressive with weaning in the SAGE-547 group;

- Placebo control is not without its challenges since the preliminary efficacy data for SAGE-547 show that the compound exerts central pharmacological effects and is associated with positive outcomes in around 70% of patients. There is therefore a potential ethical concern about administering placebo to desperately ill patients who have often exhausted all treatment options for SRSE. This concern has been addressed in two ways: firstly all patients receive current standard of care; secondly, all subjects who fail to be weaned from their third-line agents at the end of the blinded infusion of study drug will be administered open-label SAGE-547 without un-blinding their initial treatment allocation, so treatment with the investigational product is not denied, but delayed about a week in the setting of ongoing receipt of full current standard of care.

It was therefore decided that a blinded, placebo-controlled design was appropriate for Study 547-SSE-301.

### **3.5.2. Justification for the Dose Regimen**

The standard dose regimen has been studied in 19 subjects in the 547-SSE-201 Phase 2 trial; the average peak plasma concentration of SAGE-547 at the end of the loading dose was approximately 144 ng/ml. The average plasma concentration during the maintenance infusion was approximately 70 ng/ml. At these concentrations, there were no clear safety signals although two-thirds of subjects experienced an SAE and there were four deaths, all related to the underlying comorbid conditions. The standard dosing regimen was associated with an approximate 70% successful treatment outcome. For these reasons, the standard dosing regimen has been adopted for the initial SAGE-547 infusion to be compared in a blinded fashion to placebo.

In the 547-SSE-201 trial, three subjects have thus far received the higher dose regimen. This dose regimen has also been well tolerated. The average peak plasma concentrations at the end of the loading dose for both dosing regimens will be in the same range, as the loading dose is the same for both regimens. The average plasma concentrations observed during the higher maintenance dose are 102 ng/ml (n=2). The rationale for adopting the higher dose regimen as the open-label infusion of SAGE-547 for subjects who are retreated in this 547-SSE-301 trial is that those who fail on the standard SAGE-547 dose regimen are afforded the opportunity to have access to a higher dose. The justification to also administer the higher dose regimen to failures on placebo is that the regimen has thus far been well tolerated, and this methodology preserves the blind for the initial infusion.

A five-day dosing regimen with SAGE-547 was investigated in the Phase 2 study, 547-SSE-201. There were some cases when weaning off all third-line agents was not possible within 48 hours, but weaning was completed after the end of the infusion of SAGE-547. For this reason, the duration of dosing with SAGE-547 has been increased from 120 hours (five days) in Phase 2 to 144 hours (six days) in this Phase 3 study.

### **3.5.3. Rationale for Genetic Testing Sub-study**

Sage Therapeutics intends to perform genetic research in the SAGE-547 development program in order to explore how genetic variations may affect the metabolism and activity of SAGE-547. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials, and, possibly, to genetically-guided treatment strategies for optimizing decision making with respect to individual benefit:risk. Participation of subjects in genetic research as part of the overall clinical study is optional.

### **3.6. Benefit-Risk Evaluation of the Present Study**

Previous reports of human administration of exogenous allopregnanolone indicate that for exposures in men and women up to 150 nM, the most commonly reported AEs were sedation (recorded as sleepiness or tiredness), feelings of intoxication (like alcohol), flushing, and mild headache (Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007). No SAEs were reported (Navarro, Kaddouz et al. 2003; Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007; Kask, Backstrom et al. 2008; Kask, Backstrom et al. 2009; Timby, Hedstrom et al. 2011a). In view of the reduced consciousness and sedation of study subjects at entry into this protocol, none of these previously-reported events are likely to impact subjects in this study.

To date, in the SAGE-547 Phase 2 study and the EIND subjects, a majority of subjects demonstrated a successful therapy outcome (>70%). The majority in the clinical trial (65%) have also experienced SAEs, but none has been considered related to SAGE-547 by the Sponsor (SAEs in 2 subjects (10%) were considered possibly related by Investigator). Five deaths have been reported in 30 subjects (20%), all related to the underlying cause of SRSE and not related to SAGE-547 – this is in the context of published mortality rates between 35% and 65%. These preliminary data suggest that SAGE-547 has the potential to provide clinically relevant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate.

The underlying etiologies of SE are heterogeneous, and each one conveys a different risk of mortality. Subjects who survive SRSE still have a high risk of severe morbidity (Neligan and Shorvon 2010). The subjects treated with SAGE-547 in Study 547-SSE-201, are heterogeneous in factors such as age and etiology of SE, factors that usually complicate treatment and can increase morbidity and mortality. Even with this heterogeneity, the preliminary efficacy and safety data for SAGE-547 are very encouraging, and the mortality rate suggests that the risk to benefit assessment of this treatment rests on the side of benefit.

## **4. ETHICS**

### **4.1. Institutional Review Board or Independent Ethics Committee**

This protocol will be reviewed and approved by the Institutional Review Board (IRB) where the study is conducted. The IRB will meet all FDA requirements governing IRBs (CFR, Title 21, Part 56).

### **4.2. Ethical Conduct of the Study**

The Sponsor, the Medical Monitor, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable ICH and GCP guidelines, and must also conduct the study in accordance with local regulations.

### **4.3. Subject Information and Informed Consent**

Subjects prospectively enrolled in this study will be unable to give consent. Therefore, consent will be given by proxy by a legally authorized representative (LAR). Written informed consent is required for each subject prior to any testing under this protocol not considered standard of care, including screening tests and evaluations. Should a subject gain the ability to sufficiently

comprehend the situation and consent during the course of the study, written informed consent or verbal assent will be documented as required or recommended by the institution's IRB.

The form of consent to be obtained will depend on the condition of the subject as determined by the Principal Investigator. The informed consent form (ICF), as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50.

It is the responsibility of the Investigator to obtain consent and to provide the subject's LAR with a copy of the signed and dated informed consent form. The informed consent form for subject participation must also be available as part of the subject file for review by the site's dedicated study monitor or any authorized auditor of the Sponsor or regulatory authorities.

All ICFs used in this study must be approved by the appropriate IRB and by the Sponsor. The ICF must not be altered without the prior agreement of the relevant IRB and the Sponsor.

#### **4.4. Ethical and Regulatory Considerations for Pharmacogenetic Sub-study**

##### **4.4.1. Informed Consent for Pharmacogenetics**

The genetic component of this study is optional and subjects may participate in other components of the main study without having to agree to participate in the genetic component. If subject chooses to participate in the genetic component of the study, the subject or LAR must sign and date a specific consent form for the genetic component of the study in addition to the main study consent form. The principal investigator(s) is responsible for ensuring that consent is freely given and that the subject understands that they may discontinue from the genetic aspect of the study independent of their decision to remain within or withdrawal from the main study.

##### **4.4.2. Subject Data Protection Relative to Pharmacogenomics**

Sage Therapeutics will not provide individual genotype results to subjects, their family members, their general physician, their employer or any insurance company unless required to do so by law. While extra precautions will be taken to preserve confidentiality and to prevent genetic data from being linked to an individual's identity outside of a restricted access site, in certain exceptional situations (e.g. in case of a medical emergency or as a consequence of a specific regulatory need), certain individuals may see both genetic data and the personal identifiers of a subject; however in all cases a subject's medical information and genetic files will remain physically separated.

## **5. STUDY OBJECTIVES**

### **5.1. Primary Objective**

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult subjects with SRSE, and for the response to endure at least 24 hours after cessation of the SAGE-547 or placebo infusion (primary response).

## 5.2. Secondary Objectives

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in Clinical Global Impression Scale between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

## 5.3. Safety Objectives

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

## 5.4. Other Objectives

1. To evaluate the impact of treatment with a higher dose SAGE-547 infusion;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;

6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS).

## **6. ENDPOINTS**

### **6.1. Primary Endpoint**

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### **6.2. Secondary Endpoints**

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) and to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### **6.3. Safety Endpoints**

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.

### **6.4. Other Endpoints**

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who are treated with a higher dose of SAGE-547;



2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS).

## 7. INVESTIGATIONAL PLAN

### 7.1. Overview of Study Design

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

[Figure 1](#) provides an overview of the study design and [Figure 2](#) gives the details of treatment and follow-up on the active treatment arm. Patients will follow one of three paths to entry to the study. The first path is for patients who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst or seizure suppression with a third-line agent. These patients will be consented for the study after admission to the intensive care unit, before or after any third-line agents are administered for burst or seizure suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their LAR. Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours. Once burst or seizure suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned during the QW will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The second path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst or seizure suppression pattern on the EEG. These patients may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst or seizure suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst or seizure suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst or seizure suppression has been achieved, the third-line agent or agents will be weaned.

This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The third path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst or seizure suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These patients may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst suppression or seizure pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within eight hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third line agent wean attempts prior to randomization (one vs two or more).

The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

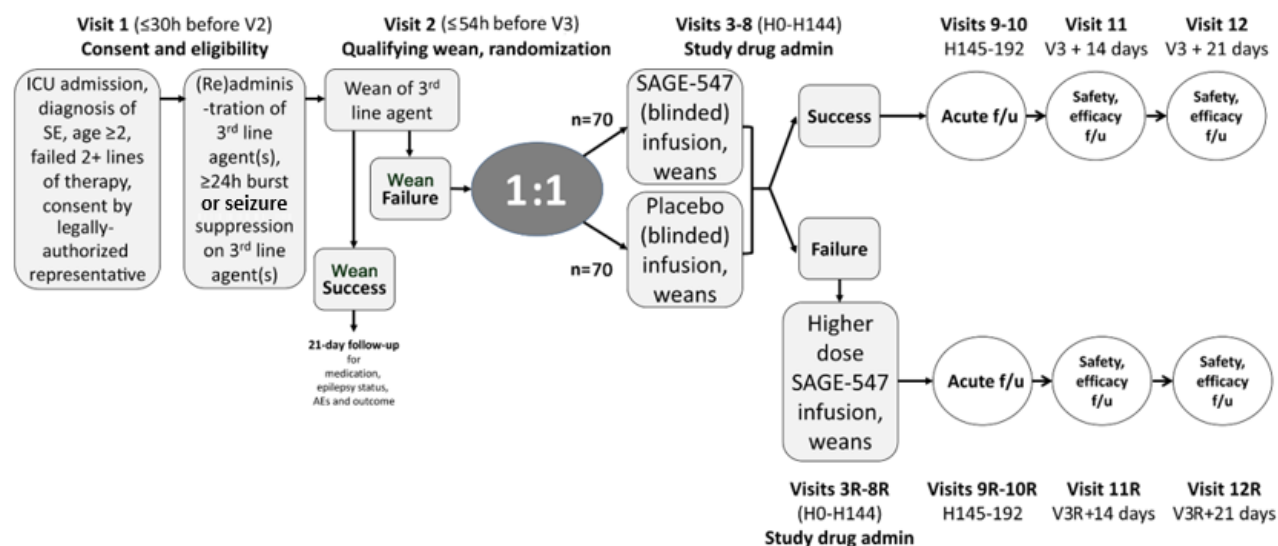
For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as the ability to wean the subject off all third-line agents before the end of the first infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication. Subjects must also have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) at the end of the primary endpoint assessment period as determined by EEG in order to be deemed a success. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#), [Table 2](#) and [Table 3](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion may be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. Eligibility for the open-label treatment must be confirmed in writing by the medical monitor prior to the open-label infusion starting. The blind will

be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo may all subsequently be eligible to be administered SAGE-547 at the higher dose.

**Figure 1: Study Design**



## 7.2. Trial Conduct

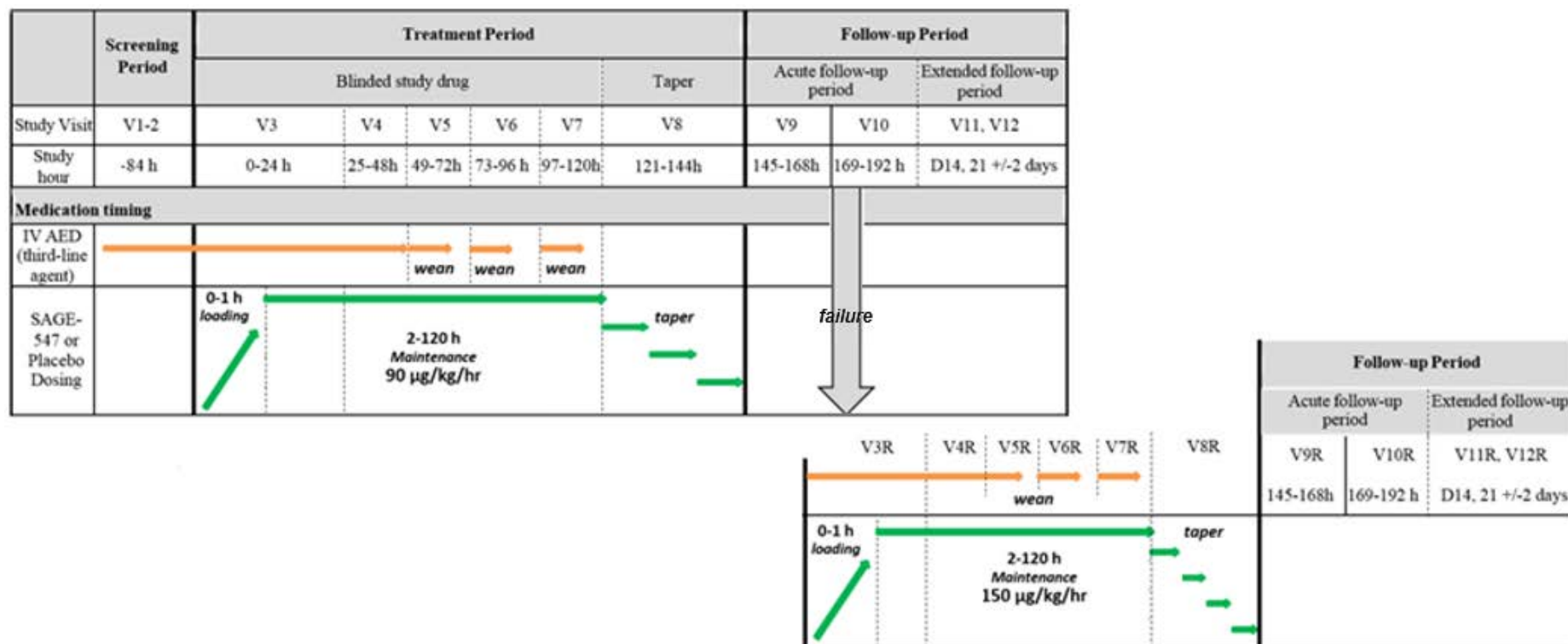
This study will be conducted according to the principles of the World Medical Association Declaration of Helsinki and most recent amendment, and in compliance with the protocol approved by the IRBs/Independent Ethics Committees (IECs), and in accordance with ICH Guidelines on GCP standards.

## 7.3. Blinding and Randomization

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo). Details of the dynamic randomization process will be included in the SAP.

The randomized portion of the study will be blinded, with the two treatment products (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

The second infusion of SAGE-547 will be administered on an open-label basis to subjects who meet the criteria for open-label treatment.

**Figure 2: Details of Treatment Administration and Follow-up**

## 8. SELECTION AND WITHDRAWAL OF SUBJECTS

The study will randomize 140 patients at up to 180 sites. All subjects deemed eligible to enroll must have written Medical Monitor approval on a case-by-case basis prior to undertaking the qualifying wean.

### 8.1. Inclusion Criteria

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects 18 years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; *or* who have previously failed zero, one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst or seizure suppression pattern; *or* who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst or seizure suppression pattern.

### 8.2. Exclusion Criteria

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy with highly malignant/malignant EEG features ([Westhall, Rosetti et al. 2016](#)).
4. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis but for whatever reason, dialysis that would adequately remove Captisol® is not planned;
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the experience of the investigator, is less than 30 days.
5. Subjects who are being administered more than three third-line agents concomitantly or for whom the qualifying wean cannot be completed within 24 hours or who are being

administered a third-line agent for indications such as raised intra-cranial pressure that would preclude weaning according to this protocol.

6. Subjects with a living will that does not allow heroic measure.
7. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
8. Subjects who have been treated or randomized in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not have received study drug/placebo and then re-enroll).

### **8.3. Selection and Consent of Subjects for Pharmacogenetic Substudy**

All subjects will be asked to participate in pharmacogenetic research; however, participation in research is voluntary and a subject can decide to decline his/her participation without penalty or loss of benefit. Participation or lack thereof will not be a cause for exclusion from any aspect of the main study. In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **8.4. Subject Withdrawal / Study Termination**

#### **8.4.1. Withdrawal/Discontinuation of Individual Subjects**

The reasons for study drug discontinuation and/or subject withdrawal from the study must be recorded in the subject's electronic case report form (eCRF). The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject has been discontinued/withdrawn due to an AE.

##### **8.4.1.1. Withdrawal from the Study**

Subjects or their LAR may withdraw subjects from the study at any time for any reason without compromising the subject's medical care. The Investigator will also withdraw subjects upon the request of Sage Therapeutics or upon termination of the study.

Subjects who withdraw from the study prior to Visit 10 (or 10R) should complete the procedures scheduled for the day of study drug taper (Hour 121-144; Visit8/8R) on the day of their withdrawal, including the SAGE-547 taper schedule, with the addition of the mortality assessment from Visit 12/12R. Subjects who withdraw from the study after Visit 10/10R should undergo study procedures as outlined for Visit 12/12R on the day of their withdrawal. In all cases, the reason for subject withdrawal will be recorded in the eCRF.

Withdrawal of subjects for any reason should be discussed with the Medical Monitor.

##### **8.4.1.2. Discontinuation of Study Drug**

If it is necessary to discontinue the study drug earlier than planned, subjects should continue to be followed per protocol to capture safety and efficacy assessments for the duration of the study period.

The investigator may withdraw the subject from the study drug for the following reasons:

- Upon subject's or LAR's request
- The subject or LAR is unwilling or unable to adhere to the protocol-specified visits
- The subject experiences an intolerable adverse event
- During the course of the study, the subject develops symptoms or conditions listed in the exclusion criteria.
- Other medical reason, at the discretion of the Investigator and/or the Medical Monitor

Subjects who discontinue the study due to an AE considered related to study drug should be followed until the event is resolved, considered stable, or the Investigator determines the event is no longer clinically significant. Study drug discontinuation due to AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

#### **8.4.2. Study Termination**

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of AEs or other findings suggesting unacceptable risk to subjects, administrative or operational reasons. In the event of study termination, Sage Therapeutics will provide written notification to the Investigator. Investigational sites must promptly notify their IRB and initiate withdrawal procedures for participating subjects.

## **9. INVESTIGATIONAL PRODUCT**

### **9.1. Identity of Investigational Product**

SAGE-547 Injection (allopregnanolone)

### **9.2. Clinical Supplies**

#### **9.2.1. SAGE-547**

Adequate supplies of SAGE-547 Injection and materials for intravenous administration will be provided to each site.

SAGE-547 Injection is a clear, colorless sterile solution of allopregnanolone intended for intravenous injection. SAGE-547 Injection is an aqueous solution of 5 mg/mL allopregnanolone in 250 mg/mL Captisol® (betadex sulfobutyl-ether sodium, NF). It is presented either un-buffered or buffered with 10 mM citrate at a pH of 6.0 in either 20 mL or 50 mL vials. SAGE-547 is further diluted according to the Pharmacy Manual to achieve an approximately isotonic solution and will be administered intravenously.

No preservatives are included in the drug product, which is intended to be used as a single-use vial. All inactive components (excipients) used in the formulation are compendial grade and conform to current USP/EP, and include sodium citrate, citric acid and betadex sulfobutyl-ether sodium (Captisol®).

#### **9.2.2. Placebo**

Placebo will be identical to SAGE-547 and presented in identical vials. Placebo will be manufactured in a similar way to SAGE-547 and comprises all excipients but no SAGE-547.



### 9.2.3. Blinding

The vials of SAGE-547 and placebo will be identical in every way so that they are indistinguishable by the pharmacist, investigator, anyone treating or managing the patient, the monitors, and the sponsor. In this way the first infusion of study drug administered to each patient will be double-blind.

For the blinded study drug infusions, subject-specific dosing kits will be provided. These dosing kits will be pre-labelled with kit number for the first blinded infusion. For the second-infusion, open-label kits will be provided, which will require subject assignment by the pharmacy for reconciliation purposes. The study kits must be stored under refrigerated conditions (2-8 °C). IV administration bags and lines may be provided for the blinded and open-label infusions. Refer to the Pharmacy Manual for additional details.

The label for the SAGE-547 Injection vials will include standard product identification information according to the Code of Federal Regulations, 21CFR 312.6. All study labels will also contain the following statement:

Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use.

### 9.3. Preparation of SAGE-547 or Placebo Injection for Dosing

The Pharmacy will be responsible for preparing the blinded and open-label study drug for subject dosing. The prepared admixture will be assigned a room temperature (20-25 °C) storage shelf life of 24 hours from time of compounding.

SAGE-547, which is hypertonic, will require dilution with SWFI to achieve an approximately isotonic solution according to the instructions provided in the Pharmacy Manual. Exactly the same procedures will be used to prepare the placebo admixture, so that all site staff remain blinded as to treatment allocation for the first infusion of study drug. SAGE-547 Injection is not intended to be administered to patients undiluted.

Refer to the Pharmacy Manual for specific instructions regarding infusion preparation.

### 9.4. Administration and Accountability

The Pharmacy will maintain accurate records of all investigational product supplies. Accurate records will be kept regarding the volume of SAGE-547 Injection or placebo used for each IV preparation, as well as the required infusion rate or rates, and the date and time of preparation. Reasons for departure from the expected dosing regimen must also be recorded. To satisfy regulatory requirements regarding drug accountability, all study medication will be reconciled in full. Refer to the Pharmacy Manual for additional details.

## 10. TREATMENT OF SUBJECTS

### 10.1. Dosing Schedule (Blinded Infusions)

SAGE-547 Injection or placebo will be administered according to the dosing schedules in [Table 5](#). The infusion rates to accomplish these µg/kg/h doses will be calculated according to the weight of the subject obtained within the eight-hour window that follows the declaration of the QW failure at V2 and prior to dosing at V3. The infusion rates will be applied to blinded study drug for the first infusion of study medication.



**Table 5: SAGE-547 or Placebo Dosing Schedule**

Hour	Type and Duration of Study Drug Infusion	Description
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	90 µg/kg/h
H121 – H128	8 hour taper	65 µg/kg/h
H129 – H136	8 hour taper	45 µg/kg/h
H137 – H144	8 hour taper	25 µg/kg/h

## 10.2. Dosing Schedule (Open-Label Infusions)

Those subjects that qualify for the open-label study drug will be administered SAGE-547 Injection according to the dosing schedule in Table 6. The dose will be administered on a µg/kg/h basis, and the subject's weight measured prior to dosing during V10 will be used to calculate the doses. These infusion rates will be applied to SAGE-547 re-treatment for the open-label second infusions of study medication.

**Table 6: SAGE-547 Open-Label Dosing Schedule**

Hour	Type and Duration of SAGE-547 Infusion	Description
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	150 µg/kg/h
H121 – H126	6 hour taper	125 µg/kg/h
H127 – H132	6 hour taper	95 µg/kg/h
H133 – H138	6 hour taper	65 µg/kg/h
H139 – H144	6 hour taper	35 µg/kg/h

## 10.3. Route of Administration

SAGE-547 Injection is intended for IV administration only. The compatibility of SAGE-547 with other drugs is unknown, and the product should be administered via a dedicated peripheral IV line using any Sage-supplied study-specific IV administration bags and lines. In order to preserve blinding, these instructions also apply to the blinded placebo infusions.

## 10.4. Treatment Period

The treatment period with double-blind SAGE-547 or placebo is six 24-hour periods (144 hours), which may encompass 6-7 calendar days. The open-label study drug treatment period is of identical duration.

## 10.5. Concomitant Medications, Procedures and Treatments

Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. For all randomized and the first 50 qualifying wean success (QWS) subjects, detailed information on all concomitant medications (concomitant AEDs, third-line agents, pressors, and other concomitant medications), procedures, and treatments should

be documented throughout the study from Screening through Visit 12/12R, as described below, and recorded on the eCRF. For subsequent QWS subjects, after the detailed information on all concomitant AEDs, pressors, third-line agents, procedures, and treatments collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant AED or pressor, third-line agent, procedure, and/or treatment, and the start and stop dates and times) from Visit 3 through Visit 12 will be recorded in the eCRF. For subsequent QWS subjects, after the detailed information on all concomitant medications collected during the screening period (Visits 1 and 2) has been recorded, only minimal information, to include the name of the concomitant medications and indication only will be recorded from Visit 3 through Visit 12.

SAGE-547 has demonstrated inhibitory effects on cytochrome P450 isoenzyme 2C9 (CYP2C9). Therefore, AEDs such as phenytoin and phenobarbital that are primarily metabolized by CYP2C9 should be closely monitored during SAGE-547 administration to ensure target exposures are maintained.

#### **10.5.1. Concomitant AEDs**

Subjects may enter the study on AEDs, and be administered AEDs during the study. All of these must be recorded on the eCRF with details including date and time of starting and stopping each AED, the route of administration, changes in doses, and frequency of administration. In addition, details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the eCRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.

#### **10.5.2. Concomitant Third-Line Agents**

All third-line agents (as defined in [Section 8](#)) administered since the diagnosis of SE will be recorded on the eCRF, whatever path the patient took for entry into the study. Details will include the name of the drug, the start and stop dates and times, and, after consent, the doses with start and stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

In addition, those changes in dose that constitute a wean attempt will be marked as such on the eCRF. In this way the start and stop dates and times of all wean attempts (see [Section 11](#) for definitions) will be recorded, as will the type of wean (QW, OW, or TW) and the outcome of the wean attempt (successful, failed and dose of this third-line agent increased or failed and this third-line agent stopped and another third-line agent started). Those wean attempts that occur after the TW up to and including Visit 12/12R will be marked “AW”.

Some third-line agents (such as propofol) are also used to induce sedation to facilitate a subject’s ability to tolerate the ventilator. For subjects requiring such sedation, propofol is the preferred agent unless there are contraindications. The eCRF will make clear from the indication for the third-line agent when it is being used for burst or seizure suppression and when it is being used as ventilator support or for another purpose. The investigator will add a note to the eCRF to justify that the doses used are appropriate for sedation and not for seizure or burst suppression. The doses used for ventilator support and other similar uses are usually much lower than those used for seizure or burst suppression, and use of these third-line agents for these other purposes does not constitute a wean failure under this protocol.

### **10.5.3. Concomitant Pressors**

The start and stop dates and times of all pressors will be recorded as well as the start and stop dates and times of all dose changes.

### **10.5.4. Other Concomitant Medications**

All other concomitant medications must be recorded on the eCRF with details including date and time of starting and stopping, the route of administration, dose, and frequency of administration.

## **11. STUDY ASSESSMENTS**

### **11.1. Efficacy Assessments**

#### **11.1.1. Primary Efficacy**

Success or failure will be determined, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo infusion and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the blinded (first) infusion of SAGE-547 or placebo. In addition, subjects must have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) to be deemed to be successes. All subjects who fail to complete their infusion of randomized treatment or do not have at least one attempt during study treatment to wean off all third-line agents will be considered as “failures” for the primary endpoint.

##### **11.1.1.1. Weaning**

Third-line agents are anesthetic agents that are administered in order to reach a seizure or burst suppression EEG pattern. For the purposes of this study, third-line agents are defined as continuous intravenous infusions of pentobarbital/thiopental, midazolam, propofol, and ketamine at maintenance doses alone or in combination sufficient to produce a burst or seizure suppression pattern on the EEG. The following are considered to be minimum maintenance doses of these agents that may be expected alone or in combination to achieve EEG burst suppression. If subjects are on lower doses than these and are not in EEG burst suppression for the first 12 hours of the blinded study drug infusion, they will be considered to be protocol violators and will exit the study.

- Pentobarbital: 1 mg/kg/hour
- Thiopental: 3 mg/kg/hour
- Midazolam: 0.1 mg/kg/hour
- Propofol: 3 mg/kg/hour
- Ketamine 1.2 mg/kg/hour

The timing and nature of the third-line agent weans will be guided by the Clinical Standardization Guidelines for the study, and the clinical judgment of the investigator, and will always be primarily done in the best medical interests of the subject. Advice about weaning may be sought from the Clinical Standardization Team, a group of fellow investigators with experience of performing clinical trials in subjects with SRSE. The Clinical Standardization Team will be able to discuss EEGs related to key study timepoints (terminal wean and the period after the end of the blinded

study drug infusion if the terminal wean was successful) in a timely manner in order to provide advice about compliance with the Clinical Standardization Guidelines.

The following guidance for weaning applies to all weans of third-line agents undertaken during the study. Continued determined efforts to liberate subjects from sedation must be undertaken for the entire duration of the blinded study drug infusion. Each failed wean from third-line agents should be followed by a 6-24 hour period of suppression and then another wean attempt, with further optimization of the AED regimen.

Weans include the qualifying wean (QW); the terminal wean (TW), which is the wean of the third-line agent if the subject is on only one third-line agent or the wean of the last third-line agent if the subject is on more than one third-line agent; the other weans (OW), which are the weans of the third-line agents other than the TW if the subject is on more than one third-line agent. The guidance also applies to additional weans (AW), which are the weans from third-line agents that take place after the TW for the first blinded study drug infusion or the second open-label study drug infusion.

### **QW Guidance**

- Wean to be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace that third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Investigators should allow 24 hours to lapse after the end of a “successful” qualifying wean before finally declaring the QW a success. If a third-line agent needs to be re-instituted within that 24 hours, the QW is a failure, and the subject may then be randomized in the study.

### **OW Guidance**

- First OW should not begin before H49 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- If the subject is on two third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the TW. However the OW may be completed over a shorter or longer time period and may overlap if clinically indicated with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- If the subject is on three third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the wean of the second agent. The second agent should be weaned over 24 hours and that wean completed before starting the TW. However the OWs may be completed over a shorter or longer time period and may overlap if clinically indicated with each other and with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the

dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.

- All OWs should be completed before H96 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **TW Guidance**

- The TW is defined as the wean of the last third-line agent.
- If the subject is on one third-line agent, the TW should not begin before H49 and should begin no later than H97 after starting administration of study drug or starting the open-label infusion of SAGE-547. If the subject has had one or more OWs, the TW should ideally begin as soon as the last OW is complete but in any case not later than H97 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- The TW must be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace this third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Every effort must be made to complete the TW before H120 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547, but the TW must be complete before H144 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **AW Guidance**

- AWs will take place when medically indicated in the opinion of the investigator.
- Ideally the AW should take place over 24 hours, but completion may be over a shorter or longer time period than this. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.

#### **11.1.1.2. EEG**

Electroencephalographs (EEGs) that are representative of the intermittent or continuous EEG being used to support key investigator decisions will be collected at the following time points:

- A 24-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst or seizure suppression for the second path to eligibility, and a variable pattern for the third path to eligibility. This EEG also aims to capture the burst or seizure suppression pattern during the 24 hours that precede the QW. If the CEEG does not capture the 24 hours that precede the QW, additional EEG data collected as standard of care prior to the CEEG and prior to the

QW may be collected to assess the depth of burst or seizure suppression in the 24 hour period prior to the QW.

- EEG will be performed to cover the qualifying wean (QWEEG). EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for up to 24 hours after the end of the QW. The duration of the QWEEG will be up to 48.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s), the decision to re-institute a third-line agent(s) at doses intended to induce burst or seizure suppression, and the decision that the QW is a success.
- EEG will be performed from three hours prior to the start of the blinded infusion to 12 hours after the start of the blinded infusion. This will be called the BIEEG. The intent of this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG and to assess the depth of burst suppression in the first 12 hours of blinded study drug infusion.
- EEG will be performed to cover the final or terminal wean of third-line agent (TWEEG). The TW is the wean of the final third-line agent during the blinded administration of study drug or the open-label infusion of SAGE-547; if the subject was on one third-line agent, the TW is the wean of that agent. If the subject was on three third-line agents, the TW is the wean of the third and final agent. EEG recording will start 30 minutes prior to the start of the TW, continue for up to 24 hours during the TW, and then continue for the one hour after the end of the TW. The duration of the TWEEG will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the final third-line agent or the decision to re-institute a third-line agent at doses intended to induce burst or seizure suppression because any seizure activity could not be managed using intermittent bolus doses of AEDs.
- EEG will be performed during the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 (TAEED). The TAEED is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the start of the taper (at Hour 119.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours during the taper, and then continue for the one hour after the end of the taper (to Hour 145 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547). The duration of the TAEED will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst or seizure suppression because any seizure activity seen during the taper could not be managed using intermittent bolus doses of AEDs.
- EEG will be obtained to cover the end of the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 and the ensuing 24-hour period, during which the primary endpoint is assessed (PAEED). The PAEED is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the end of taper (at Hour 143.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours after the end of the blinded administration of study treatment or the open-label infusion of SAGE-547, and then continue for the one hour after the end of the 24-hour assessment period (to Hour 169 after starting the blinded administration of study

treatment or after starting the open-label infusion of SAGE-547). The duration of the PAEEG will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst or seizure suppression because any seizure activity seen in the 24 hours following the end of the blinded administration of study treatment or the open-label infusion of SAGE-547 that could not be managed using intermittent bolus doses of AEDs.

In practice, most subjects are on continuous EEG monitoring or long periods of intermittent EEG monitoring. However, this protocol does not mandate continuous EEG monitoring and breaks from EEG monitoring to provide relief to the scalp from the irritating effects of the electrodes are advised according to local practice. If a break in EEG monitoring is mandated by local practice guidelines at a time when one of the protocolled EEG segments is to be collected, the break in EEG monitoring will take precedence, with the reason for missing the EEG reading noted on the eCRF. The EEGs obtained for the study are therefore part of the existing EEG record rather than being obtained de-novo at each timepoint. For timepoints where there might be some ambiguity, such as the TWEEG, the final EEG record is that of the final attempt to wean the last third-line agent, even if earlier attempts to wean that agent took place. In some cases (the TAEED and PAEEG, for instance), the EEG records will overlap, but different cuts are taken to service the different EEG record requirements.

The electronic EEG file will be de-identified, the date and time of the start and stop of the EEG and the subject number will be attached to the file, and the study time point will be indicated (CEEG, QWEEG, BIEEG, TWEEG, TAEED, and PAEEG). The PI will indicate on the eCRF what the EEG shows, as follows:

- For the CEEG, the PI will describe the EEG pattern that determined which path to eligibility the subject was on.
- For the QWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure or success on the qualifying wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst or seizure suppression during the qualifying wean constitutes a failure); the QWEEG will extend to cover the 24 hours after the end of third line agents in order to confirm that the QW was a success.
- For the BIEEG, the PI will note the date and time of the start of the EEG and the pattern seen on the EEG.
- For the TWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure on the terminal wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst or seizure suppression during the terminal wean).
- For the TAEED, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst or seizure suppression before the end of the SAGE-547 infusion).
- For the PAEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary

endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst suppression in the 24 hours following the end of the SAGE-547 infusion).

A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm the depth of burst or seizure suppression prior to the QW and during the first 12 hours of the blinded study drug infusion, the PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period (average EEG power at the end of Visit 9 of more than two microvolts):

- All subjects will have the CEEG and QWEEG collected and stored, and the CEEG and QWEEG read;
- Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;
- Those subjects randomized who are not administered the open-label study drug will have the QWEEG, BIEEG, TWEED, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the BIEEG, QWEEG, TWEED, and PAEEG related to the blinded study drug infusion read;
- Those subjects randomized who later undergo the open-label infusion will have the QWEEG, BIEEG, TWEED, TAEED and PAEEG related to the blinded study drug infusion and the TWEED, TAEED, and PAEEG related to the open-label study drug infusion collected and stored, and the BIEEG, QWEEG, TWEED, and PAEEG related to the blinded study drug infusion read.

All EEG records may be subject to quantitative EEG analysis.

### **11.1.2. Secondary Efficacy**

#### **11.1.2.1. Clinical Global Impression Scale (CGI)**

The clinical global impression scales are often utilized in clinical trials to allow clinicians to integrate several sources of information into a single rating of the subject's condition. Both the CGI-Severity (Question 1, CGI-S) and the CGI-Improvement (Question 2, CGI-I) employ a 7-point Likert scale measuring severity of the disease state in the subject and improvement, respectively. All severity assessments after initiation of SAGE-547 treatment should consider the general state of the subject over the preceding week. The third question on the scale will not be employed in this trial, and where the scale states "mental illness", this means "physical illness" in this trial.

The CGI-S will be evaluated at Visit 1 and at the last visit, Visit 12 or 12R. The CGI-I will be evaluated at Visit 12 or 12R.

#### **11.1.2.2. Epilepsy Status**

At Visit 1, the diagnosis of epilepsy will be documented as a no/yes question. If there was a previous diagnosis of epilepsy, further details will be documented, including:

- Date of diagnosis;
- Details of anti-epileptic drugs currently being taken;



- Type of epilepsy;
- Seizure frequency in the past month.

Information about the current (index) episode of status epilepticus will be obtained at Visit 1:

- Date of onset
- Date of failure to respond to first line agent(s) and the name(s) of the agent(s)
- Date of failure to respond to second line agent(s) and the name(s) of the agent(s)
- Any previous treatment with third line agents and the response to those agents (details of the third line agent drugs and previous wean attempts will be recorded on the Third Line Agent Medication CRF)
- The cause of the index episode of status epilepticus
- If the subject was transferred from another hospital or from within the hospital, the reason for the transfer will be recorded (such as for study enrollment, due to lack of medical options at original hospital or unit, due to lack of beds at the original hospital or unit, family request, other)

Previous (non-index) diagnosis of status epilepticus will be documented as a no/yes question. If SE did occur in the past 12 months, further information will be gathered, including:

- SE, RSE, or SRSE diagnosis, whichever was the most severe diagnosis for each episode;
- Cause;
- Treatment, including experimental treatments and need for intubation/ventilation;
- Dates of onset and duration.

At Visit 12 or Visit 12R, the following information will be gathered:

- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of SE up to and including Visit 12 or Visit 12R;
- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of seizures (convulsive and non-convulsive) up to and including Visit 12 or Visit 12R;
- Number of separate episodes of SE after H144 at the end of Visit 8 or Visit 8R (no/yes); if yes,
  - SE, RSE, or SRSE diagnosis;
  - Cause;
  - Treatment, including experimental treatments and need for intubation/ventilation;
  - Dates of onset and duration.

Note that a separate episode of SE is defined as an episode of SE separated from other periods of status epilepticus by at least 24 hours.

- Diagnosis of epilepsy since Visit 11 or Visit 11R will be documented as a no/yes question. If a diagnosis of epilepsy has been made, further details will be documented, including:

- Status as ongoing or new epilepsy since Visit 11 or Visit 11R after initiation of SAGE-547 treatment;
- Details of anti-epileptic drugs currently being taken;
- Type of epilepsy and seizure frequency in the past week.

## **11.2. Safety Assessments**

The safety and tolerability of SAGE-547 will be assessed using adverse events, clinical laboratory measures, vital signs, ECG intervals and morphology, and mortality. All safety assessments should be performed per hospital standard of care and will be collected periodically throughout the study according to [Table 1](#), [Table 2](#), and [Table 3](#) (Schedules of Assessments).

### **11.2.1. Adverse Events**

AEs will be collected after informed consent has been signed and prior to study-specific screening procedures not considered standard of care, during subject preparation for SAGE-547 administration and through Visit 12 or Visit 12R. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™) coding system (current version). See [Section 14](#) for additional details.

### **11.2.2. Clinical Laboratory Tests**

Blood samples will be taken for hematology, and serum chemistry and GFR will be calculated at:

- Visit 1 and then at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.
- Blood samples will be taken at Visit 11 or Visit 11R for serum chemistry (renal panel only).

Urine samples (20 ml) will be taken for urinalysis and urine NAG analysis at:

- Visit 1 and at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.

These samples will be analyzed at a central laboratory; hour-to-hour medical decisions will be based on sampling for laboratory testing done outside the protocol as part of normal standard of care. GFR will be calculated by the central laboratory.

Any out-of-range values will be flagged by the laboratory; the investigator will add a comment about whether the abnormality is clinically significant. Clinical significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

#### **11.2.2.1. Hematology and Serum Chemistry**

Hematology will include complete blood count (CBC) white blood cell count with differential, platelet count and red blood cell (RBC) count, hemoglobin and hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatine kinase,

lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose. In addition triglycerides will be measured in serum chemistry samples (to aid assessment of lipemia in pharmacokinetic samples).

#### **11.2.2.2. Pregnancy Test**

Females of child-bearing potential will be tested for pregnancy by serum pregnancy test at Visit 1. In this study, since an accurate history of menstruation in girls and menopause in older women may not be available at Visit 1, “child-bearing potential” is taken to mean any female aged 18 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy. Female subjects with a positive pregnancy test will be ineligible for study participation.

Females of child-bearing potential who regain consciousness and gain the ability to consent during the course of the study, and leave the ICU, will be counseled on use of suitable method of birth control for 10 days following the end of the last infusion of study drug. Acceptable methods of birth control include:

- Total abstinence (no sexual intercourse)
- Hormonal contraceptives including birth control pills, implantable, or injectable contraceptives
- An intrauterine devices (IUD)
- A barrier form of contraception such as a condom or occlusive cap with a spermicide

#### **11.2.2.3. Urinalysis**

Urinalysis will include assessment of protein, blood, leukocytes, glucose, ketones, urobilinogen, pH, and specific gravity.

#### **11.2.3. Vital Signs**

Blood pressure, heart rate, and temperature will be recorded at the following time points relative to the first infusion of study drug, and to the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547:

- Visit 1;
- At 0, +30, +60 minutes (+/-15 minutes) and +2, +4 and +8 hours (+/- 30 minutes) after the start of the infusion;
- At +24, +48, +72, +96, +120, +144, +168, and +192 hours (+/- 2 hours) after the start of the infusion.

#### **11.2.4. Weight and Height**

Weight and height will be measured at Visit 1. Weight will also be obtained at V2, within the eight hour window that follows the declaration of the QW failure and prior to the initiation of the blinded infusion loading dose at H0 of V3, and will be used to calculate the infusion rates throughout the entire blinded treatment course. If a subject qualifies for open-label study drug, the infusion rates

for the open-label infusion will be calculated using the subject's weight measured prior to dosing during V10.

If this is not possible to obtain an actual weight at the above-referenced time points, permission from the Clinical Monitor must be obtained to use another method to obtain the subject's weight (such as information from the LAR or estimating using an established local protocol).

In addition, a daily weight will be obtained and recorded if this is easily obtained, such as the use of a scale bed.

#### **11.2.5. ECG**

For the first 50 subjects randomized in the study, 12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours. If it is not possible to perform ECG immediately after the collection of PK samples up to 160 hours, ECG must be performed within 15 minutes prior to the collection of PK samples up to 160 hours; at other times the allowed time window for ECGs is +/- 2 hours:

- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +128, +136, +144, +152, +160, and +192 hours after the start of the blinded (first) study drug infusion
- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +126, +132, +138, +144, +152, +160, and +192 hours after the start of the open-label (second) study drug

The heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm.

For the subsequent subjects randomized in the study, the following timepoints for ECG will be used:

- pre-dose and at +1, +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the blinded (first) study drug infusion
- pre-dose and at +1, +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the open-label (second) study drug infusion

It is not necessary to collect these ECGs with the PK samples at these timepoints and, apart from the +1h ECG, there is +/- 2 hour time window for these ECGs.

#### **11.2.6. Mortality**

Mortality will be recorded on the Visit 12 or Visit 12R case report form. If the subject has died, the following information will be collected:

- Date of death;
- Cause of death.

As accurate as possible cause of death will be collected, which will be further categorized as due to one of the following causes:

- SE;
- complications of long term intubation and third-line agent infusions;
- underlying cause of qualifying SE;

- co-morbidity existing at the time of the qualifying SE;
- new co-morbidity or trauma;
- study drug;
- other (specify).

#### **11.2.7. Pharmacogenetic Samples**

If a subject's LAR consents to pharmacogenetic sampling, a blood sample for genetic research will be collected at Visit 1 in order to avoid the possible introduction of bias through the exclusion of patients who may withdraw from study due to an AE (a subject population that may be of specific interest for subsequent genetic analysis). If for any reason a sample cannot be taken prior to treatment, a sample can be drawn at any point prior to completion with the restriction that no more than one genetic sample be taken per subject.

The objective of this research is to collect and store blood samples for possible DNA extraction and exploratory research into how genes or specific genetic variation may influence response (i.e. distribution, safety, tolerability, and efficacy) to SAGE-547. Specific genetic variations of interest include but are not limited to: classes of metabolizing enzymes (e.g. Cytochrome P450 supra-family genes), genes encoding enzymes involved in the production and metabolism of allopregnanolone (e.g. AKR1C4 (3 $\alpha$ -hydroxysteroid dehydrogenase)), genes associated with the GABA receptor (e.g. GABRA1-A6, GABRB1-B3, GABRD, GABRE, GABRG1-3) and genes associated with the production and degradation of GABA.

Future research may suggest other genes or gene categories as candidates for influencing not only response to SAGE-547 but also susceptibility to disorders for which SAGE-547 is being evaluated. Thus, the genetic research may involve study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.

##### **11.2.7.1. Biological Sampling and Coding Procedures (Pharmacogenetics)**

To ensure patient confidentiality, utmost care will be taken in the coding and storage of pharmacogenetic samples.

*Extraction and coding:* DNA will be extracted from the blood sample and the DNA sample will be assigned a unique number replacing information from sampling tube. The assigned DNA number will be used to identify the sample and its corresponding information within Sage Therapeutics or at any designated contract laboratory for the purpose of sequencing of other DNA specific analysis. No personal details sufficient for individual identification will be available to any person (internal or external to Sage Therapeutics) working with the DNA.

*Genotype/Phenotype Analysis:* Samples and data from genetic analysis will be coded. The link between subject enrollment / randomization code and DNA number will be maintained and stored in a secure environment with restricted access. The established link will be used to identify relevant DNA samples for analysis, facilitated correlation of genotype results with clinical data, allow regulatory audit, and to trace samples for destruction in case of withdrawal of consent.

##### **11.2.7.2. Retention of Biological Samples for Pharmacogenetic Analysis**

Extracted DNA is a finite research that is destroyed in the process of being analyzed. Primary blood samples from which DNA can be extracted will be stored and used until no further analyses are

possible, a maximum storage period of 25 years from time of last subject last visit has been reached, or an individual or LAR withdraws his/her or their consent.

### **11.2.8. Other Outcomes**

#### **11.2.8.1. Pharmacokinetic Data**

Formal plasma analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS)). In addition, all samples will be analyzed for important SAGE-547 metabolites (if and when these are identified) and Captisol® concentrations.

##### Plasma Analysis

Plasma will be collected to assay for SAGE-547 concentrations at the following time points relative to the start of each infusion of study drug:

- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion.
- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open-label SAGE-547 study drug infusion.
- All samples will also be analyzed for plasma concentrations of important metabolites of SAGE-547 if and when these are identified.
- All samples from the first 50 subjects randomized will also be analyzed for plasma concentrations of Captisol®.

The plasma samples will be drawn from the arm contralateral to that used for drug administration. Drawing samples from peripheral arterial or venous lines or from a central line is permissible. PK collection times should be adhered to as strictly as possible. The allowed time window for all samples is: pre-dose in the two hours prior to starting the infusion of study drug; samples up to and including 1h, +/- 5 minutes; subsequent samples, +/- 15 minutes. Subject-specific PK kits for sampling including instructions on collection and processing methods, and storage and shipping conditions, will be provided separately. To maintain the blind, all subjects will have samples taken as outlined above: subjects receiving SAGE-547 will have all samples analyzed for all analytes. Subjects on placebo may have samples analyzed to investigate endogenous allopregnanolone and metabolite concentrations, as well as Captisol® concentrations; experience with the plasma concentration data will determine if and which placebo samples are analyzed.

Each blood sample will be 3 ml in volume for subjects weighing 30 kg or more, and 1 ml in volume for subjects weighing less than 30 kg. Separate aliquots will be obtained from each sample to service the different analytical laboratories and provide a back-up sample at each timepoint for each subject.

The maximum blood draw for PK analysis for a subject having two infusions of study drug will be 99 ml (33 ml for subjects weighing less than 30 kg).

Plasma PK parameters for SAGE-547 will be calculated where appropriate (e.g.,  $C_{max}$ ,  $C_{min}$ ,  $t_{max}$ ,  $AUC_{last}$ ,  $AUC_{\infty}$ ,  $CL_s$ ). In addition, similar PK parameters will be calculated for Captisol®. PK parameters for important metabolites of SAGE-547 may be calculated. An evaluation will be made of the feasibility of adopting a population-PK approach to assess drug-drug-interactions with SAGE-547 as victim of AEDs.

In addition, the Visit 9 sample may be analyzed for plasma concentrations of third-line agents.

#### Other Analysis

If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations. The minimum volume of cerebrospinal fluid for analysis is 100 microlitres.

Full details of all pharmacokinetic analyses will be described in the Pharmacokinetic Analysis Plan.

#### **11.2.8.2. Correlation of QT/QTc Changes and Plasma Concentrations of SAGE-547**

An analysis will be performed to determine whether there is any correlation between changes in QT/QTc interval and plasma concentrations of SAGE-547, in order to investigate any effect that SAGE-547 may have on QT/QTc interval.

#### **11.2.8.3. Pharmacoeconomic Data**

At Visit 12 or Visit 12R, the following information will be collected: number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital. If the subject dies before Visit 12 or Visit 12R, data will be collected up to the date of death. The definition of “hospital” is the institution that the subject was initially treated in. If the subject is transferred to another hospital, that hospital would be the “discharge destination from the hospital” and the “number of days in hospital” would be the number of days in the initial treating hospital.

For those subjects discharged from hospital before Visit 12/12R, the following questions will be asked:

- On what study day was the subject discharged from hospital?
- What type of facility was the subject discharged to (another hospital, a rehabilitation center, a supported care facility, home, other)?
- How many days did the subject stay in this facility?

The following questions will be answered regarding the stay in the ICU and hospital:

- Was the subject still in the ICU at the end of Visit 10/10R?
- If the FOUR Score was  $\geq 12$  at Visit 10/10R and the subject was in the ICU at Visit 10/10R, what was the reason for the subject not being discharged from the ICU (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, other)?
- Was the subject still an in-patient in the hospital at the end of Visit 12/12R?

- If the FOUR Score was  $\geq 15$  at Visit 12/12R and the subject was in the hospital at Visit 12/12R, what was the reason for the subject not being discharged from the hospital (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, unsuitable home circumstances, other)?

#### 11.2.8.4. STESS

The STESS will be assessed during Visit 1 in order to assess the severity of the status epilepticus.

#### 11.2.8.5. FOUR Score

The Full Outline of UnResponsiveness or FOUR Score is designed to assess conscious level and unlike other scores, is suitable for subjects who are intubated. It assesses four domains of neurological function (eye responses, motor responses, brainstem reflexes, and breathing pattern).

The FOUR Score will be collected at the following time points relative to each infusion of study drug (the initial blinded infusion and the second open-label infusion if this is administered):

- baseline, +24, +48, +72, +96, +120, +144, +168, and +192 hours (all +/- 2 hours) after the start of the infusion, and at Visit 11/11R and Visit 12/12R.

#### 11.2.8.6. Glasgow Outcome Scale (GOS)

The GOS is a relatively common assessment scale used to standardize descriptions of the objective degree of recovery from brain injury such as cerebral trauma, or in this case SRSE. It was first used in 1975 ([Jennett and Bond 1975](#)) and allows a prediction of the long-term course of rehabilitation to return to work and everyday life. The scale classifies subjects into 5 groups:

- Death
- Persistent vegetative state
- Severe disability
- Moderate disability
- Good recovery

The GOS will be assessed at Visit 12 or Visit 12R.

#### 11.2.8.7. Supervision Rating Scale (SRS)

The Supervision Rating (SRS) measures the level of supervision that a patient/subject receives from caregivers. The SRS rates level of supervision on a 13-point ordinal scale that can optionally be grouped into five ranked categories (Independent, Overnight Supervision, Part-Time Supervision, Full-Time Indirect Supervision, and Full-Time Direct Supervision). The SRS was designed to be rated by a clinician based on interviews with the subject and an informant who has observed at first hand the level of supervision received by the subject ([Boake 2000](#)). Scoring is a one-step procedure in which the clinician assigns the rating that is closest to the subject's level. Ratings are based on the level of supervision received, not on how much supervision a subject is judged or predicted to need.

The SRS will be assessed at Visit 1 and Visit 12 or Visit 12R. The Visit 1 assessment will be a retrospective assessment of the supervision required by the subject immediately prior to the admission that included the index episode of status epilepticus.



**11.2.8.8. Modified Rankin Scale – 9Q (mRS-9Q)**

The Modified Rankin Scale (mRS) is a commonly used scale to determine disability and functional dependence due to neurological insult such as stroke in adults. The 7-point scale (0 – 6) denotes functional capacity from no symptoms (0) to severe disability (5) and death (6). The Modified Rankin Scale – 9Q is a shortened version consisting of 9 questions that reliably determines the mRS score and was developed to both simplify the assessment and expand the rater base to non- medically trained personnel ([Patel, Rao et al. 2012](#)). The assessment is a web-based tool in the public domain with automatic score calculation and error checking found at [www.modifiedrankin.com](http://www.modifiedrankin.com).

The mRS will be assessed at Visit 1 and at Visit 12 or Visit 12R. The baseline assessment will be a retrospective assessment of the disability and dependence of the subject immediately prior to the admission that included the index episode of status epilepticus.

## 12. STUDY PROCEDURES

The study procedures listed below by study day reflect the required data collection times for this protocol. When a time window is necessary, this is specified below. If no time window is specified, the test may be performed at any time within the specified 24-hour period.

### 12.1. Visit 1 (V2-≤30h)

The baseline period will be up to approximately 84 hours prior to starting blinded study treatment and should include the assessments/procedures listed below and summarized in [Table 1 and Table 2 \(for open-label treatment\)](#), the Schedules of Events.

- Informed consent
- Eligibility checklist
- Verification of inclusion/exclusion criteria.
- Demographic information and medical history obtained by proxy and confirmed by the subject when possible.
- SE and wean history
- Blood will be collected from female subjects 18 years to 55 years for a serum pregnancy test unless they are known to be pre-menstrual or post-menopausal or to have had a hysterectomy.
- Blood and urine samples collected for clinical laboratory testing.
- Pharmacogenetic sample will be collected from consenting/eligible subjects.
- Vital signs
- Height
- Weight
- An ECG reading taken.
- Administration of the STESS.
- Administration of the FOUR Score.
- Administration of SRS.
- Administration of the mRS-9Q assessment.
- Assessment of the CGI scale.
- Evaluation of epilepsy status.
- Administration of continuous IV third-line agents.
- Perform EEG.
- Recording of adverse events.
- Recording of previous and concomitant anti-epileptic drugs.
- Recording of previous and concomitant third-line agents.
- Recording of concomitant pressors.

- Recording of other concomitant medications, procedures, and treatments.

## **12.2. Visit 2 (V3-≤54h)**

- Recording of adverse events.
- Recording of concomitant anti-epileptic drugs.
- Recording of concomitant third-line agents.
- Recording of concomitant pressors.
- Recording of other concomitant medications, procedures, and treatments.
- Wean of continuous third-line agent (QW):
  - If wean is successful, subject is followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (these subjects are Qualifying Wean Success subjects or QWS subjects);
  - If wean is not successful, there is ongoing intravenous administration of at least one continuous IV third-line agent and EEG is performed and the subject is randomized.
- Weight
  - Subject weight will be obtained within the eight-hour period from the declaration of failure of QW and prior to the initiation of the blinded infusion loading dose at H0 of V3. This weight will be the dosing weight used to determine the infusion rate for the entire blinded infusion treatment course.

## **12.3. SAGE-547 Treatment Period**

### **12.3.1. Visit 3/3R (0-24 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs will be recorded at:
  - 0, +30, +60 minutes (+/-15 minutes) and +2, +4, +8 (+/- 30 minutes) and +24 hours (+/- 2 hours) after the start of the infusion
- For the first 50 subjects randomized in the study, ECG readings will be recorded immediately after PK sampling, or within 15 minutes prior to PK sampling, at the following time points:
  - 0 (pre-dose) and at +0.5, +1, +3, +6, +12, and +24 hours after the start of the study drug infusion.
  - Subsequent subjects randomized in the study will have ECG readings recorded at 0 (pre-dose) and +1, +12, and +24 hours after the start of the study drug infusion, it will not be necessary to collect these ECGs with PK samples at these timepoints and, apart from the +1 h ECG, there is +/- 2 hour time window for these ECGs.
- A blood sample for PK analysis should be collected at the following time points (all +/- 15 minutes except where otherwise stated):

- 0 (pre-dose, within two hours of the start of the infusion) and at +0.5, +1 (+/- 5 minutes), +3, +6, +12, and +24 hours after the start of the study drug infusion.
- Completion of the FOUR Score
  - +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the final declaration of QW success)
- Ongoing intravenous administration of a continuous IV third-line agent.
- Study drug administration in loading (Hour 0-1) and maintenance infusions (at completion of Hour 1).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.2. Visit 4/4R (25-48 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +48 hours (+/- 2 hours) after the start of the infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +48 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +48 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +48 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +48 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent.
- Ongoing study drug maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

**12.3.3. Visit 5/5R (49-72 hours)**

- Weight if easily obtained
- Vital signs should be recorded at:
  - +72 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +72 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +72 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +72 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +72 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

**12.3.4. Visit 6/6R (73-96 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +96 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +96 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +96 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.

- A blood sample for PK analysis should be collected:
  - +96 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +96 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Perform EEG.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.5. Visit 7/7R (97-120 hours)**

- Weight if easily obtained
- Vital signs should be recorded at:
  - +120 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +120 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +120 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +120 hours (+/- 15 minutes) after the start of study drug infusion, immediately prior to the end of the maintenance infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +120 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled. Complete wean by 120 hours if at all possible.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).

- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## **12.4. SAGE-547 Taper Period**

### **12.4.1. Visit 8/8R (121-144 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +144 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after each PK sampling, or within 15 minutes prior to PK sampling at the following time points:
  - +128, +136 hours and +144 hours after the start of the blinded study drug infusion
  - +126, +132, +138 hours and +144 hours after the start of the open-label study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +144 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected (+/- 15 minutes unless otherwise stated):
  - +128 (immediately prior to the end of the first taper step), +136 hours (+/- 5 minutes, immediately prior to the end of the second taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of study drug infusion.
  - During the open-label study drug phase of the study PK blood draws at: +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 hours (+/- 5 minutes, immediately prior to the end of the third taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of the study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +144 hours (+/- 2 hours) after the start of the infusion
- Complete wean of third line agents by H144 if not completed by H120.
- Perform EEG.
- Taper of SAGE-547 infusion begins at hour 121.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## **12.5. Follow-up Period**

### **12.5.1. Visit 9/9R (145-168 hours)**

- Vital signs should be recorded at:
  - +168 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at + 152 hours:
  - +152, +160 hours (+/- 2 hours) after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +152 and +160 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +168 hours (+/- 2 hours) after the start of the infusion
- Perform EEG.
- Assessment of the presence of physiologic brain activity using EEG.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.5.2. Visit 10/10R (169-192 hours)**

- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +192 hours (+/- 2 hours) after the start of the infusion
- At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine eligibility for the open-label treatment with the higher dose of study drug. This determination may occur at any point during Visit 10: the higher dose open-label infusion must begin within the Visit 10 window. All patients receiving the higher dose open-label treatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.
- Weight if the subject qualifies for the open-label study drug (Visit 10 only, not Visit 10R).
- Recording of adverse events (QWS subjects also).



- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.3. Visit 11/11R (Visit 3/3R + 14d (±2))**

- Blood samples collected for clinical laboratory testing (renal panel only).
- Completion of the FOUR Score (QWS subjects also).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.4. Visit 12/12R (Visit 3/3R + 21d (±2))**

All assessments also performed for QWS subjects.

- Completion of the FOUR Score.
- Administration of the GOS.
- Administration of the SRS.
- Administration of the mRS-9Q assessment.
- Evaluation of epilepsy status (see [Section 11.1.2.2](#) for details).
- Assessment of the CGI Scale.
- Recording of adverse events.
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications.
- Collection of pharmacoeconomic data.
- Mortality will be assessed throughout the study period.

## **13. STATISTICS**

### **13.1. Statistical Plan**

Complete details for the analysis and reporting of data from this study will be contained in the Statistical Analysis Plan (SAP).

#### **13.1.1. Interim Analysis**

When approximately 50% of subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### 13.1.2. Study Populations

The **Safety Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to actual treatment. This analysis population will be used for all safety analyses.

The **Intent to Treat Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to randomized treatment. This analysis population will be used for all efficacy analyses.

The **Modified Intent to Treat Population** is defined as all subjects who:

1. complete their initial course of blinded SAGE-547 or placebo treatment unless the non-completion was due a drug-related adverse event; and
2. have at least one attempt to wean from third-line agents prior to the end of blinded study treatment infusion unless the failure to wean was because seizures were not controlled.

Subjects will be classified according to randomized treatment. This analysis population will be used for sensitivity analyses of the primary endpoint and select secondary efficacy endpoints.

Narratives will be prepared for all subjects who do not complete the infusion of blinded study medication or were not subjected to any wean attempts. Narratives will include details of the cause of SE, the comorbid conditions, the adverse event(s), and reasons for non-completion of the infusion or failure to attempt weaning. This blinded narrative will be reviewed by the medical monitors and the patient adjudicated as MITT eligible or ineligible. Acceptable reasons for defining a subject as MITT ineligible include death or withdrawal of consent due to progression of the underlying cause of SE or comorbid conditions, unless the cause of death or progression of disease were thought by the investigator, sponsor, or DSMB to be related to study drug.

The **Per-Protocol (PP) Population** is defined as a subset of the MITT population but will exclude data from all subjects with significant protocol violations or deviations. Subjects will be classified according to actual treatment received. This data set will be used for sensitivity analyses to examine the robustness of results for the primary and key secondary efficacy endpoints.

The **Pharmacokinetics Population** is defined as all subjects who at least had an infusion of blinded SAGE-547 initiated and have at least one pharmacokinetic sample collected.

The **Pharmacogenetic Population** is defined all subjects who consent to being included in the pharmacogenetic assessment and provide a pharmacogenetic sample.

Summary statistics of all data collected will be presented for subjects who were QW successes.

### 13.1.3. General Aspects

Tabular displays of descriptive statistics will be provided for all variables. Summary tables will include n, mean, mean, standard deviation, minimum and maximum for continuous variable and frequency and percentage for categorical variables.

### 13.1.4. Analysis of Primary Endpoint

The analysis of response to treatment (see Section 11.1.1 for definition of primary endpoint) between SAGE-547 treated subjects and placebo treated subjects will be performed on the ITT population using a Cochran-Mantel-Haenszel (CMH) test with variables for treatment, concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior

to randomization (one vs two or more). The CMH general association statistic and its associated p-value will be presented. The comparison of treatment response rates will be conducted at the 5% level of significance. To confirm the CMH results, a permutation test will also be conducted.

An additional analysis of the primary endpoint will also be performed on the MITT population. In addition sensitivity analyses of the primary endpoint will be performed using the ITT population based on:

- the number of third-line agents (one, two, or three) subjects were administered post-randomization; and
- which third line agent was the subject of the first TW.

### **13.1.5. Analysis of Secondary Efficacy Endpoints**

Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section (Section 6). Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. The analysis of the secondary endpoints will also be performed on the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

### **13.1.6. Analysis of Other Endpoints**

Safety and “Other” endpoints will only be summarized by treatment group.

Summaries of safety endpoints will be based on the overall Safety Population.

### **13.1.7. Epilepsy and SRSE Status**

Diagnosis of epilepsy and recurrence of RSE or SRSE will be documented as the percentage of subjects by time point and overall. Kaplan-Meier curves may be plotted if sufficient data are available.

Utilization of AEDs during follow-up and during recurrence will be summarized.

### **13.1.8. Questionnaires**

The data collected from each questionnaire will be interpreted according to the standard methodology for that questionnaire. There will be no adjustment for missing values.

### **13.1.9. Pharmacokinetic Data Analysis**

Details of the pharmacokinetic data analysis will be described in detail in a separate Pharmacokinetic Analysis Plan.

### **13.1.10. Pharmacogenetic Data Analysis**

Any genotype data generated in this study will be stored within a secured database within Sage Therapeutics and / or a third party contracted to work with Sage Therapeutics to analyze the samples. Because the number of subjects agreeing to participate in the genetic research component of the study is unknown, it is not possible to establish, a priori, whether sufficient samples will be obtained to support formal statistical evaluation of data. As a consequence a Pharmacogenetic Analysis Plan will only be prepared where appropriate and the results obtained from any genetic research will be reported in a report separate from the main study CSR.

### **13.1.11. Open-Label Study Drug Subjects**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are treated with SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo.

### **13.1.12. EEG-Responders**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who are classified as EEG-responders/non-responders based on the independent assessment of the PAEEG. Summaries will be derived for the two randomized treatment groups.

### **13.1.13. QT/QTc Assessment**

An analysis of the correlation between changes in QT/QTc intervals and SAGE-547 plasma levels will be performed to investigate if there is a potential effect that SAGE-547 may have on QT/QTc interval. A detailed description of the QT/QTc assessment will be included in the SAP.

### **13.1.14. Quantitative EEG**

The nine EEG records for each subject may be subjected to exploratory quantitative EEG analysis, the details of which will be included in the EEG Analysis Plan. In summary the following comparisons may be made, SAGE-547 versus placebo: the QWEEG versus the TWEEG (main analysis); the CEEG versus PAEEG (subsidiary analysis); and TAEEG versus PAEEG (exploratory analysis).

## **13.2. Determination of Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between treatment groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

**13.3. Statistical Analysis Plan**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

## **14. ADVERSE EVENTS**

The safety procedures in this study will be detailed in a Safety Management Plan, which will be agreed and signed before the first subject is randomized in the study. [Section 14.1](#) summarizes Investigator responsibilities regarding the identification and documentation of AEs, the classification of AEs for relationship to study drug and severity, and the reporting of AE information to the Sponsor and the IRB.

[Section 14.2](#) summarizes Sponsor/Medical Monitor Responsibilities regarding monitoring of AE data and reporting relevant safety information to FDA.

[Section 14.3](#) lists important AE definitions.

### **14.1. Investigator Responsibilities**

#### **14.1.1. Identification and Documentation of Adverse Events by Investigator**

Subjects will be evaluated and questioned generally (if possible) to identify AEs during the course of the study. AEs will be collected from the signature of the consent form through Visit 12/12R. Adverse events that occur prior to completion of screening will be captured on the Medical History eCRF. Adverse events that occur after completion of screening will be recorded on the Adverse Event eCRF.

All AEs revealed by observation, other diagnostic procedures, or spontaneously reported by the subject and/or in response to an open question from study personnel will be recorded on the Adverse Event Form. Any clinically significant deterioration in laboratory assessments or other clinical findings are considered an AE and must be recorded on the Adverse Event Form, unless otherwise stated. AE information recorded will be entered into the database on an ongoing basis.

AEs with a relationship considered related to study drug (probable, possible) should be followed until the event is resolved or the Investigator determines the event is stable or no longer clinically significant. AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

For SAEs, an electronic Serious Adverse Event eCRF must be completed with as much information as possible and submitted in the time frame described below in [Section 14.1.3](#). When new significant information is obtained as well as when the outcome of an event is known, the electronic SAE eCRF should be updated within 24 hours. If the subject was an outpatient at the time of the SAE and was re-hospitalized due to the SAE, a copy of relevant hospital records (e.g., admission report, laboratory test results, discharge summary, etc.) may be requested to be included as part of the subject medical file.

All SAEs will be followed until resolved or until a stable status has been achieved.

**14.1.2. Adverse Event Classification****14.1.2.1. Relationship to Investigational Drug**

None:	No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state.
Possible:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject, but this is not known for sure.
Probable:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

**14.1.2.2. Severity**

Mild	Discomfort noticed, but no disruption to daily activity.  For subjects that are unconscious, this may be a slight or minor change in a lab result or clinical sign or symptom that does not require immediate corrective action.
Moderate	Discomfort sufficient to reduce or affect normal daily activity, but is not hazardous to health; prescription drug therapy may be employed to treat the AE.  For subjects that are unconscious, this may be a clinically meaningful change that may require immediate corrective action.
Severe	Inability to work or perform normal daily activity and represented a definite hazard to health; prescription drug therapy and/or hospitalization may be employed to treat the AE.  For unconscious subjects, this may be a significant clinical change that requires immediate corrective action.

**14.1.2.3. Action Taken with Investigational Drug**

None	Study medication was continued without change.
Discontinued	Study medication was terminated.
Dose adjusted	Study medication dose/infusion rate was changed and then continued per protocol.
Interrupted	Study medication was interrupted and then continued per protocol.
Unknown	The action taken with regard to study medication is unknown.
Not applicable	Administration of study medication was not ongoing.

**14.1.2.4. Assessment of Outcome**

Ongoing	At the end of the study, the event has not resolved or stabilized.
Ongoing and stable	The event is ongoing but has stabilized and is unlikely to change
Resolved	The event has resolved or the subject recovered without sequelae.
Resolved with sequelae	The event has at least one secondary outcome that may result in permanent disability and/or functional limitation.
Unknown	The status of the event is unknown.
Death	The subject has expired.

**14.1.3. Investigator Reporting to Sponsor and Sponsor Emergency Contact**

All new SAEs that come to the Investigator and/or Sponsor's notice during the course of the study (up to and including the last study visit) must be reported by the Investigator on the designated electronic report form within 24 hours of the point in time when the Investigator becomes aware of the SAE. As additional information becomes available, the designated electronic report form must be updated within 24 hours.

Investigators must report any SAE, whether or not considered drug related. The report must include an assessment of whether there is a reasonable possibility that the drug caused the event.

In a medical emergency (ie, an event that requires immediate attention regarding the treatment of a subject, operation of the clinical study, and/or the use of investigational drug), study site staff will apply appropriate medical intervention according to current standards of care, and contact the Medical Monitor.

**14.1.4. Medical Monitor and Emergency Contact Information**

[REDACTED], MD  
[REDACTED]

In a study related medical emergency situation, when the assigned Medical Monitor cannot be reached by a caller, an on-call Physician can be reached 24 hours per day, 7 days per week via an [REDACTED] Call-Center:

- Telephone: [REDACTED]  
(this is a chargeable telephone number allowing a global reach from both landlines and mobile phones)



- [REDACTED]

On this internet page a list of country-specific toll-free telephone numbers is provided. It should be noted that not all countries globally have access to toll-free numbers as indicated on the “24/7 Medical Help desk” index. Countries without toll-free numbers need to dial the chargeable number as indicated above. Furthermore, toll-free numbers are not available from mobile phones.

#### **14.1.5. SAE Reporting Contact Information**

Contact information and reporting instructions are provided in the Safety Management Plan.

#### **14.1.6. Reporting to Institutional Review Boards (IRBs)**

It is the responsibility of the Investigator to promptly notify the institution’s IRB of all serious and unexpected suspected adverse reactions (see [Section 14.3](#) for definitions).

### **14.2. Sponsor/Medical Monitor Responsibilities**

#### **14.2.1. Monitoring of Adverse Event Data**

The Medical Monitor will review any newly reported adverse events in an ongoing basis. If the aggregate assessment indicates that an event is occurring more frequently than would normally be expected in this population, or as previously observed, and the sponsor believes that the events are causally related to the administration of SAGE-547, the Sponsor will then report that information in an IND safety report.

#### **14.2.2. Data Safety Monitoring Board**

An independent DSMB will monitor the clinical, PK and PD data for safety signals throughout the study and will be asked to assess the placebo response rate at the time of the interim analysis to determine final sample size. In order to perform their monitoring function the DSMB will have access to un-blinded safety data as necessary.

The composition and procedures for the board will be described in a separate DSMB Charter.

#### **14.2.3. Reporting to FDA**

The Sponsor must report in an IND safety report any suspected adverse reaction to study treatment that is both serious and unexpected (21 CFR 312.32(c)(1)(i)). Before submitting an IND safety report, the Sponsor will ensure the event meets all three of the definitions: (1) suspected adverse reaction, (2) serious, (3) unexpected. If the AE does not meet all three of the definitions, it should not be submitted as an IND safety report. The Sponsor should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the adverse event and, therefore, that the event meets the definition of a suspected adverse reaction.

If there is a serious and unexpected suspected adverse reaction, the Sponsor will notify the appropriate regulatory agency(ies) and all appropriate parties on an expedited basis. In addition, Sponsors must submit expedited reports of an increased rate of occurrence or severity of serious suspected adverse reactions over that listed in the protocol or Investigational Brochure.

SUSARs will be unblinded prior to reporting to FDA. Unless it is necessary to unblind for the safety of the patient, the investigator will not be informed of the unblinding of the subject.

Under 21 CFR 312.32, Sponsors should identify in the protocol SAEs that it does not plan to report individually in an expedited manner, because they are known consequences of the disease or otherwise common in the study population. Given the grave condition and prognosis of SRSE being studied, individual occurrences of seizures or seizure activity will not be reported expeditiously in this study. Regardless of which events are reported in an expedited manner, all adverse events will be closely monitored throughout the study.

#### **14.2.4. Reporting to European Regulatory Authorities**

The Sponsor or its designee is responsible for SUSAR notification to the relevant regulatory authorities as outlined in the ICH Guidelines. All investigators participating in the study will also be informed as required by regulations.

Any SUSAR is subject to expedited reporting in the EU. The Sponsor or its designee, will report any single SUSAR to the appropriate National CAs and IECs within 7 days if the SUSAR is life-threatening or fatal (with the relevant follow-up information subsequently communicated within an additional eight days), and within 15 days if the SUSAR is neither life-threatening nor fatal.

SUSARs reported will be those that have arisen in the present clinical trial and SUSARs that have arisen in other clinical trials conducted by the Sponsor with the same medicinal product.

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to competent authorities of the concerned Member States and to IEC(s)/IRBs as required by national laws.

### **14.3. Adverse Event Definitions**

#### **14.3.1. Adverse Event**

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

#### **14.3.2. Suspected Adverse Reaction**

Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

#### **14.3.3. Life-Threatening**

An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

#### **14.3.4. Serious**

An AE or suspected adverse reaction is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE – see definition above

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disability
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

#### **14.3.5. Unexpected**

An AE or suspected adverse reaction is considered “unexpected”:

- If it is not listed in the Investigational Brochure or is not listed at the specificity or severity that has been observed, or
- If an Investigational Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigational Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigational Brochure listed only cerebral vascular accidents.

“Unexpected,” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigational Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

#### **14.4. Emergency Identification of Study Medication**

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject’s treatment in the study via the IVRS; this normally requires prior approval by the medical monitor. However, if the subject is at immediate risk and the Investigator believes that immediate knowledge of the study treatment will alter medical management, discussion with the medical monitor may take place after unblinding. The Investigator will not unblind the medical monitor during that discussion. The process of unblinding will ensure that only the investigator is unblinded; the medical monitor, study management team, and data management team will not be made aware of the treatment allocation of an individual subject. All cases of emergency unblinding will be fully documented in a way that does not unblind the medical monitor, study management team, and data management team.

## **15. STUDY ADMINISTRATIVE CONSIDERATIONS**

### **15.1. Quality Control and Quality Assurance**

The Investigators and institutions will permit trial related monitoring, audits, IRB review, and regulatory inspections as requested by FDA, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed informed consent forms, etc.) in addition to case report forms.

Quality assurance and quality control systems with written standard operating procedures (SOPs) will be followed to ensure this trial will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The site's dedicated study monitor will arrange to visit the Investigator at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be identified and resolved. The study monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality assurance officers named by Sage Therapeutics or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements, made by the Sponsor with the Investigator/institution and any other parties involved with the clinical trial, will be in writing in a separate agreement.

### **15.2. Data Handling and Recordkeeping**

#### **15.2.1. Data Handling**

Procedures for data handling (including electronic data) used in this protocol will be documented in a Data Management Plan.

#### **15.2.2. Case Report Form Completion**

eCRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of demographics, study drug administration, study procedures, AEs, questionnaire completion, efficacy assessments and subject status, including survival.

The Investigator will maintain copies of the eCRFs at the study site. For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate eCRF.

### **15.2.3. Retention of Study Records**

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval and until there are no pending or contemplated marketing applications or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to an appropriate person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

### **15.3. Confidentiality**

To maintain subject privacy, all eCRFs, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available trial registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by Sage Therapeutics to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

### **15.4. Publication Policy**

All information concerning SAGE-547 is considered confidential and shall remain the sole property of Sage Therapeutics. The Investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval from Sage Therapeutics. No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between Sage Therapeutics and the Investigator.

### **15.5. Protocol Amendments**

Changes to the conduct of the study should be prepared as a protocol amendment by the Sponsor. Protocol amendments should receive written IRB/IEC approval prior to implementation at the investigative site, except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the trial (eg, change of monitor, telephone numbers). In this case, Sage Therapeutics will amend and implement the protocol change and subsequently notify the regulatory authorities and the Investigative sites who will notify the respective IRB, as appropriate.

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## APPENDIX 1. FOUR SCORE

### FOUR score

#### Full Outline of UnResponsiveness

##### Eye response

- E4: eyelids open or opened, tracking, or blinking to command
- E3: eyelids open but not tracking
- E2: eyelids closed but open to loud voice
- E1: eyelids closed but open to pain
- E0: eyelids remain closed with pain

##### Motor response

- M4: thumbs-up, fist or peace sign
- M3: localizing to pain
- M2: flexion response to pain
- M1: extension response to pain
- M0: no response to pain or generalized myoclonus status

##### Brainstem reflexes

- B4: pupil and corneal reflexes present
- B3: one pupil wide and fixed
- B2: pupil or corneal reflexes absent
- B1: pupil and corneal reflexes absent
- B0: absent pupil, corneal and cough reflex

##### Respiration pattern

- R4: not intubated, regular breathing pattern
- R3: not intubated, Cheyne-Stokes breathing pattern
- R2: not intubated, irregular breathing
- R1: breathes above ventilatory rate
- R0: breathes at ventilator rate or apnea

Reference ([Iyer, Hoel et al. 2009](#)).



**APPENDIX 2. GLASGOW OUTCOME SCALE (GOS)****GLASGOW  
OUTCOME  
SCALE**

Patient Name: \_\_\_\_\_  
 Rater Name: \_\_\_\_\_  
 Date: \_\_\_\_\_

*Note:* The scale presented here is based on the original article by Jennett and Bond. It has become common practice in clinical trial administration, however, to use a modified version that places the scores in reverse order (i.e., "good recovery" = 1, "moderate disability" =2, etc.).

Score	Description
1	DEATH
2	PERSISTENT VEGETATIVE STATE Patient exhibits no <i>obvious cortical</i> function.
3	SEVERE DISABILITY (Conscious but disabled). Patient depends upon others for daily support due to mental or physical disability or both.
4	MODERATE DISABILITY (Disabled but independent). Patient is independent as far as daily life is concerned. The disabilities found include varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes.
5	GOOD RECOVERY Resumption of normal activities even though there may be minor neurological or psychological deficits.

**TOTAL (1-5):** \_\_\_\_\_

Reference ([Jennett and Bond 1975](#)).

## APPENDIX 3. SUPERVISION RATING SCALE (SRS)

### SUPERVISION RATING SCALE (SRS)

**Instructions:** Circle the rating that is closest to the amount of supervision that the patient *actually receives*. "Supervision" means that someone is responsible for being with the patient.

<u>Rating</u>	<u>Description</u>
<u>Level 1: INDEPENDENT</u>	
1	The patient lives alone or independently. Other persons can live with the patient, but they cannot take responsibility for supervision (for example, a child or elderly person).
2	The patient is unsupervised overnight. The patient lives with one or more persons who <i>could</i> be responsible for supervision (for example, a spouse or roommate), but they are <i>all</i> sometimes absent overnight.
<u>Level 2: OVERNIGHT SUPERVISION</u>	
3	The patient is only supervised overnight. One or more supervising persons are always present overnight but they are <i>all</i> sometimes absent for the rest of the day.
<u>Level 3: PART-TIME SUPERVISION</u>	
4	The patient is supervised overnight and part-time during waking hours, but is allowed on independent outings. One or more supervising persons are always present overnight and are also present during part of waking hours every day. However, the patient is sometimes allowed to leave the residence without being accompanied by someone who is responsible for supervision.
5	The patient is supervised overnight and part-time during waking hours, but is unsupervised during working hours. Supervising persons are <i>all</i> sometimes absent for enough time for them to work full-time outside the home.
6	The patient is supervised overnight and during most waking hours. Supervising persons are <i>all</i> sometimes absent for periods longer than one hour, but less than the time needed to hold a full-time job away from home.
7	The patient is supervised overnight and during almost all waking hours. Supervising persons are <i>all</i> sometimes absent for periods shorter than one hour.
<u>Level 4: FULL-TIME INDIRECT SUPERVISION</u>	
8	The patient is under full-time indirect supervision. At least one supervising person is <i>always</i> present, but the supervising person does not check on the patient more than once every 30 minutes.
9	Same as #8 plus requires overnight safety precautions (for example, a deadbolt on outside door).
<u>Level 5: FULL-TIME DIRECT SUPERVISION</u>	
10	The patient is under full-time direct supervision. At least one supervising person is always present and the supervising person checks on the patient more than once every thirty minutes.
11	The patient lives in a setting in which the exits are physically controlled by others (for example, a locked ward).
12	Same as #11 plus a supervising person is designated to provide full-time line-of-sight supervision (for example, an escape watch or suicide watch).
13	The patient is in physical restraints.

3/12/93

Corwin Boake, Ph.D., TIRR, 1333 Moursund, Houston, TX 77030-3405, 713/799-6990

## APPENDIX 4. MODIFIED RANKIN SCALE – LEVEL OF FUNCTION SURVEY (mRS-9Q)

1. Do you have any symptoms that are bothering you? (For example, trouble with reading or writing, trouble speaking, problems with vision, numbness, weakness, balance trouble, or problems with swallowing?)	YES <input type="radio"/>	NO <input type="radio"/>
2. Are you able to do the same work as before?	YES <input type="radio"/>	NO <input type="radio"/>
3. Are you able to keep up with your hobbies?	YES <input type="radio"/>	NO <input type="radio"/>
4. Have you maintained your ties to friends and family?	YES <input type="radio"/>	NO <input type="radio"/>
5. Do you need help making a simple meal, doing household chores, or balancing a checkbook?	YES <input type="radio"/>	NO <input type="radio"/>
6. Do you need help with shopping or traveling close to home?	YES <input type="radio"/>	NO <input type="radio"/>
7. Do you need another person to help you walk?	YES <input type="radio"/>	NO <input type="radio"/>
8. Do you need help with eating, going to the toilet, or bathing?	YES <input type="radio"/>	NO <input type="radio"/>
9. Do you stay in bed most of the day and need constant nursing care?	YES <input type="radio"/>	NO <input type="radio"/>

## APPENDIX 5. CLINICAL GLOBAL IMPRESSION (CGI)

### Clinical Global Impression (CGI)

#### 1. Severity of illness

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- |                             |   |
|-----------------------------|---|
| 0 = Not assessed            | 4 = Moderately ill                        |
| 1 = Normal, not at all ill  | 5 = Markedly ill                          |
| 2 = Borderline mentally ill | 6 = Severely ill                          |
| 3 = Mildly ill              | 7 = Among the most extremely ill patients |

#### 2. Global improvement: Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.

Compared to his condition at admission to the project, how much has he changed?

- |                        |                     |
|------------------------|---------------------|
| 0 = Not assessed       | 4 = No change       |
| 1 = Very much improved | 5 = Minimally worse |
| 2 = Much improved      | 6 = Much worse      |
| 3 = Minimally improved | 7 = Very much worse |

#### 3. Efficacy index: Rate this item on the basis of drug effect only.

Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.

EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect		Side effects			
		None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
<b>Marked</b>	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
<b>Moderate</b>	Decided improvement. Partial remission of symptoms	05	06	07	08
<b>Minimal</b>	Slight improvement which doesn't alter status of care of patient	09	10	11	12
<b>Unchanged or worse</b>		13	14	15	16
Not assessed = 00					

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

**APPENDIX 6. STATUS EPILEPTICUS SEVERITY SCORE (STESS)**

Outcome Predictor	Feature	Score
Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type (prior to first treatment)	Simple-partial, complex-partial, absence, myoclonic (complicating idiopathic generalized epilepsy)	0
	Generalized-convulsive	1
	Nonconvulsive status epilepticus in coma	2
Age	< 65 years	0
	≥ 65 years	2
History of previous seizures	Yes	0
	No or unknown	1
Summed Total		

**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY  
TO EVALUATE THE EFFICACY AND SAFETY OF SAGE-547 INJECTION  
IN THE TREATMENT OF SUBJECTS WITH SUPER-REFRACTORY  
STATUS EPILEPTICUS**

**PROTOCOL NUMBER: 547-SSE-301  
ADULT ONLY VERSION**

**IND NUMBER: 117901**

**EudraCT Number: 2015-002142-31**

Product: SAGE-547 Injection (allopregnanolone)

Sponsor Contact: [REDACTED], MD  
Sage Therapeutics  
215 First Street  
Cambridge, MA 02142  
[REDACTED]

Medical Monitor: [REDACTED], MD  
[REDACTED]

Date of Protocol:	09 March 2015
Date of Amendment One	27 May 2015
Date of Date of Amendment One (Denmark Specific)	01 Mar 2016
Date of Amendment Two For Adults Only (Denmark Specific [not implemented])	17 November 2015
Date of Amendment Three For Adults Only (Denmark Specific [not implemented])	22 April 2016
Date of Amendment Four For Adults Only (Denmark Specific)	18 August 2016

**Confidentiality Statement**

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

**PROTOCOL NUMBER: 547-SSE-301**

Sponsor [REDACTED]:

[REDACTED]  
[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]  
[REDACTED]

[REDACTED]  
[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]  
[REDACTED]

[REDACTED]  
[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

CRO [REDACTED]:

[REDACTED]

## 1. SIGNATURE PAGE

Title of Protocol:

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus

Protocol No: 547-SSE-301

**Sponsor Approval**

[Redacted Signature]

06 SEP 2016

Date (dd/mmm/yyyy)

[Redacted Signature], MD

Sage Therapeutics

[Redacted Signature]

MPH

07 Sept 2016

Date (dd/mmm/yyyy)

Sage Therapeutics

[Redacted Signature]

MPH

07 Sep 2016

Date (dd/mmm/yyyy)

Sage

[Redacted Signature]

07 SEP 2016

Date (dd/mmm/yyyy)

[Redacted Signature]

Sage Therapeutics



**Investigator Agreement**

By signing this page I attest that I have read and understand the contents of Clinical Protocol 547-SSE-301 and any current amendments. I agree to adhere to the design, conduct, and reporting requirements of the study as stated in the clinical protocol and to my obligations to the Sponsor as described in the protocol and executed contracts between myself, my Institution, and the Sponsor. I also agree to adhere to any subsequent amendments to the clinical protocol.

Investigator's Signature: \_\_\_\_\_

Investigator's Name: \_\_\_\_\_

Institution: \_\_\_\_\_

Date: \_\_\_\_\_

## 2. SYNOPSIS

<b>Name of Sponsor:</b> Sage Therapeutics 215 First Street Cambridge, MA 02142		
<b>Protocol No.</b> 547-SSE-301	<b>Phase:</b> 3	
<b>Name of Investigational Product:</b> SAGE-547 Injection		
<b>Name of Active Ingredient:</b> Allopregnanolone		
<b>Title of the Protocol:</b> A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus		
<b>Dosing Regimen: SAGE-547 or Placebo Dosing Schedule</b>		
<b>Hour</b>	<b>Type and Duration of SAGE-547 Infusions</b>	<b>Dose</b>
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	90 µg/kg/h
H121 – H128	8 hour taper	65 µg/kg/h
H129 – H136	8 hour taper	45 µg/kg/h
H137 – H144	8 hour taper	25 µg/kg/h
<b>Dosing Regimen: SAGE-547 Open-Label Dosing Schedule</b>		
<b>Hour</b>	<b>Type and Duration of SAGE-547 Infusion</b>	<b>Dose</b>
H1	One hour loading infusion	300 µg/kg/h
H2 –H120	119 hour maintenance infusion	150 µg/kg/h
H121 – H126	6 hour taper	125 µg/kg/h
H127 – H132	6 hour taper	95 µg/kg/h
H133 – H138	6 hour taper	65 µg/kg/h
H139 – H144	6 hour taper	35 µg/kg/h
<b>Study Sites</b> Up to 180 sites in the USA, Israel, Europe, and Canada.		
<b>Number of Subjects</b>		

The study will randomize 140 subjects at up to 180 sites.

### Study Population

Subjects will be aged 18 years or more, in SRSE<sup>1</sup> (as defined in the Inclusion Criteria [Section 8.1](#)), and being managed in an intensive care setting.

### Duration of Subject Involvement

Individual subject participation will be up to 30 days.

### Study Design

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

Patients will follow one of three paths to entry to the study. The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst or seizure suppression with a third-line agent. These subjects will be consented for the study after admission to the intensive care unit, before or after any third-line agents are administered for burst or seizure suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their legally authorized representative (LAR). Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours. Once burst or seizure suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The second path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst or seizure suppression pattern on the EEG. These subjects may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst or seizure suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst or seizure suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst or seizure suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

<sup>1</sup> In this study, the term Super-Refractory Status Epilepticus or SRSE is equivalent to “Refractory Status Epilepticus (RSE) that has failed standard treatment” and the two terms are used interchangeably.

The third path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst or seizure suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These subjects may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 treatment or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within eight hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo).

The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that subjects, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as both the ability to wean the subject off all third-line agents before the end of the infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication infusion, and concurrent signs of physiologic brain activity as determined by EEG. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#) and [Table 2](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo will all subsequently be eligible to be administered SAGE-547 at the higher dose.

### Visit Schedule

The visit schedule and an overview of events at each visit is provided in [Table 1](#), [Table 2](#) and [Table 3](#) Schedule of Assessments.

**Study Objectives*****Primary objective:***

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult subjects with SRSE, and for the response to endure at least 24 hours after the end of the SAGE-547 or placebo infusion (primary response).

***Secondary objectives:***

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in the Clinical Global Impression scale (CGI) between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

***Safety objectives:***

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

***Other objectives:***

1. To evaluate the impact of treatment with a higher dose SAGE-547 infusion;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;

3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;
6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS).

**Endpoints*****Primary endpoint:***

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

***Secondary endpoints:***

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

***Safety endpoints:***

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.

**Other endpoints:**

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who are treated with a higher dose of SAGE-547.
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS).

**Inclusion Criteria**

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects 18 years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed zero or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst or seizure suppression pattern; or who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst or seizure suppression pattern.

**Exclusion Criteria**

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone or any excipients in SAGE-547.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy with highly malignant/malignant EEG features ([Westhall, Rosetti et al. 2016](#)).
4. Subjects who have any of the following:

- a. a GFR low enough to warrant dialysis but for whatever reason, dialysis that would adequately remove Captisol® is not planned;
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the opinion of the investigator, of less than 30 days.
5. Subjects who are being administered more than three third-line agents concomitantly or in whom the qualifying wean cannot be completed within 24 hours, or who are being administered a third-line agent for other indications such as management of raised intra-cranial pressure that would preclude weaning according to this protocol.
  6. Subjects with a living will that does not allow heroic measures.
  7. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
  8. Subjects who have been treated or randomized in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not have received study drug/placebo and then re-enroll).

### **Pharmacogenetic Research**

In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **Statistical Analysis**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

### **Interim Analysis**

When approximately 50% of the subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### **Analysis of Primary Endpoint**

The analysis of response to treatment between SAGE-547 treated subjects and placebo treated subjects will be performed using a Cochran-Mantel-Haenszel test with variables for treatment, concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). In this analysis, a treatment responder is a subject who is successfully weaned off all third-line agents and blinded study medication prior to the end of study treatment infusion.



and remains off third-line agents for at least 24 hours following cessation of the blinded study medication, and who has concurrent signs of physiologic brain activity as determined by EEG. The analysis will be based on the ITT Population. The comparison of treatment response rates will be conducted at the 5% level of significance.

### **Analysis of Secondary Efficacy Endpoints**

The primary analysis will be repeated for the MITT population. Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section. Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. Secondary analyses will be repeated for the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from Baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third-line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

Summaries of safety endpoints will be based on the overall Safety Population which is defined as all subjects who at least initiated the infusion with blinded study treatment.

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects are treated with a higher dose of SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo. Summary statistics will be presented for subjects who were QW successes.

### **Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

**Table 1: Schedule of Assessments for Protocol 547-SSE-301: One Infusion of Study Drug (blinded)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical/SE/Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X	X	X	X	X	X	X	X		X		
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X		X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X		X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X		X	X		X		X		X		
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X			
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>n</sup>											X
Modified Rankin Score (mRS)	X <sup>n</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV 3rd-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>o</sup>				
EEG	X	X				X		X	X			
Randomization		X										
Study Drug Administration <sup>p</sup>			X	X	X	X	X	X				
TW Outcome & Open-label Treatment Decision										X <sup>q</sup>		
Physiologic Brain Activity									X			
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

**Table 2: Schedule of Assessments for Protocol 547-SSE-301: Two Infusions of Study Drug (one blinded, one open-label)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V3R
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	0-24h
Eligibility Checklist	X										S
Informed Consent <sup>a</sup>	X										E
Inclusion/Exclusion Criteria	X										E
Demography <sup>b</sup>	X										
Medical and SE and Wean History <sup>c</sup>	X										T
Height	X										A
Weight <sup>d</sup>	X	X	X	X	X	X	X	X		X	B
Serum Pregnancy Test <sup>e</sup>	X										L
Hematology <sup>f</sup>	X		X	X		X		X		X	E
Serum Chemistry and GFR <sup>f</sup>	X		X	X		X		X		X	
Urinalysis <sup>h</sup>	X		X	X		X		X		X	E
Pharmacogenetic sample	X										X
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X	T
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X	E
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X		N
STESS	X										I
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	O
Glasgow Outcome Score (GOS)											N
Supervision Rating Scale (SRS)	X <sup>n</sup>										
Modified Rankin Score (mRS)	X <sup>n</sup>										
Epilepsy Status	X										N
Clinical Global Impression (CGI)	X										E
Continuous IV Third-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>o</sup>			X
EEG	X	X				X		X	X		T
Randomization		X									
Study Drug Administration <sup>p</sup>			X	X	X	X	X	X			
TW Outcome and Open-label Treatment Decision										X <sup>q</sup>	P
Physiologic Brain Activity									X		
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X	A
Concomitant Anti-Epileptic Drugs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	G
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	E
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X	
Pharmacoeconomic Data											
Mortality											

**Table 2 continued**

	V3R	V4R	V5R	V6R	V7R	V8R	V9R	V10R	V11R	V12R
	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3R+14d (±2d)	V3R+21d (±2d)
Weight <sup>d</sup>	X	X	X	X	X	X				
Serum Pregnancy Test <sup>e</sup>										
Hematology <sup>f</sup>	X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X	X		X		X		X		
Vital Signs <sup>i</sup>	X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>	X	X	X	X	X	X	X			
STESS										
FOUR Score <sup>m</sup>	X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)										X
Supervision Rating Scale (SRS)										X
Modified Rankin Score (mRS)										X
Epilepsy Status										X
Clinical Global Impression Scale (CGI)										X
Continuous IV Third-Line Agent(s)	X	X	Wean	Wean	Wean	Wean <sup>o</sup>				
EEG			X			X	X			
Randomization										
Study Drug Administration <sup>p</sup>	X	X	X	X	X	X				
TW Success and Physiologic Brain Activity							X			
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data										X
Mortality										X

**Table 3: Schedule of Assessments for Protocol 547-SSE-301: Qualifying Wean Successes**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical and SE and Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X											
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X											
Serum Chemistry and GFR <sup>f</sup>	X											
Urinalysis <sup>h</sup>	X											
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X											
ECG <sup>j</sup>	X											
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>n</sup>											X
Modified Rankin Score (mRS)	X <sup>n</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV Third-Line Agent(s)	X	Wean										
EEG	X	X										
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

<sup>a</sup> Written informed consent by proxy (LAR) will be obtained prior to starting any study-related procedures not considered standard of care.

<sup>b</sup> Demographic information will be obtained by proxy and confirmed by the subject when possible.

<sup>c</sup> Medical history will be obtained by proxy and confirmed by the subject when possible. All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Dosing changes with the third-line agent(s) that constitute a wean attempt will be marked as such on the CRF, and the start/stop dates and times of all wean attempts prior to V3 will be recorded, as well as the outcome of the wean attempt.

<sup>d</sup> Weight will be collected at Screening (V1) and prior to administration of the blinded study drug infusion at V2 and the open-label study drug infusion at V10. The weights at V2 and V10 will be used to determine the appropriate infusion rate of the blinded and open-label infusions respectively. If easily obtained (such as via a scale-bed), weight will also be recorded once during each subsequent 24 hour period of the initial study drug infusion period (V3-V8) and second infusion period (V3R-V8R, if applicable).

<sup>e</sup> Serum pregnancy test for females aged 18 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy.

<sup>f</sup> Blood samples will be taken for hematology and serum chemistry and GFR calculation at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will document whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

<sup>g</sup> Blood samples will be taken at V11 or V11R for serum chemistry (renal panel only).

<sup>h</sup> Urine samples will be taken for urinalysis and NAG at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will add a comment about whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

<sup>i</sup> Vital signs will be recorded at the following time points relative to the start of each infusion of study drug: Screening (V1), at 0, 30, 60 minutes ( $\pm 15$  minutes), at 2, 4, and 8 hours ( $\pm 30$  minutes), and at 24, 48, 72, 96, 120, 144, 168, and 192 hours ( $\pm 2$  hours).

<sup>j</sup> For the first 50 subjects randomized in the study, ECG (12-lead) should be performed at Screening (V1) and at the following times relative to the start of study drug infusion. For the blinded (first) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 128, 136, 144, 152, 160, and 192 hours ( $\pm 2$  hours). For the open-label SAGE-547 (second) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 126, 132, 138, 144, 152, 160, and 192 hours ( $\pm 2$  hours). Heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours. Following randomization of the first 50 subjects, subsequent subjects randomized in the study will have ECG collected at the following timepoints: Pre-dose and at 1, 12, 24, 48, 72, 96, 120, 144, and 192 hours after the start of the blinded (first) study drug infusion; and, Pre-dose and at 1, 12, 24, 48, 72, 96, 120, 144, and 192 hours after the start of the open-label (second) study drug infusion. It is not necessary to collect these ECGs with the PK samples at these timepoints and, apart from the 1 h ECG, there is  $\pm 2$  hour time window for these ECGs.

<sup>k</sup> Plasma will be collected to assay for study drug concentrations at the following time points relative to the start of each infusion of study drug: For the blinded (first) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion. For the open-label SAGE-547 (second) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open-label SAGE-547 study drug infusion. Pre-dose samples may be taken within two hours before starting the infusion of study drug; timepoints up to and including 1h will have a time window of  $\pm 5$  minutes; all other timepoints will have a window of  $\pm 15$  minutes.

<sup>m</sup> FOUR Score assessments will be performed at Screening (V1), 24, 48, 72, 96, 120, 144, 168, and 192 hours (all  $\pm 2$  hours) relative to the start of each infusion of study drug, and at V11 or V11R, and at V12 or V12R.

<sup>n</sup> SRS at V1 will be a retrospective assessment of the supervision required by the subject immediately prior to admission that includes the index episode of the SE, and mRS at V1 will be a retrospective assessment of the disability and dependence of the subject immediately prior to admission that includes the index episode of the SE.

<sup>o</sup> Target for complete wean of all continuous IV third-line agents by 144 hours at V8/V8R if not completed by 120 hours at V7/V7R.

<sup>p</sup> Study drug infusion is intended for IV administration only with a dedicated peripheral IV line using Sage-approved IV administration bags and lines.

<sup>q</sup> At V10 only a decision to re-treat at a higher dose of SAGE-547 will be made by the Investigator if the continuous IV third-line agent wean has failed or the third-line agent requires re-introduction during V9. Subjects who become eligible for open-label study drug at a higher dose of SAGE-547 will discontinue the planned visit schedule at V10, then repeat V3 (V3R) and all applicable subsequent visits.

<sup>r</sup> AEs will be collected from the time Informed Consent is obtained and prior to the start of study-specific screening procedures not considered standard of care. Collection of AEs will continue throughout the study from V1 through V12 or V12R.

<sup>s</sup> Subjects may enter the study on AEDs and Pressors and be administered AEDs and Pressors during the study. For all randomized and the first 50 QWS subjects, all Concomitant AEDs and Pressors must be recorded on the CRF with details including date and time of starting/stopping each AED and Pressor, the route of administration, changes in doses, and

frequency of administration. Details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the CRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”. For subsequent QWS subjects, after the detailed information on all concomitant AEDs and Pressors collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant AED and Pressor and the start and stop dates and times) from Visit 3 to Visit 12 will be recorded in the eCRF.

<sup>†</sup> All third-line agents administered since the diagnosis of SE will be recorded on the CRF. For all randomized and the first 50 QWS subjects, details will include the name of the drug, the start/stop dates and times, and, after consent, the doses with start/stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R. For subsequent QWS subjects, after the detailed information on all concomitant third-line agents collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant third-line agent and the start and stop dates and times) from Visit 3 to Visit 12 will be recorded in the eCRF.

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**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
AE	adverse event
AED	anti-epileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the time-concentration curve
AW	additional weans
BDZ	benzodiazepine
BIEEG	blinded infusion electroencephalogram
BUN	blood urea nitrogen
CBC	complete blood count
CEEG	consent electroencephalogram
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
C <sub>max</sub>	maximum plasma concentration
C <sub>min</sub>	minimum plasma concentration
CNS	central nervous system
CRF	case report form
CSR	clinical study report
CYP2C9	cytochrome P450 enzyme involved in drug metabolism
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EEG	electroencephalogram
EIND	Emergency Use Investigational New Drug Application
EP	European Pharmacopeia
ESETT	Established Status Epilepticus Treatment Trial
FDA	Food and Drug Administration
FOUR	Full Outline of UnResponsiveness
GABA	$\gamma$ -aminobutyric acid
GABA <sub>A</sub>	$\gamma$ -aminobutyric acid-gated chloride channel
GCP	Good Clinical Practice

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
GFR	glomerular filtration rate
GOS	Glasgow Outcome Scale
H	hour
HPLC	high performance liquid chromatography
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent to Treat
IV	intravenous
IVRS	Interactive Voice Randomization System
LAR	legally authorized representative
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent to Treat
mRS-9Q	Modified Rankin Score - 9Q
MS/MS	tandem mass spectrometry
nM	nanomolar
NMDA	n-methyl-D-aspartic acid
OW	other weans
PAEEG	primary endpoint electroencephalogram
PD	pharmacodynamics
PK	pharmacokinetic
QOL	quality of life
QW	qualifying wean
QWEEG	qualifying wean electroencephalogram
RBC	red blood cell
RSE	refractory status epilepticus



<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
SAE	serious adverse event
SAP	Statistical Analysis Plan
SE	status epilepticus
SOP	standard operating procedure
SRS	Severity Rating Scale
SRSE	Super-refractory status epilepticus
SSRI	Selective serotonin re-uptake inhibitors
STESS	Status Epilepticus Severity Score
SUSAR	Suspected Unexpected Serious Adverse Reactions
SWFI	Sterile Water for Injection
TAEEG	taper electroencephalogram
T <sub>max</sub>	time at maximum plasma concentration
TW	terminal wean
TWEEG	terminal wean electroencephalogram
US	United States
USP	United States Pharmacopeia

### 3. INTRODUCTION AND RATIONALE

#### 3.1. Status Epilepticus

Status epilepticus (SE) is a life-threatening seizure condition in which the brain is in a state of persistent seizure triggered by neuronal hyperexcitability. The Neurocritical Care Society defines SE as one continuous unremitting seizure lasting longer than five minutes or recurrent seizures without regaining consciousness between seizures for greater than five minutes (Brophy, Bell et al. 2012). Common causes of SE include preexisting epilepsy, cerebrovascular disease (in adults), electrolyte and metabolic disturbances, anoxia, encephalopathies, head trauma, high fever (in children, especially in the first year of life) and drug or substance intoxication. SE is associated with substantial morbidity and mortality.

##### 3.1.1. Epidemiology of SE

Geography, sex, age, and race influence the epidemiology of SE, whose incidence has a bimodal distribution, peaking in infants/young children and the elderly (Hauser 1990; DeLorenzo, Pellock et al. 1995; Wu, Shek et al. 2002). The incidence of SE in the elderly population is at least twice that in the general population. Concurrent medical conditions often exist in the elderly population, which can complicate therapy and worsen the prognosis of SE (Chapman, Smith et al. 2001).

The annual incidence of SE in the US is generally quoted to be within the range of 18/100,000 to 61/100,000, based on a 19-year retrospective study in Rochester, Minnesota (Hesdorffer, Logroscino et al. 1998) and a 2-year prospective study in Richmond, Virginia (DeLorenzo, Pellock et al. 1995), respectively. Two studies from Europe give annual incidences of a similar magnitude, ranging between 9.9/100,000 and 15.8/100,000 (Coeytaux, Jallon et al. 2000; Knake, Rosenow et al. 2001). It is thus estimated that in the United States each year there are as many as 150,000 cases of SE (DeLorenzo, Pellock et al. 1995).

#### 3.2. Refractory SE

When a patient begins to seize, the emergency medical technician will administer a first-line intravenous (IV) benzodiazepine (BDZ), such as diazepam, lorazepam or midazolam (Silbergleit, Durkalski et al. 2012), which is done either at the scene of the seizure or in the ambulance. If this is unsuccessful at abating the seizure, additional doses of the first-line therapy will be administered in the emergency room. Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line therapy, which is an IV anti-epileptic drug (AED) such as phenytoin or valproic acid (Novy, Logroscino et al. 2010; Shorvon 2011; Hocker, Britton et al. 2013).

Approximately 20-30% of patients refractory to first-line treatment will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to approximately 70-80% of patients who receive second-line therapy refractory to that therapy.

If a patient's SE continues after administration of BDZs and AEDs, the subject is diagnosed as having refractory status epilepticus (RSE), which must be treated quickly to terminate the seizure activity, maintain the patient's airway, and prevent cerebral damage. RSE patients are immediately admitted to the Intensive Care Unit (ICU) and placed in a medically-induced coma to stop all seizure-related activity. The drugs used to induce coma are continuously-infused IV agents,

commonly propofol, midazolam, or pentobarbital, referred to as third-line agents (Brophy, Bell et al. 2012).

The RSE patient is continually monitored using electroencephalography (EEG) to ensure that seizure and/or burst suppression is achieved. Burst suppression is a pattern of brain waves seen on an EEG, characterized by periods of activity alternating with periods of little or no activity in the brain, informing medical personnel of the effectiveness of the medically-induced coma. The goal of burst suppression is to allow the brain and corresponding neuronal tissue to restore function and reset to normal pre-seizure levels.

### **3.2.1. Epidemiology of RSE**

Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line AED therapy. In turn, approximately 20 – 30% of these patients treated with AEDs will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to 28% of the total estimated SE patient population refractory to second-line therapy. Based on the previously-cited estimated incidence in the US, this means that there are up to 42,000 incident cases of RSE in the USA, annually (DeLorenzo, Pellock et al. 1995).

## **3.3. Super-refractory SE**

After 24 hours of burst or seizure suppression, the patient is weaned off of the third-line therapy. If the weaning is unsuccessful (neuronal activity has not returned to normal), the third-line agent is re-administered or a different third-line agent is started, and the patient is considered to be in super-refractory status epilepticus (SRSE) (Chapman, Smith et al. 2001; Shorvon 2011; Brophy, Bell et al. 2012). SAGE-547 is being developed as an adjunct to third-line therapy in patients in RSE who have failed standard treatment. In this protocol, the term “RSE that has failed standard treatment” is deemed to be equivalent to the term “SRSE” and the two may be used interchangeably.

### **3.3.1. Epidemiology of SRSE**

The incidence of SRSE is very poorly understood, mainly because the diagnostic codes used for SE do not generally differentiate its nature as responding or refractory to treatment. Based on the variable reporting of outcomes data, the incident cases of SRSE could represent between one and two-thirds of the RSE patients (Novy, Logroscino et al. 2010; Ferlisi and Shorvon 2012; Hocker, Britton et al. 2013; Sutter, Marsch et al. 2013). More detailed epidemiology studies are needed to better elucidate the proportion of RSE patients whose condition becomes super-refractory. A recent review of ICU discharge data in the USA suggests an annual incidence of approximately 35,000, based on patients who required at least three days in the ICU for SE [Sage data on file].

### **3.3.2. Outcomes of SRSE**

SE has varying degrees of mortality depending on the underlying etiologies. Table 4 outlines the acute mortality in patients with SE by etiology (Neligan and Shorvon 2010). The mortality rate of SRSE is estimated to be 30% to 50% using current standard of care.

The causes of death from SE (and therefore SRSE) are heterogeneous, resulting from neuronal cell death, complications of underlying medical conditions, or adverse effects of the current standard treatments. Prognosis worsens and mortality increases with longer duration of SE, i.e. with SE that develops into RSE or SRSE (Neligan and Shorvon 2010), and with longer duration of

medically-induced coma ([Ferlisi and Shorvon 2012](#)). There is an obvious unmet medical need to improve upon the current standard of care treatment regimens.

Morbidity is high and survivors have outcomes ranging from poor function to vegetative state ([Shorvon 2011](#)). Approximately one third of patients with RSE and SRSE will recover, but with chronic neurologic or other deficits ([Neligan and Shorvon 2010](#); [Hocker, Britton et al. 2013](#)). In all, it is estimated that less than 25-30% of all SRSE patients have a favorable functional outcome.

**Table 4: Approximate Mortality of Status Epilepticus in Different Etiologies**

Underlying Etiology	Associated Acute Mortality in Patients with SE (%)
Drug reduction/withdrawal, poor AED compliance, or low AED levels	0-10
Cerebrovascular Disease	20-60
Metabolic Disorders	10-35
Acute CNS Infection	0-30
Anoxia	60-100
Alcohol Abuse	0-10
Head Trauma	0-25
Drug Overdose/Toxicity	10-25
Brain Tumors	0-20
Cryptogenic/Idiopathic	5-20

### 3.3.3. Unmet Medical Need in Super-refractory Status Epilepticus

Treatment approaches for SRSE consist of diagnosis and treatment of underlying medical conditions, adding and changing anti-seizure drugs, and repeated attempts at weaning from IV anesthetic agents. Treatment of SRSE has three aims:

- to prevent excitotoxicity, which begins within 24 hours of SE onset;
- to prevent cerebral damage by initiating neuroprotective burst or seizure suppression;
- to prevent the complications of extended periods of anesthesia or unconsciousness ([Shorvon 2011](#)).

Currently, there are no therapies that have been specifically approved for RSE or SRSE. The primary drugs used to induce coma are continuously infused IV anesthetics such as propofol, midazolam, or pentobarbital/thiopental, known as third-line agents. Use of these drugs to control SRSE has only been studied in small retrospective reviews or small prospective studies without controls ([Hocker, Britton et al. 2013](#)) therefore there is no agreement on which drug is optimal nor on an optimal dosing regimen for the treatments that are used.

The most common adverse effect of the third-line agents is hemodynamic instability; in addition, they are not universally effective, with breakthrough seizures and withdrawal seizures requiring dose adjustments and changes in third-line agent(s). The drug thought to be most effective in SRSE, pentobarbital, is also associated with the most toxic adverse effect profile, comprising

decreased blood pressure and cardiorespiratory collapse (Claassen, Hirsch et al. 2002). The ability to wean patients successfully off the third-line agents as quickly as possible is therefore paramount, and an adjunct to SRSE treatment that enhances the success of the third-line agents and supports their successful weaning in a short timeframe would be an important addition to the therapeutic armamentarium. Preliminary clinical data show that SAGE-547 has been a successful adjunct to third-line therapy in this regard.

### 3.4. SAGE-547 Injection

Allopregnanolone is an endogenous, naturally occurring neuroactive steroid formed in the corpus luteum of the ovary, adrenal cortex and central nervous system (CNS) (Holzbauer, Birmingham et al. 1985; Paul and Purdy 1992; Ottander, Poromaa et al. 2005). It is a metabolite of progesterone created by the actions of 5- $\alpha$  reductase and 3- $\alpha$  hydroxy-steroid dehydrogenase. Allopregnanolone is a potent positive allosteric modulator of both synaptic and extra-synaptic GABA<sub>A</sub> receptors.

SAGE-547 Injection (allopregnanolone aqueous formulation in Captisol<sup>®</sup>) is being developed for the treatment of patients in RSE who have not responded to standard treatment. SAGE-547 Injection is a solution of 5 mg/mL allopregnanolone in Sterile Water for Injection (SWFI), USP and 250 mg/mL betadex sulfobutyl-ether sodium, NF. It is further diluted with Sterile Water for Injection, USP (SWFI) in IV bags to achieve an allopregnanolone concentration of approximately 1.67 mg/mL in an approximately isotonic solution and will be administered intravenously.

#### 3.4.1. Scientific Rationale for SAGE-547 in SRSE

Ineffective recruitment of inhibitory neurotransmission, together with excessive neuronal excitation, likely plays a role in the initiation and propagation of the electrical disturbance occurring in SE. GABA ( $\gamma$ -aminobutyric acid), the major inhibitory neurotransmitter in the central nervous system (CNS), is released from GABAergic neurons and binds to several types of GABA receptors (GABA<sub>A</sub>, GABA<sub>B</sub>, and GABA<sub>C</sub>) on target neurons. GABA<sub>A</sub> receptors are macromolecular proteins that form a chloride ion channel complex and contain specific binding sites for GABA and a number of allosteric regulators, including barbiturates, benzodiazepines, and some anesthetic agents. GABA receptor-mediated inhibition contributes significantly to the normal termination of a seizure (Kapur and Macdonald 1997). SAGE-547 is a positive allosteric modulator of the GABA<sub>A</sub> receptor.

The importance of terminating seizure activity as soon as possible is underpinned by a growing body of evidence from research and clinical observation that SE becomes more difficult to control as its duration increases. It has been postulated that this occurs due to a mechanistic shift from inadequate GABAergic inhibitory receptor-mediated transmission to excessive N-methyl-D-aspartic acid (NMDA) excitatory receptor-mediated transmission (Kapur and Macdonald 1997). As prolonged epileptiform bursting results in a reduction of GABA<sub>A</sub>-mediated synaptic inhibition, antiepileptic treatments which rely on enhancing intrasynaptic GABA<sub>A</sub> neurotransmission become less effective the longer SE continues.

Furthermore, the constitutive process of synaptic GABA<sub>A</sub> receptor internalization is accelerated by the increased neuronal activity associated with seizures. These findings suggest that the rate of GABA<sub>A</sub> receptor internalization is regulated by neuronal activity, and its acceleration contributes to the reduction of inhibitory transmission observed during prolonged seizures (Kapur and Macdonald 1997). Of note is that SAGE-547 binds to extrasynaptic as well as intrasynaptic GABA<sub>A</sub> receptors;

extrasynaptic receptors remain active with ongoing seizure activity, resulting in a putative mode of action for SAGE-547 in SRSE.

Status epilepticus induces cerebral damage that includes neuronal cell necrosis, gliosis, and network reorganization. The major cause of cell death in cerebral damage is excitotoxicity, which is initiated by glutaminergic receptor over-activation, causing calcium to flood the cell, thereby leading to apoptosis and necrosis. This process is initiated within a few hours of the start of seizure activity, and provides the medical imperative to terminate SE as quickly as possible. To prevent the consequences of the excitotoxicity cascade, it is recommended that anesthesia be initiated within 1-2 hours of onset of seizures at doses designed to induce EEG suppression patterns (Shorvon and Ferlisi 2011).

### **3.4.2. SAGE-547 Clinical Program in the Treatment of SRSE**

The current SAGE-547 development program includes:

- a completed Phase 2 open-label trial, Study 547-SSE-201;
- this proposed Phase 3 randomized, double-blind, placebo-controlled trial, Study 547-SSE-301;
- an ongoing open-label, expanded access protocol, Study 547-SSE-302;
- a number of EINDs for SAGE-547 in patients with SRSE.

The designs of these studies are all similar, with a five to six day infusion of SAGE-547 (or placebo), during which time attempts are made to wean the subject off all third-line agents. In the Phase 3 studies, those subjects who cannot be weaned off third-line agents while being administered SAGE-547 (or placebo) may be eligible for a second open-label infusion of SAGE-547 at a higher dose. Follow up of subjects is for 21 – 30 days after the first infusion of study medication.

### **3.4.3. Data from the SAGE-547 Development Program**

The data from 30 subjects included in the on-going clinical evaluation of SAGE-547 for the treatment of adults and children with SRSE clearly offers preliminary evidence that SAGE-547 could provide substantial and clinically significant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate. These subjects comprise 20 from the ongoing Phase 2 trial (71% success rate in 12/17 evaluable subjects) and 10 subjects who received EIND treatments (78% success rate in 7/9 evaluable subjects).

Successful therapy of SRSE has been defined as “the SE is completely controlled by the therapy, without breakthrough of withdrawal seizures, or discontinuation due to side effects or death during therapy,” (Ferlisi and Shorvon 2012). By this definition, which is in accord with the efficacy assessments used in the overall clinical evaluation of SAGE-547, 19 of the 26 (73%) subjects with SRSE who completed the SAGE-547 infusion were treatment successes. As data collection is ongoing, this information is preliminary and subject to change upon further monitoring.

Published reports on RSE and SRSE have stated mortality rate ranges from 35% to 65%. The underlying etiologies of SE in the 547-SAGE-201 study and EINDs are heterogeneous, and each one conveys a different risk of mortality and longer term morbidity. However, the death rate in subjects who have received SAGE-547, 6 out of 30 (20%) subjects, appears to be lower than the published rates. None of the deaths were considered related to SAGE-547: brain tumor, organophosphate toxicity, respiratory failure, respiratory arrest due to ventilator support withdrawal, and breast cancer.

In the Phase 2 study, 20 SAEs (15 non-fatal) have been reported in 13 (65%) subjects, and of these 3 events in 2 subjects (10%) were considered by the investigator to be related to SAGE-547: pulmonary emboli and tracheostomy dehiscence/infection. The Sponsor did not consider these events to be related to SAGE-547, rather to the underlying disease states. Four of the 20 subjects (20%) experienced AEs considered possibly related to SAGE-547 by the investigator, namely moderate myopathy and severe pulmonary emboli in 1 subject, moderate tracheostomy dehiscence and tracheostomy infection in 1 subject, moderate thrombocytosis in 1 subject and moderate BUN, ALT and AST elevation in 1 subject.

Review of the most current safety data from 547-SAGE-201 reveals that there were changes in serum chemistry, hematology, and urinalysis during the study, but that none of those changes were assessed as related to SAGE-547. There were also no SAGE-547-related changes to vital signs.

Despite the heterogeneity in the underlying causes of SE, the ages of the subject, comorbidities, which normally complicate the treatment of SE, and the fact that all subjects had failed current standard of care treatment, a large majority of subjects had a successful therapy outcome, with discontinuation of all third-line agents and resolution of SE.

Refer to the Investigational Brochure for further information on the pre-clinical and clinical data supporting the use of SAGE-547 in SRSE.

### **3.5. Study Rationale - SAGE-547 in SRSE**

#### **3.5.1. Justification for the Control Group**

Although SAGE-547 has demonstrated extremely promising activity in subjects with SRSE, both in the Phase 2 study and during the EINDs, these have been open-label investigations with no control data for comparison. Generally in the literature there are few data describing the success rates of wean attempts of third-line agents, and few comparative data on the effectiveness of the three main third-line agents, propofol, pentobarbital/thiopental, and midazolam.

Several options for a control group in Study 547-SSE-301 were considered:

- No control group was thought to be unacceptable since there are no reliable published data on success rates in this population that could be used for broad comparisons;
- An active control was considered but found to be impractical since none of the third-line agents are approved for their use in SRSE, no standardized dosing regimens or treatment guidelines have been adopted for the management of SRSE, and clinicians were unlikely to agree which of the available third-line agents would be reserved for the active control arm;
- Historical controls were considered but abandoned because of the practical difficulties of obtaining high quality data, the lack of ability to prospectively match cases, and a suspicion that clinical practice in the standard of care of SRSE is evolving, mandating the use of prospective, concurrent control data;
- Comparison to standard of care alone was considered as a feasible design. However, in a field where no widely adopted treatment guidelines exist, there was a concern that knowledge of the treatment group (SAGE-547 plus standard of care versus standard of care alone) would alter the behavior of the investigators such that they could be more aggressive with weaning in the SAGE-547 group;



- Placebo control is not without its challenges since the preliminary efficacy data for SAGE-547 show that the compound exerts central pharmacological effects and is associated with positive outcomes in around 70% of patients. There is therefore a potential ethical concern about administering placebo to desperately ill patients who have often exhausted all treatment options for SRSE. This concern has been addressed in two ways: firstly all patients receive current standard of care; secondly, all subjects who fail to be weaned from their third-line agents at the end of the blinded infusion of study drug will be administered open-label SAGE-547 without un-blinding their initial treatment allocation, so treatment with the investigational product is not denied, but delayed about a week in the setting of ongoing receipt of full current standard of care.

It was therefore decided that a blinded, placebo-controlled design was appropriate for Study 547-SSE-301.

### **3.5.2. Justification for the Dose Regimen**

The standard dose regimen has been studied in 19 subjects in the 547-SSE-201 Phase 2 trial; the average peak plasma concentration of SAGE-547 at the end of the loading dose was approximately 144 ng/ml. The average plasma concentration during the maintenance infusion was approximately 70 ng/ml. At these concentrations, there were no clear safety signals although two-thirds of subjects experienced an SAE and there were four deaths, all related to the underlying comorbid conditions. The standard dosing regimen was associated with an approximate 70% successful treatment outcome. For these reasons, the standard dosing regimen has been adopted for the initial SAGE-547 infusion to be compared in a blinded fashion to placebo.

In the 547-SSE-201 trial, three subjects have thus far received the higher dose regimen. This dose regimen has also been well tolerated. The average peak plasma concentrations at the end of the loading dose for both dosing regimens will be in the same range, as the loading dose is the same for both regimens. The average plasma concentrations observed during the higher maintenance dose are 102 ng/ml (n=2). The rationale for adopting the higher dose regimen as the open-label infusion of SAGE-547 for subjects who are retreated in this 547-SSE-301 trial is that those who fail on the standard SAGE-547 dose regimen are afforded the opportunity to have access to a higher dose. The justification to also administer the higher dose regimen to failures on placebo is that the regimen has thus far been well tolerated, and this methodology preserves the blind for the initial infusion.

A five-day dosing regimen with SAGE-547 was investigated in the Phase 2 study, 547-SSE-201. There were some cases when weaning off all third-line agents was not possible within 48 hours, but weaning was completed after the end of the infusion of SAGE-547. For this reason, the duration of dosing with SAGE-547 has been increased from 120 hours (five days) in Phase 2 to 144 hours (six days) in this Phase 3 study.

### **3.5.3. Rationale for Genetic Testing Sub-study**

Sage Therapeutics intends to perform genetic research in the SAGE-547 development program in order to explore how genetic variations may affect the metabolism and activity of SAGE-547. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials, and, possibly, to genetically-guided treatment strategies for optimizing decision making with respect to individual benefit:risk. Participation of subjects in genetic research as part of the overall clinical study is optional.



### **3.6. Benefit-Risk Evaluation of the Present Study**

Previous reports of human administration of exogenous allopregnanolone indicate that for exposures in men and women up to 150 nM, the most commonly reported AEs were sedation (recorded as sleepiness or tiredness), feelings of intoxication (like alcohol), flushing, and mild headache (Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007). No SAEs were reported (Navarro, Kaddouz et al. 2003; Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007; Kask, Backstrom et al. 2008; Kask, Backstrom et al. 2009; Timby, Hedstrom et al. 2011a). In view of the reduced consciousness and sedation of study subjects at entry into this protocol, none of these previously-reported events are likely to impact subjects in this study.

To date, in the SAGE-547 Phase 2 study and the EIND subjects, a majority of subjects demonstrated a successful therapy outcome (>70%). The majority in the clinical trial (65%) have also experienced SAEs, but none has been considered related to SAGE-547 by the Sponsor (SAEs in 2 subjects (10%) were considered possibly related by Investigator). Five deaths have been reported in 30 subjects (20%), all related to the underlying cause of SRSE and not related to SAGE-547 – this is in the context of published mortality rates between 35% and 65%. These preliminary data suggest that SAGE-547 has the potential to provide clinically relevant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate.

The underlying etiologies of SE are heterogeneous, and each one conveys a different risk of mortality. Subjects who survive SRSE still have a high risk of severe morbidity (Neligan and Shorvon 2010). The subjects treated with SAGE-547 in Study 547-SSE-201, are heterogeneous in factors such as age and etiology of SE, factors that usually complicate treatment and can increase morbidity and mortality. Even with this heterogeneity, the preliminary efficacy and safety data for SAGE-547 are very encouraging, and the mortality rate suggests that the risk to benefit assessment of this treatment rests on the side of benefit.

## **4. ETHICS**

### **4.1. Institutional Review Board or Independent Ethics Committee**

This protocol will be reviewed and approved by the Institutional Review Board (IRB) where the study is conducted. The IRB will meet all FDA requirements governing IRBs (CFR, Title 21, Part 56).

### **4.2. Ethical Conduct of the Study**

The Sponsor, the Medical Monitor, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable ICH and GCP guidelines, and must also conduct the study in accordance with local regulations.

### **4.3. Subject Information and Informed Consent**

Subjects prospectively enrolled in this study will be unable to give consent. Therefore, consent will be given by proxy by a legally authorized representative (LAR). Written informed consent is required for each subject prior to any testing under this protocol not considered standard of care, including screening tests and evaluations. Should a subject gain the ability to sufficiently

comprehend the situation and consent during the course of the study, written informed consent or verbal assent will be documented as required or recommended by the institution's IRB.

The form of consent to be obtained will depend on the condition of the subject as determined by the Principal Investigator. The informed consent form (ICF), as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50.

It is the responsibility of the Investigator to obtain consent and to provide the subject's LAR with a copy of the signed and dated informed consent form. The informed consent form for subject participation must also be available as part of the subject file for review by the site's dedicated study monitor or any authorized auditor of the Sponsor or regulatory authorities.

All ICFs used in this study must be approved by the appropriate IRB and by the Sponsor. The ICF must not be altered without the prior agreement of the relevant IRB and the Sponsor.

#### **4.4. Ethical and Regulatory Considerations for Pharmacogenetic Sub-study**

##### **4.4.1. Informed Consent for Pharmacogenetics**

The genetic component of this study is optional and subjects may participate in other components of the main study without having to agree to participate in the genetic component. If subject chooses to participate in the genetic component of the study, the subject or LAR must sign and date a specific consent form for the genetic component of the study in addition to the main study consent form. The principal investigator(s) is responsible for ensuring that consent is freely given and that the subject understands that they may discontinue from the genetic aspect of the study independent of their decision to remain within or withdrawal from the main study.

##### **4.4.2. Subject Data Protection Relative to Pharmacogenomics**

Sage Therapeutics will not provide individual genotype results to subjects, their family members, their general physician, their employer or any insurance company unless required to do so by law. While extra precautions will be taken to preserve confidentiality and to prevent genetic data from being linked to an individual's identity outside of a restricted access site, in certain exceptional situations (e.g. in case of a medical emergency or as a consequence of a specific regulatory need), certain individuals may see both genetic data and the personal identifiers of a subject; however in all cases a subject's medical information and genetic files will remain physically separated.

## **5. STUDY OBJECTIVES**

### **5.1. Primary Objective**

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult subjects with SRSE, and for the response to endure at least 24 hours after cessation of the SAGE-547 or placebo infusion (primary response).

## 5.2. Secondary Objectives

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in Clinical Global Impression Scale between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

## 5.3. Safety Objectives

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

## 5.4. Other Objectives

1. To evaluate the impact of retreatment with a higher dose of SAGE-547 infusion;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;

6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS).

## **6. ENDPOINTS**

### **6.1. Primary Endpoint**

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### **6.2. Secondary Endpoints**

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) and to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### **6.3. Safety Endpoints**

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.

### **6.4. Other Endpoints**

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who are treated with a higher dose of SAGE-547;

2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS).

## 7. INVESTIGATIONAL PLAN

### 7.1. Overview of Study Design

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

[Figure 1](#) provides an overview of the study design and [Figure 2](#) gives the details of treatment and follow-up on the active treatment arm. Patients will follow one of three paths to entry to the study. The first path is for patients who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst or seizure suppression with a third-line agent. These patients will be consented for the study after admission to the intensive care unit, before or after any third-line agents are administered for burst or seizure suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their LAR. Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours. Once burst or seizure suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned during the QW will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst or seizure suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The second path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst or seizure suppression pattern on the EEG. These patients may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst or seizure suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst or seizure suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst or seizure suppression has been achieved, the third-line agent or agents will

be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst or seizure suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The third path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst or seizure suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These patients may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst or seizure suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within eight hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third line agent wean attempts prior to randomization (one vs two or more).

The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

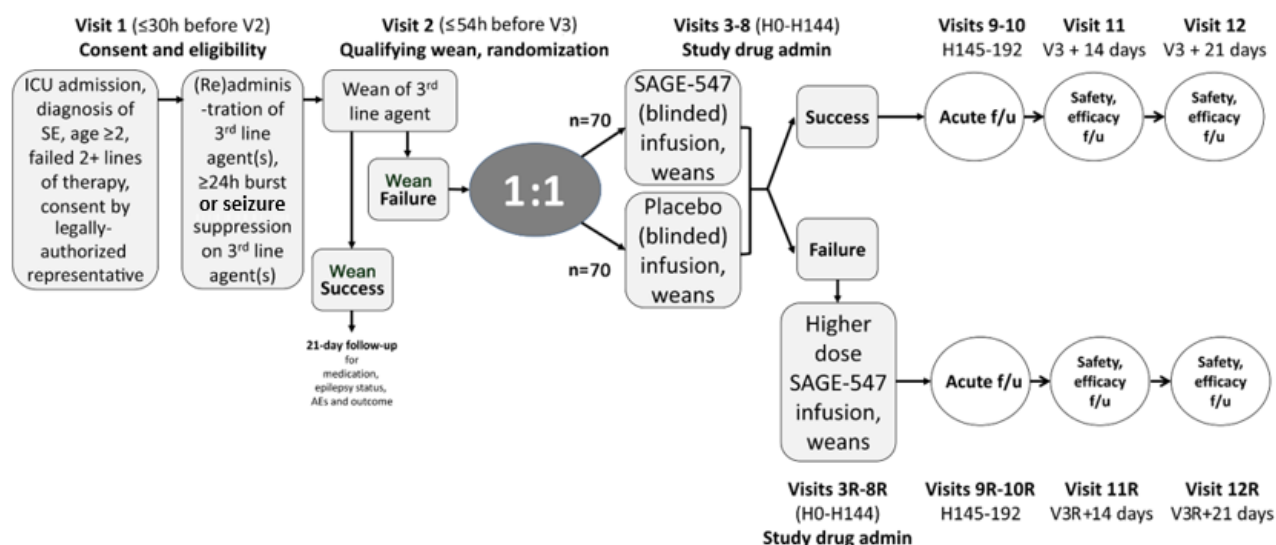
For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as the ability to wean the subject off all third-line agents before the end of the first infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication. Subjects must also have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) at the end of the primary endpoint assessment period as determined by EEG in order to be deemed a success. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#), [Table 2](#) and [Table 3](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion may be eligible to receive an open-label infusion of SAGE-547 at a dose higher than

that administered in the blinded part of the study. Eligibility for the open-label treatment must be confirmed in writing by the medical monitor prior to the open-label infusion starting. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo may all subsequently be eligible to be administered SAGE-547 at the higher dose.

**Figure 1: Study Design**



## 7.2. Trial Conduct

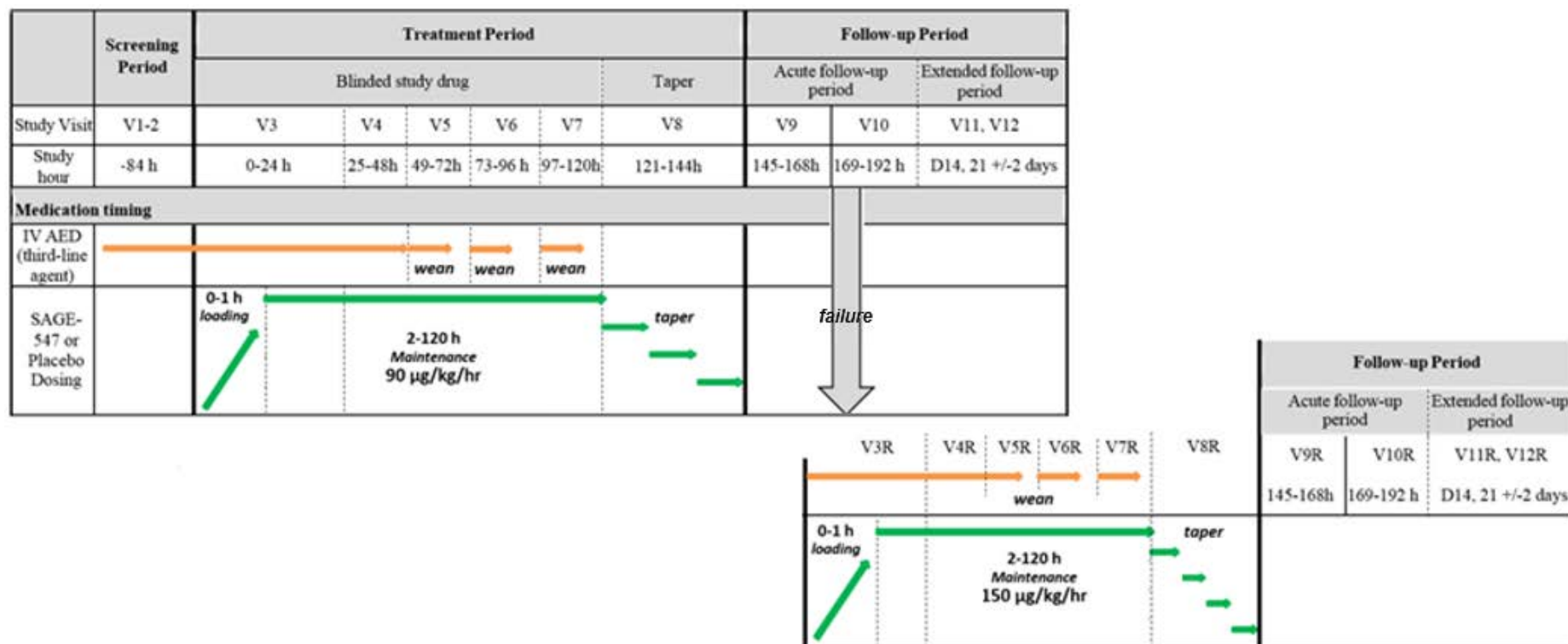
This study will be conducted according to the principles of the World Medical Association Declaration of Helsinki and most recent amendment, and in compliance with the protocol approved by the IRBs/Independent Ethics Committees (IECs), and in accordance with ICH Guidelines on GCP standards.

## 7.3. Blinding and Randomization

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo). Details of the dynamic randomization process will be included in the SAP.

The randomized portion of the study will be blinded, with the two treatment products (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

The second infusion of SAGE-547 will be administered on an open-label basis to subjects who meet the criteria for open-label treatment.

**Figure 2: Details of Treatment Administration and Follow-up**



## 8. SELECTION AND WITHDRAWAL OF SUBJECTS

The study will randomize 140 patients at up to 180 sites. All subjects deemed eligible to enroll must have written Medical Monitor approval on a case-by-case basis prior to undertaking the qualifying wean.

### 8.1. Inclusion Criteria

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects 18 years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; *or* who have previously failed zero or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst or seizure suppression pattern; *or* who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst or seizure suppression pattern.

### 8.2. Exclusion Criteria

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy with highly malignant/malignant EEG features ([Westhall, Rosetti et al. 2016](#)).
4. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis but for whatever reason, dialysis that would adequately remove Captisol® is not planned;
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the experience of the investigator, is less than 30 days.
5. Subjects who are being administered more than three third-line agents concomitantly or for whom the qualifying wean cannot be completed within 24 hours or who are being

administered a third-line agent for indications such as raised intra-cranial pressure that would preclude weaning according to this protocol.

6. Subjects with a living will that does not allow heroic measure.
7. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
8. Subjects who have been treated or randomized in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not have received study drug/placebo and then re-enroll).

### **8.3. Selection and Consent of Subjects for Pharmacogenetic Substudy**

All subjects will be asked to participate in pharmacogenetic research; however, participation in research is voluntary and a subject can decide to decline his/her participation without penalty or loss of benefit. Participation or lack thereof will not be a cause for exclusion from any aspect of the main study. In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **8.4. Subject Withdrawal / Study Termination**

#### **8.4.1. Withdrawal/Discontinuation of Individual Subjects**

The reasons for study drug discontinuation and/or subject withdrawal from the study must be recorded in the subject's electronic case report form (eCRF). The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject has been discontinued/withdrawn due to an AE.

##### **8.4.1.1. Withdrawal from the Study**

Subjects or their LAR may withdraw subjects from the study at any time for any reason without compromising the subject's medical care. The Investigator will also withdraw subjects upon the request of Sage Therapeutics or upon termination of the study.

Subjects who withdraw from the study prior to Visit 10 (or 10R) should complete the procedures scheduled for the day of study drug taper (Hour 121-144; Visit8/8R) on the day of their withdrawal, including the SAGE-547 taper schedule, with the addition of the mortality assessment from Visit 12/12R. Subjects who withdraw from the study after Visit 10/10R should undergo study procedures as outlined for Visit 12/12R on the day of their withdrawal. In all cases, the reason for subject withdrawal will be recorded in the eCRF.

Withdrawal of subjects for any reason should be discussed with the Medical Monitor.

##### **8.4.1.2. Discontinuation of Study Drug**

If it is necessary to discontinue the study drug earlier than planned, subjects should continue to be followed per protocol to capture safety and efficacy assessments for the duration of the study period.

The investigator may withdraw the subject from the study drug for the following reasons:

- Upon subject's or LAR's request
- The subject or LAR is unwilling or unable to adhere to the protocol-specified visits
- The subject experiences an intolerable adverse event
- During the course of the study, the subject develops symptoms or conditions listed in the exclusion criteria.
- Other medical reason, at the discretion of the Investigator and/or the Medical Monitor

Subjects who discontinue the study due to an AE considered related to study drug should be followed until the event is resolved, considered stable, or the Investigator determines the event is no longer clinically significant. Study drug discontinuation due to AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

#### **8.4.2. Study Termination**

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of AEs or other findings suggesting unacceptable risk to subjects, administrative or operational reasons. In the event of study termination, Sage Therapeutics will provide written notification to the Investigator. Investigational sites must promptly notify their IRB and initiate withdrawal procedures for participating subjects.

## **9. INVESTIGATIONAL PRODUCT**

### **9.1. Identity of Investigational Product**

SAGE-547 Injection (allopregnanolone)

### **9.2. Clinical Supplies**

#### **9.2.1. SAGE-547**

Adequate supplies of SAGE-547 Injection and materials for intravenous administration will be provided to each site.

SAGE-547 Injection is a clear, colorless sterile solution of allopregnanolone intended for intravenous injection. SAGE-547 Injection is an aqueous solution of 5 mg/mL allopregnanolone in 250 mg/mL Captisol® (betadex sulfobutyl-ether sodium, NF). It is presented either un-buffered or buffered with 10 mM citrate at a pH of 6.0 in either 20 mL or 50 mL vials. SAGE-547 is further diluted according to the Pharmacy Manual to achieve an approximately isotonic solution and will be administered intravenously.

No preservatives are included in the drug product, which is intended to be used as a single-use vial. All inactive components (excipients) used in the formulation are compendial grade and conform to current USP/EP, and include sodium citrate, citric acid and betadex sulfobutyl-ether sodium (Captisol®).

#### **9.2.2. Placebo**

Placebo will be identical to SAGE-547 and presented in identical vials. Placebo will be manufactured in a similar way to SAGE-547 and comprises all excipients but no SAGE-547.

### **9.2.3. Blinding**

The vials of SAGE-547 and placebo will be identical in every way so that they are indistinguishable by the pharmacist, investigator, anyone treating or managing the patient, the monitors, and the sponsor. In this way the first infusion of study drug administered to each patient will be double-blind.

For the blinded study drug infusions, subject-specific dosing kits will be provided. These dosing kits will be pre-labelled with kit number for the first blinded infusion. For the second-infusion, open-label kits will be provided, which will require subject assignment by the pharmacy for reconciliation purposes. The study kits must be stored under refrigerated conditions (2-8 °C). IV administration bags and lines may be provided for the blinded and open-label infusions. Refer to the Pharmacy Manual for additional details.

The label for the SAGE-547 Injection vials will include standard product identification information according to the Code of Federal Regulations, 21CFR 312.6. All study labels will also contain the following statement:

Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use.

### **9.3. Preparation of SAGE-547 or Placebo Injection for Dosing**

The Pharmacy will be responsible for preparing the blinded and open-label study drug for subject dosing. The prepared admixture will be assigned a room temperature (20-25 °C) storage shelf life of 24 hours from time of compounding.

SAGE-547, which is hypertonic, will require dilution with SWFI to achieve an approximately isotonic solution according to the instructions provided in the Pharmacy Manual. Exactly the same procedures will be used to prepare the placebo admixture, so that all site staff remain blinded as to treatment allocation for the first infusion of study drug. SAGE-547 Injection is not intended to be administered to patients undiluted.

Refer to the Pharmacy Manual for specific instructions regarding infusion preparation.

### **9.4. Administration and Accountability**

The Pharmacy will maintain accurate records of all investigational product supplies. Accurate records will be kept regarding the volume of SAGE-547 Injection or placebo used for each IV preparation, as well as the required infusion rate or rates, and the date and time of preparation. Reasons for departure from the expected dosing regimen must also be recorded. To satisfy regulatory requirements regarding drug accountability, all study medication will be reconciled in full. Refer to the Pharmacy Manual for additional details.

## **10. TREATMENT OF SUBJECTS**

### **10.1. Dosing Schedule (Blinded Infusions)**

SAGE-547 Injection or placebo will be administered according to the dosing schedules in [Table 5](#). The infusion rates to accomplish these µg/kg/h doses will be calculated according to the weight of the subject obtained within the eight-hour window that follows the declaration of the QW failure at V2 and prior to dosing at V3. The infusion rates will be applied to blinded study drug for the first infusion of study medication.

**Table 5: SAGE-547 or Placebo Dosing Schedule**

Hour	Type and Duration of Study Drug Infusion	Description
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	90 µg/kg/h
H121 – H128	8 hour taper	65 µg/kg/h
H129 – H136	8 hour taper	45 µg/kg/h
H137 – H144	8 hour taper	25 µg/kg/h

## 10.2. Dosing Schedule (Open-Label Infusions)

Those subjects that qualify for the open-label study drug will be administered SAGE-547 Injection will be re-administered according to the dosing schedule in [Table 6](#). The dose will be administered on a µg/kg/h basis, and the subject's weight measured prior to dosing during V10 will be used to calculate the doses. These infusion rates will be applied to SAGE-547 treatment for the open-label second infusions of study medication.

**Table 6: SAGE-547 Open-Label Dosing Schedule**

Hour	Type and Duration of SAGE-547 Infusion	Description
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	150 µg/kg/h
H121 – H126	6 hour taper	125 µg/kg/h
H127 – H132	6 hour taper	95 µg/kg/h
H133 – H138	6 hour taper	65 µg/kg/h
H139 – H144	6 hour taper	35 µg/kg/h

## 10.3. Route of Administration

SAGE-547 Injection is intended for IV administration only. The compatibility of SAGE-547 with other drugs is unknown, and the product should be administered via a dedicated peripheral IV line using any Sage-supplied study-specific IV administration bags and lines. In order to preserve blinding, these instructions also apply to the blinded placebo infusions.

## 10.4. Treatment Period

The treatment period with double-blind SAGE-547 or placebo is six 24-hour periods (144 hours), which may encompass 6-7 calendar days. The open-label study drug treatment period is of identical duration.

## 10.5. Concomitant Medications, Procedures and Treatments

Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. For all randomized and the first 50 qualifying wean success (QWS) subjects, detailed information on all concomitant medications (concomitant AEDs, third-line agents, pressors, and other concomitant medications), procedures, and treatments should

be documented throughout the study from Screening through Visit 12/12R, as described below, and recorded on the eCRF. For subsequent QWS subjects, after the detailed information on all concomitant AEDs, pressors, third-line agents, procedures, and treatments collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant AED or pressor, third-line agent, procedure, and/or treatment, and the start and stop dates and times) from Visit 3 through Visit 12 will be recorded in the eCRF. For subsequent QWS subjects, after the detailed information on all concomitant medications collected during the screening period (Visits 1 and 2) has been recorded, only minimal information, to include the name of the concomitant medications and indication only will be recorded from Visit 3 through Visit 12.

SAGE-547 has demonstrated inhibitory effects on cytochrome P450 isoenzyme 2C9 (CYP2C9). Therefore, AEDs such as phenytoin and phenobarbital that are primarily metabolized by CYP2C9 should be closely monitored during SAGE-547 administration to ensure target exposures are maintained.

#### **10.5.1. Concomitant AEDs**

Subjects may enter the study on AEDs, and be administered AEDs during the study. All of these must be recorded on the eCRF with details including date and time of starting and stopping each AED, the route of administration, changes in doses, and frequency of administration. In addition, details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the eCRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.

#### **10.5.2. Concomitant Third-Line Agents**

All third-line agents (as defined in [Section 8](#)) administered since the diagnosis of SE will be recorded on the eCRF, whatever path the patient took for entry into the study. Details will include the name of the drug, the start and stop dates and times, and, after consent, the doses with start and stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

In addition, those changes in dose that constitute a wean attempt will be marked as such on the eCRF. In this way the start and stop dates and times of all wean attempts (see [Section 11](#) for definitions) will be recorded, as will the type of wean (QW, OW, or TW) and the outcome of the wean attempt (successful, failed and dose of this third-line agent increased or failed and this third-line agent stopped and another third-line agent started). Those wean attempts that occur after the TW up to and including Visit 12/12R will be marked “AW”.

Some third-line agents (such as propofol) are also used to induce sedation to facilitate a subject’s ability to tolerate the ventilator. For subjects requiring such sedation, propofol is the preferred agent unless there are contraindications. The eCRF will make clear from the indication for the third-line agent when it is being used for burst or seizure suppression and when it is being used as ventilator support or for another purpose. The investigator will add a note to the eCRF to justify that the doses used are appropriate for sedation and not for seizure or burst suppression. The doses used for ventilator support and other similar uses are usually much lower than those used for seizure or burst suppression, and use of these third-line agents for these other purposes does not constitute a wean failure under this protocol.

### **10.5.3. Concomitant Pressors**

The start and stop dates and times of all pressors will be recorded as well as the start and stop dates and times of all dose changes.

### **10.5.4. Other Concomitant Medications**

All other concomitant medications must be recorded on the eCRF with details including date and time of starting and stopping, the route of administration, dose, and frequency of administration.

## **11. STUDY ASSESSMENTS**

### **11.1. Efficacy Assessments**

#### **11.1.1. Primary Efficacy**

Success or failure will be determined, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo infusion and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the blinded (first) infusion of SAGE-547 or placebo. In addition, subjects must have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) to be deemed to be successes. All subjects who fail to complete their infusion of randomized treatment or do not have at least one attempt during study treatment to wean off all third-line agents will be considered as “failures” for the primary endpoint.

##### **11.1.1.1. Weaning**

Third-line agents are anesthetic agents that are administered in order to reach a seizure or burst suppression EEG pattern. For the purposes of this study, third-line agents are defined as continuous intravenous infusions of pentobarbital/thiopental, midazolam, propofol, and ketamine at maintenance doses alone or in combination sufficient to produce a burst or seizure suppression pattern on the EEG. The following are considered to be minimum maintenance doses of these agents that may be expected alone or in combination to achieve EEG burst suppression. If subjects are on lower doses than these and are not in EEG burst suppression for the first 12 hours of the blinded study drug infusion, they will be considered to be protocol violators and will exit the study.

- Pentobarbital: 1 mg/kg/hour
- Thiopental: 3mg/kg/hour
- Midazolam: 0.1 mg/kg/hour
- Propofol: 3 mg/kg/hour
- Ketamine 1.2 mg/kg/hour

The timing and nature of the third-line agent weans will be guided by the Clinical Standardization Guidelines for the study, and the clinical judgment of the investigator, and will always be primarily done in the best medical interests of the subject. Advice about weaning may be sought from the Clinical Standardization Team, a group of fellow investigators with experience of performing clinical trials in subjects with SRSE. The Clinical Standardization Team will be able to discuss EEGs in real time related to key study timepoints (terminal wean and the period after the end of the

blinded study drug infusion if the terminal wean was successful) in a timely manner in order to provide advice about compliance with the Clinical Standardization Guidelines.

The following guidance for weaning applies to all weans of third-line agents undertaken during the study. Continued determined efforts to liberate subjects from sedation must be undertaken for the entire duration of the blinded study drug infusion. Each failed wean from third-line agents should be followed by a 6-24 hour period of suppression and then another wean attempt, with further optimization of the AED regimen.

Weans include the qualifying wean (QW); the terminal wean (TW), which is the wean of the third-line agent if the subject is on only one third-line agent or the wean of the last third-line agent if the subject is on more than one third-line agent; the other weans (OW), which are the weans of the third-line agents other than the TW if the subject is on more than one third-line agent. The guidance also applies to additional weans (AW), which are the weans from third-line agents that take place after the TW for the first blinded study drug infusion or the second open-label study drug infusion.

### **QW Guidance**

- Wean to be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace that third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Investigators should allow 24 hours to lapse after the end of a “successful” qualifying wean before finally declaring the QW a success. If a third-line agent needs to be re-instituted within that 24 hours, the QW is a failure, and the subject may then be randomized in the study.

### **OW Guidance**

- First OW should not begin before H49 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- If the subject is on two third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the TW. However the OW may be completed over a shorter or longer time period and may overlap if clinically indicated with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- If the subject is on three third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the wean of the second agent. The second agent should be weaned over 24 hours and that wean completed before starting the TW. However the OWs may be completed over a shorter or longer time period and may overlap if clinically indicated with each other and with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the



dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.

- All OWs should be completed before H96 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **TW Guidance**

- The TW is defined as the wean of the last third-line agent.
- If the subject is on one third-line agent, the TW should not begin before H49 and should begin no later than H97 after starting administration of study drug or starting the open-label infusion of SAGE-547. If the subject has had one or more OWs, the TW should ideally begin as soon as the last OW is complete but in any case not later than H97 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- The TW must be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace this third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Every effort must be made to complete the TW before H120 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547, but the TW must be complete before H144 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **AW Guidance**

- AWs will take place when medically indicated in the opinion of the investigator.
- Ideally the AW should take place over 24 hours, but completion may be over a shorter or longer time period than this. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.

#### **11.1.1.2. EEG**

Electroencephalographs (EEGs) that are representative of the intermittent or continuous EEG being used to support key investigator decisions will be collected at the following time points:

- A 24-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst or seizure suppression for the second path to eligibility, and a variable pattern for the third path to eligibility. This EEG also aims to capture the burst or seizure suppression pattern during the 24 hours that precede the QW. If the CEEG does not capture the 24 hours that precede the QW, additional EEG data collected as standard of care prior to the CEEG and prior to the

QW may be collected to assess the depth of burst or seizure suppression in the 24 hour period prior to the QW.

- EEG will be performed to cover the qualifying wean (QWEEG). EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for up to 24 hours after the end of the QW. The duration of the QWEEG will be up to 48.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s), the decision to re-institute a third-line agent(s) at doses intended to induce burst or seizure suppression, and the decision that the QW is a success.
- EEG will be performed from three hours prior to the start of the blinded infusion to 12 hours after the start of the blinded infusion. This will be called the BIEEG. The intent of this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG and to assess the depth of burst suppression in the first 12 hours of blinded study drug infusion.
- EEG will be performed to cover the final or terminal wean of third-line agent (TWEEG). The TW is the wean of the final third-line agent during the blinded administration of study drug or the open-label infusion of SAGE-547; if the subject was on one third-line agent, the TW is the wean of that agent. If the subject was on three third-line agents, the TW is the wean of the third and final agent. EEG recording will start 30 minutes prior to the start of the TW, continue for up to 24 hours during the TW, and then continue for the one hour after the end of the TW. The duration of the TWEEG will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the final third-line agent or the decision to re-institute a third-line agent at doses intended to induce burst or seizure suppression because any seizure activity could not be managed using intermittent bolus doses of AEDs.
- EEG will be performed during the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 (TAEED). The TAEED is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the start of the taper (at Hour 119.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours during the taper, and then continue for the one hour after the end of the taper (to Hour 145 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547). The duration of the TAEED will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst or seizure suppression because any seizure activity seen during the taper could not be managed using intermittent bolus doses of AEDs.
- EEG will be obtained to cover the end of the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 and the ensuing 24-hour period, during which the primary endpoint is assessed (PAEED). The PAEED is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the end of taper (at Hour 143.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours after the end of the blinded administration of study treatment or the open-label infusion of SAGE-547, and then continue for the one hour after the end of the 24-hour assessment period (to Hour 169 after starting the blinded administration of study

treatment or after starting the open-label infusion of SAGE-547). The duration of the PAEEG will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst or seizure suppression because any seizure activity seen in the 24 hours following the end of the blinded administration of study treatment or the open-label infusion of SAGE-547 that could not be managed using intermittent bolus doses of AEDs.

In practice, most subjects are on continuous EEG monitoring or long periods of intermittent EEG monitoring. However, this protocol does not mandate continuous EEG monitoring and breaks from EEG monitoring to provide relief to the scalp from the irritating effects of the electrodes are advised, according to local practice. If a break in EEG monitoring is mandated by local practice guidelines at a time when one of the protocolled EEG segments is to be collected, the break in EEG monitoring will take precedence, with the reason for missing the EEG reading noted on the eCRF. The EEGs obtained for the study are therefore part of the existing EEG record rather than being obtained de-novo at each timepoint. For timepoints where there might be some ambiguity, such as the TWEEG, the final EEG record is that of the final attempt to wean the last third-line agent, even if earlier attempts to wean that agent took place. In some cases (the TAEED and PAEEG, for instance), the EEG records will overlap, but different cuts are taken to service the different EEG record requirements.

The electronic EEG file will be de-identified, the date and time of the start and stop of the EEG and the subject number will be attached to the file, and the study time point will be indicated (CEEG, QWEEG, BIEEG, TWEEG, TAEED, and PAEEG). The PI will indicate on the eCRF what the EEG shows, as follows:

- For the CEEG, the PI will describe the EEG pattern that determined which path to eligibility the subject was on.
- For the QWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure or success on the qualifying wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst or seizure suppression during the qualifying wean constitutes a failure); the QWEEG will extend to cover the 24 hours after the end of third line agents in order to confirm that the QW was a success.
- For the BIEEG, the PI will note the date and time of the start of the EEG and the pattern seen on the EEG.
- For the TWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure on the terminal wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst or seizure suppression during the terminal wean).
- For the TAEED, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst or seizure suppression before the end of the SAGE-547 infusion).
- For the PAEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary

endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst or seizure suppression in the 24 hours following the end of the SAGE-547 infusion).

A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm the depth of burst or seizure suppression prior to the QW and during the first 12 hours of the blinded study drug infusion, the PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period (average EEG power at the end of Visit 9 of more than two microvolts):

- All subjects will have the CEEG and QWEEG collected and stored, and the CEEG and QWEEG read;
- Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;
- Those subjects randomized who are not administered the open-label study drug will have the QWEEG, BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the BIEEG, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read;
- Those subjects randomized who later undergo the open-label infusion will have the QWEEG, BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion and the TWEEG, TAEED, and PAEEG related to the open-label study drug infusion collected and stored, and the BIEEG, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read.

All EEG records may be subject to quantitative EEG analysis.

### **11.1.2. Secondary Efficacy**

#### **11.1.2.1. Clinical Global Impression Scale (CGI)**

The clinical global impression scales are often utilized in clinical trials to allow clinicians to integrate several sources of information into a single rating of the subject's condition. Both the CGI-Severity (Question 1, CGI-S) and the CGI-Improvement (Question 2, CGI-I) employ a 7-point Likert scale measuring severity of the disease state in the subject and improvement, respectively. All severity assessments after initiation of SAGE-547 treatment should consider the general state of the subject over the preceding week. The third question on the scale will not be employed in this trial, and where the scale states "mental illness", this means "physical illness" in this trial.

The CGI-S will be evaluated at Visit 1 and at the last visit, Visit 12 or 12R. The CGI-I will be evaluated at Visit 12 or 12R.

#### **11.1.2.2. Epilepsy Status**

At Visit 1, the diagnosis of epilepsy will be documented as a no/yes question. If there was a previous diagnosis of epilepsy, further details will be documented, including:

- Date of diagnosis;
- Details of anti-epileptic drugs currently being taken;

- Type of epilepsy;
- Seizure frequency in the past month.

Information about the current (index) episode of status epilepticus will be obtained at Visit 1:

- Date of onset
- Date of failure to respond to first line agent(s) and the name(s) of the agent(s)
- Date of failure to respond to second line agent(s) and the name(s) of the agent(s)
- Any previous treatment with third line agents and the response to those agents (details of the third line agent drugs and previous wean attempts will be recorded on the Third Line Agent Medication CRF)
- The cause of the index episode of status epilepticus
- If the subject was transferred from another hospital or from within the hospital, the reason for the transfer will be recorded (such as for study enrollment, due to lack of medical options at original hospital or unit, due to lack of beds at the original hospital or unit, family request, other)

Previous (non-index) diagnosis of status epilepticus will be documented as a no/yes question. If SE did occur in the past 12 months, further information will be gathered, including:

- SE, RSE, or SRSE diagnosis, whichever was the most severe diagnosis for each episode;
- Cause;
- Treatment, including experimental treatments and need for intubation/ventilation;
- Dates of onset and duration.

At Visit 12 or Visit 12R, the following information will be gathered:

- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of SE up to and including Visit 12 or Visit 12R;
- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of seizures (convulsive and non-convulsive) up to and including Visit 12 or Visit 12R;
- Number of separate episodes of SE after H144 at the end of Visit 8 or Visit 8R (no/yes); if yes,
  - SE, RSE, or SRSE diagnosis;
  - Cause;
  - Treatment, including experimental treatments and need for intubation/ventilation;
  - Dates of onset and duration.

Note that a separate episode of SE is defined as an episode of SE separated from other periods of status epilepticus by at least 24 hours.

- Diagnosis of epilepsy since Visit 11 or Visit 11R will be documented as a no/yes question. If a diagnosis of epilepsy has been made, further details will be documented, including:

- Status as ongoing or new epilepsy since Visit 11 or Visit 11R after initiation of SAGE-547 treatment;
- Details of anti-epileptic drugs currently being taken;
- Type of epilepsy and seizure frequency in the past week.

## **11.2. Safety Assessments**

The safety and tolerability of SAGE-547 will be assessed using adverse events, clinical laboratory measures, vital signs, ECG intervals and morphology, and mortality. All safety assessments should be performed per hospital standard of care and will be collected periodically throughout the study according to [Table 1](#), [Table 2](#), and [Table 3](#) (Schedules of Assessments).

### **11.2.1. Adverse Events**

AEs will be collected after informed consent has been signed and prior to study-specific screening procedures not considered standard of care, during subject preparation for SAGE-547 administration and through Visit 12 or Visit 12R. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™) coding system (current version). See [Section 14](#) for additional details.

### **11.2.2. Clinical Laboratory Tests**

Blood samples will be taken for hematology, and serum chemistry and GFR will be calculated at:

- Visit 1 and then at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.
- Blood samples will be taken at Visit 11 or Visit 11R for serum chemistry (renal panel only).

Urine samples (20 ml) will be taken for urinalysis and urine NAG analysis at:

- Visit 1 and at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.

These samples will be analyzed at a central laboratory; hour-to-hour medical decisions will be based on sampling for laboratory testing done outside the protocol as part of normal standard of care. GFR will be calculated by the central laboratory.

Any out-of-range values will be flagged by the laboratory; the investigator will add a comment about whether the abnormality is clinically significant. Clinical significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

#### **11.2.2.1. Hematology and Serum Chemistry**

Hematology will include complete blood count (CBC) white blood cell count with differential, platelet count and red blood cell (RBC) count, hemoglobin and hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatine kinase,

lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose. In addition triglycerides will be measured in serum chemistry samples (to aid assessment of lipemia in pharmacokinetic samples).

#### **11.2.2.2. Pregnancy Test**

Females of child-bearing potential will be tested for pregnancy by serum pregnancy test at Visit 1. In this study, since an accurate history of menstruation in girls and menopause in older women may not be available at Visit 1, “child-bearing potential” is taken to mean any female aged 18 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy. Female subjects with a positive pregnancy test will be ineligible for study participation.

#### **11.2.2.3. Urinalysis**

Urinalysis will include assessment of protein, blood, leukocytes, glucose, ketones, urobilinogen, pH, and specific gravity.

#### **11.2.3. Vital Signs**

Blood pressure, heart rate, and temperature will be recorded at the following time points relative to the first infusion of study drug, and to the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547:

- Visit 1;
- At 0, +30, +60 minutes (+/-15 minutes) and +2, +4 and +8 hours (+/- 30 minutes) after the start of the infusion;
- At +24, +48, +72, +96, +120, +144, +168, and +192 hours (+/- 2 hours) after the start of the infusion.

#### **11.2.4. Weight and Height**

Weight and height will be measured at Visit 1. Weight will also be obtained at V2, within the eight hour window that follows the declaration of the QW failure and prior to the initiation of the blinded infusion loading dose at H0 of V3, and will be used to calculate the infusion rates throughout the entire blinded treatment course. If a subject qualifies for open-label study drug, the infusion rates for the open-label infusion will be calculated using the subject’s weight measured prior to dosing during V10.

If it is not possible to obtain the actual weight at the above-referenced timepoints, permission from the Clinical Monitor must be obtained to use another method to obtain the subject’s weight (such as information from the LAR or estimating using an established local protocol).

In addition, a daily weight will be obtained and recorded if this is easily obtained, such as the use of a scale bed.

#### **11.2.5. ECG**

For the first 50 subjects randomized in the study, 12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours. If it is not possible to

perform ECG immediately after the collection of PK samples up to 160 hours, ECG must be performed within 15 minutes prior to the collection of PK samples up to 160 hours; at other times the allowed time window for ECGs is +/- 2 hours:

- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +128, +136, +144, +152, +160, and +192 hours after the start of the blinded (first) study drug infusion
- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +126, +132, +138, +144, +152, +160, and +192 hours after the start of the open-label (second) study drug

The heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm.

For the subsequent subjects randomized in the study, the following timepoints for ECG will be used:

- pre-dose and at +1, +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the blinded (first) study drug infusion
- pre-dose and at +1, +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the open-label (second) study drug infusion

It is not necessary to collect these ECGs with the PK samples at these timepoints and, apart from the +1h ECG, there is +/- 2 hour time window for these ECGs.

#### **11.2.6. Mortality**

Mortality will be recorded on the Visit 12 or Visit 12R case report form. If the subject has died, the following information will be collected:

- Date of death;
- Cause of death.

As accurate as possible cause of death will be collected, which will be further categorized as due to one of the following causes:

- SE;
- complications of long term intubation and third-line agent infusions;
- underlying cause of qualifying SE;
- co-morbidity existing at the time of the qualifying SE;
- new co-morbidity or trauma;
- study drug;
- other (specify).

#### **11.2.7. Pharmacogenetic Samples**

If a subject's LAR consents to pharmacogenetic sampling, a blood sample for genetic research will be collected at Visit 1 in order to avoid the possible introduction of bias through the exclusion of patients who may withdraw from study due to an AE (a subject population that may be of specific interest for subsequent genetic analysis). If for any reason a sample cannot be taken prior to treatment, a sample can be drawn at any point prior to completion with the restriction that no more than one genetic sample be taken per subject.



The objective of this research is to collect and store blood samples for possible DNA extraction and exploratory research into how genes or specific genetic variation may influence response (i.e. distribution, safety, tolerability, and efficacy) to SAGE-547. Specific genetic variations of interest include but are not limited to: classes of metabolizing enzymes (e.g. Cytochrome P450 supra-family genes), genes encoding enzymes involved in the production and metabolism of allopregnanolone (e.g. AKR1C4 (3 $\alpha$ -hydroxysteroid dehydrogenase)), genes associated with the GABA receptor (e.g. GABRA1-A6, GABRB1-B3, GABRD, GABRE, GABRG1-3) and genes associated with the production and degradation of GABA.

Future research may suggest other genes or gene categories as candidates for influencing not only response to SAGE-547 but also susceptibility to disorders for which SAGE-547 is being evaluated. Thus, the genetic research may involve study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.

#### **11.2.7.1. Biological Sampling and Coding Procedures (Pharmacogenetics)**

To ensure patient confidentiality, utmost care will be taken in the coding and storage of pharmacogenetic samples.

*Extraction and coding:* DNA will be extracted from the blood sample and the DNA sample will be assigned a unique number replacing information from sampling tube. The assigned DNA number will be used to identify the sample and its corresponding information within Sage Therapeutics or at any designated contract laboratory for the purpose of sequencing of other DNA specific analysis. No personal details sufficient for individual identification will be available to any person (internal or external to Sage Therapeutics) working with the DNA.

*Genotype/Phenotype Analysis:* Samples and data from genetic analysis will be coded. The link between subject enrollment / randomization code and DNA number will be maintained and stored in a secure environment with restricted access. The established link will be used to identify relevant DNA samples for analysis, facilitated correlation of genotype results with clinical data, allow regulatory audit, and to trace samples for destruction in case of withdrawal of consent.

#### **11.2.7.2. Retention of Biological Samples for Pharmacogenetic Analysis**

Extracted DNA is a finite research that is destroyed in the process of being analyzed. Primary blood samples from which DNA can be extracted will be stored and used until no further analyses are possible, a maximum storage period of 25 years from time of last subject last visit has been reached, or an individual or LAR withdraws his/her or their consent.

### **11.2.8. Other Outcomes**

#### **11.2.8.1. Pharmacokinetic Data**

Formal plasma analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS)). In addition, all samples will be analyzed for important SAGE-547 metabolites (if and when these are identified) and Captisol<sup>®</sup> concentrations.

#### Plasma Analysis

Plasma will be collected to assay for SAGE-547 concentrations at the following time points relative to the start of each infusion of study drug:

- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion.
- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open-label SAGE-547 study drug infusion.
- All samples will also be analyzed for plasma concentrations of important metabolites of SAGE-547 if and when these are identified.
- All samples from the first 50 subjects randomized will also be analyzed for plasma concentrations of Captisol®.

The plasma samples will be drawn from the arm contralateral to that used for drug administration. Drawing samples from peripheral arterial or venous lines or from a central line is permissible. PK collection times should be adhered to as strictly as possible. The allowed time window for all samples is: pre-dose in the two hours prior to starting the infusion of study drug; samples up to and including 1h, +/- 5 minutes; subsequent samples, +/- 15 minutes. Subject-specific PK kits for sampling including instructions on collection and processing methods, and storage and shipping conditions, will be provided separately. To maintain the blind, all subjects will have samples taken as outlined above: subjects receiving SAGE-547 will have all samples analyzed for all analytes. Subjects on placebo may have samples analyzed to investigate endogenous allopregnanolone and metabolite concentrations, as well as Captisol® concentrations; experience with the plasma concentration data will determine if and which placebo samples are analyzed.

Each blood sample will be 3 ml in volume subjects weighing 30 kg or more, and 1 ml in volume for subjects weighing less than 30 kg. Separate aliquots will be obtained from each sample to service the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum blood draw for PK analysis for a subject having two infusions of study drug will be 99 ml (33 ml for subjects weighing less than 30 kg).

Plasma PK parameters for SAGE-547 will be calculated where appropriate (e.g.,  $C_{max}$ ,  $C_{min}$ ,  $t_{max}$ ,  $AUC_{last}$ ,  $AUC_{\infty}$ ,  $CL_s$ ). In addition, similar PK parameters will be calculated for Captisol®. PK parameters for important metabolites of SAGE-547 may be calculated. An evaluation will be made of the feasibility of adopting a population-PK approach to assess drug-drug-interactions with SAGE-547 as victim of AEDs.

In addition, the Visit 9 sample may be analyzed for plasma concentrations of third-line agents.

#### Other Analysis

If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations. The minimum volume of cerebrospinal fluid for analysis is 100 microlitres.

Full details of all pharmacokinetic analyses will be described in the Pharmacokinetic Analysis Plan.

**11.2.8.2. Correlation of QT/QTc Changes and Plasma Concentrations of SAGE-547**

An analysis will be performed to determine whether there is any correlation between changes in QT/QTc interval and plasma concentrations of SAGE-547, in order to investigate any effect that SAGE-547 may have on QT/QTc interval.

**11.2.8.3. Pharmacoeconomic Data**

At Visit 12 or Visit 12R, the following information will be collected: number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital. If the subject dies before Visit 12 or Visit 12R, data will be collected up to the date of death. The definition of “hospital” is the institution that the subject was initially treated in. If the subject is transferred to another hospital, that hospital would be the “discharge destination from the hospital” and the “number of days in hospital” would be the number of days in the initial treating hospital.

For those subjects discharged from hospital before Visit 12/12R, the following questions will be asked:

- On what study day was the subject discharged from hospital?
- What type of facility was the subject discharged to (another hospital, a rehabilitation center, a supported care facility, home, other)?
- How many days did the subject stay in this facility?

The following questions will be answered regarding the stay in the ICU and hospital:

- Was the subject still in the ICU at the end of Visit 10/10R?
- If the FOUR Score was  $\geq 12$  at Visit 10/10R and the subject was in the ICU at Visit 10/10R, what was the reason for the subject not being discharged from the ICU (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, other)?
- Was the subject still an in-patient in the hospital at the end of Visit 12/12R?
- If the FOUR Score was  $\geq 15$  at Visit 12/12R and the subject was in the hospital at Visit 12/12R, what was the reason for the subject not being discharged from the hospital (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, unsuitable home circumstances, other)?

**11.2.8.4. STESS**

The STESS will be assessed during Visit 1 in order to assess the severity of the status epilepticus.

**11.2.8.5. FOUR Score**

The Full Outline of UnResponsiveness or FOUR Score is designed to assess conscious level and unlike other scores, is suitable for subjects who are intubated. It assesses four domains of neurological function (eye responses, motor responses, brainstem reflexes, and breathing pattern).

The FOUR Score will be collected at the following time points relative to each infusion of study drug (the initial blinded infusion and the second open-label infusion if this is administered):

- baseline, +24, +48, +72, +96, +120, +144, +168, and +192 hours (all +/- 2 hours) after the start of the infusion, and at Visit 11/11R and Visit 12/12R.

#### **11.2.8.6. Glasgow Outcome Scale (GOS)**

The GOS is a relatively common assessment scale used to standardize descriptions of the objective degree of recovery from brain injury such as cerebral trauma, or in this case SRSE. It was first used in 1975 ([Jennett and Bond 1975](#)) and allows a prediction of the long-term course of rehabilitation to return to work and everyday life. The scale classifies subjects into 5 groups:

- Death
- Persistent vegetative state
- Severe disability
- Moderate disability
- Good recovery

The GOS will be assessed at Visit 12 or Visit 12R.

#### **11.2.8.7. Supervision Rating Scale (SRS)**

The Supervision Rating (SRS) measures the level of supervision that a patient/subject receives from caregivers. The SRS rates level of supervision on a 13-point ordinal scale that can optionally be grouped into five ranked categories (Independent, Overnight Supervision, Part-Time Supervision, Full-Time Indirect Supervision, and Full-Time Direct Supervision). The SRS was designed to be rated by a clinician based on interviews with the subject and an informant who has observed at first hand the level of supervision received by the subject ([Boake 2000](#)). Scoring is a one-step procedure in which the clinician assigns the rating that is closest to the subject's level. Ratings are based on the level of supervision received, not on how much supervision a subject is judged or predicted to need.

The SRS will be assessed at Visit 1 and Visit 12 or Visit 12R. The Visit 1 assessment will be a retrospective assessment of the supervision required by the subject immediately prior to the admission that included the index episode of status epilepticus.

#### **11.2.8.8. Modified Rankin Scale – 9Q (mRS-9Q)**

The Modified Rankin Scale (mRS) is a commonly used scale to determine disability and functional dependence due to neurological insult such as stroke in adults. The 7-point scale (0 – 6) denotes functional capacity from no symptoms (0) to severe disability (5) and death (6). The Modified Rankin Scale – 9Q is a shortened version consisting of 9 questions that reliably determines the mRS score and was developed to both simplify the assessment and expand the rater base to non- medically trained personnel ([Patel, Rao et al. 2012](#)). The assessment is a web-based tool in the public domain with automatic score calculation and error checking found at [www.modifiedrankin.com](http://www.modifiedrankin.com).

The mRS will be assessed at Visit 1 and at Visit 12 or Visit 12R. The baseline assessment will be a retrospective assessment of the disability and dependence of the subject immediately prior to the admission that included the index episode of status epilepticus.

## 12. STUDY PROCEDURES

The study procedures listed below by study day reflect the required data collection times for this protocol. When a time window is necessary, this is specified below. If no time window is specified, the test may be performed at any time within the specified 24-hour period.

### 12.1. Visit 1 (V2-≤30h)

The baseline period will be up to approximately 84 hours prior to starting blinded study treatment and should include the assessments/procedures listed below and summarized in [Table 1 and Table 2 \(for open-label treatment\)](#), the Schedules of Events.

- Informed consent
- Eligibility checklist
- Verification of inclusion/exclusion criteria.
- Demographic information and medical history obtained by proxy and confirmed by the subject when possible.
- SE and wean history
- Blood will be collected from female subjects 18 years to 55 years for a serum pregnancy test unless they are known to be pre-menstrual or post-menopausal or to have had a hysterectomy.
- Blood and urine samples collected for clinical laboratory testing.
- Pharmacogenetic sample will be collected from consenting/eligible subjects.
- Vital signs
- Height
- Weight
- An ECG reading taken.
- Administration of the STESS.
- Administration of the FOUR Score.
- Administration of SRS.
- Administration of the mRS-9Q assessment.
- Assessment of the CGI scale.
- Evaluation of epilepsy status.
- Administration of continuous IV third-line agents.
- Perform EEG.
- Recording of adverse events.
- Recording of previous and concomitant anti-epileptic drugs.
- Recording of previous and concomitant third-line agents.
- Recording of concomitant pressors.

- Recording of other concomitant medications, procedures, and treatments.

## **12.2. Visit 2 (V3-≤54h)**

- Recording of adverse events.
- Recording of concomitant anti-epileptic drugs.
- Recording of concomitant third-line agents.
- Recording of concomitant pressors.
- Recording of other concomitant medications, procedures, and treatments.
- Wean of continuous third-line agent (QW):
  - If wean is successful, subject is followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (these subjects are Qualifying Wean Success subjects or QWS subjects);
  - If wean is not successful, there is ongoing intravenous administration of at least one continuous IV third-line agent and EEG is performed and the subject is randomized.
- Weight
  - Subject weight will be obtained within the eight-hour period from the declaration of failure of QW and prior to the initiation of the blinded infusion loading dose at H0 of V3. This weight will be the dosing weight used to determine the infusion rate for the entire blinded infusion treatment course.

## **12.3. SAGE-547 Treatment Period**

### **12.3.1. Visit 3/3R (0-24 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs will be recorded at:
  - 0, +30, +60 minutes (+/-15 minutes) and +2, +4, +8 (+/- 30 minutes) and +24 hours (+/- 2 hours) after the start of the infusion
- For the first 50 subjects randomized in the study, ECG readings will be recorded immediately after PK sampling, or within 15 minutes prior to PK sampling, at the following time points:
  - 0 (pre-dose) and at +0.5, +1, +3, +6, +12, and +24 hours after the start of the blinded study drug infusion.
  - Subsequent subjects randomized in the study will have ECG readings recorded at 0 (pre-dose) and +1, +12, and +24 hours after the start of the study drug infusion, it will not be necessary to collect these ECGs with PK samples at these timepoints and, apart from the +1 h ECG, there is +/- 2 hour time window for these ECGs
- A blood sample for PK analysis should be collected at the following time points (all +/- 15 minutes except where otherwise stated):

0 (pre-dose, within two hours of the start of the infusion) and at +0.5, +1 (+/- 5 minutes), +3, +6, +12, and +24 hours after the start of the study drug infusion.

- Completion of the FOUR Score
  - +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the final declaration of QW success)
- Ongoing intravenous administration of a continuous IV third-line agent.
- Study drug administration in loading (Hour 0-1) and maintenance infusions (at completion of Hour 1).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.2. Visit 4/4R (25-48 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +48 hours (+/- 2 hours) after the start of the infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +48 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +48 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +48 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +48 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent.
- Ongoing study drug maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.3. Visit 5/5R (49-72 hours)**

- Weight if easily obtained

- Vital signs should be recorded at:
  - +72 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +72 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +72 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +72 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +72 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.4. Visit 6/6R (73-96 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +96 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +96 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +96 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +96 hours (+/- 15 minutes) after the start of study drug infusion.



- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +96 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Perform EEG.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.5. Visit 7/7R (97-120 hours)**

- Weight if easily obtained
- Vital signs should be recorded at:
  - +120 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +120 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +120 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +120 hours (+/- 15 minutes) after the start of study drug infusion, immediately prior to the end of the maintenance infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +120 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled. Complete wean by 120 hours if at all possible.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## 12.4. SAGE-547 Taper Period

### 12.4.1. Visit 8/8R (121-144 hours)

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +144 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after each PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +128, +136 hours and +144 hours after the start of the blinded study drug infusion
  - +126, +132, +138 hours and +144 hours after the start of the open-label study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +144 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected (+/- 15 minutes unless otherwise stated):
  - +128 (immediately prior to the end of the first taper step), +136 hours (+/- 5 minutes, immediately prior to the end of the second taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of study drug infusion.
  - During the open-label study drug phase of the study PK blood draws at: +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 hours (+/- 5 minutes, immediately prior to the end of the third taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of the study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +144 hours (+/- 2 hours) after the start of the infusion
- Complete wean of third line agents by H144 if not completed by H120.
- Perform EEG.
- Taper of SAGE-547 infusion begins at hour 121.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## **12.5. Follow-up Period**

### **12.5.1. Visit 9/9R (145-168 hours)**

- Vital signs should be recorded at:
  - +168 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +152, +160 hours (+/- 2 hours) after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +152 and +160 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +168 hours (+/- 2 hours) after the start of the infusion
- Perform EEG.
- Assessment of the presence of physiologic brain activity using EEG.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.5.2. Visit 10/10R (169-192 hours)**

- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +192 hours (+/- 2 hours) after the start of the infusion
- At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine eligibility for the open-label treatment with the higher dose of study drug. This determination may occur at any point during Visit 10: the higher dose open-label infusion must begin within the Visit 10 window. All patients receiving the higher dose open-label treatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.
- Weight if the subject qualifies for the open-label study drug (Visit 10 only, not Visit 10R).
- Recording of adverse events (QWS subjects also).

- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.3. Visit 11/11R (Visit 3/3R + 14d ( $\pm 2$ ))**

- Blood samples collected for clinical laboratory testing (renal panel only).
- Completion of the FOUR Score (QWS subjects also).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.4. Visit 12/12R (Visit 3/3R + 21d ( $\pm 2$ ))**

All assessments also performed for QWS subjects.

- Completion of the FOUR Score.
- Administration of the GOS.
- Administration of the SRS.
- Administration of the mRS-9Q assessment.
- Evaluation of epilepsy status (see [Section 11.1.2.2](#) for details).
- Assessment of the CGI Scale.
- Recording of adverse events.
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications.
- Collection of pharmacoeconomic data.
- Mortality will be assessed throughout the study period.

## **13. STATISTICS**

### **13.1. Statistical Plan**

Complete details for the analysis and reporting of data from this study will be contained in the Statistical Analysis Plan (SAP).

#### **13.1.1. Interim Analysis**

When approximately 50% of subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### 13.1.2. Study Populations

The **Safety Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to actual treatment. This analysis population will be used for all safety analyses.

The **Intent to Treat Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to randomized treatment. This analysis population will be used for all efficacy analyses.

The **Modified Intent to Treat Population** is defined as all subjects who:

1. complete their initial course of blinded SAGE-547 or placebo treatment unless the non-completion was due a drug-related adverse event; and
2. have at least one attempt to wean from third-line agents prior to the end of blinded study treatment infusion unless the failure to wean was because seizures were not controlled.

Subjects will be classified according to randomized treatment. This analysis population will be used for sensitivity analyses of the primary endpoint and select secondary efficacy endpoints.

Narratives will be prepared for all subjects who do not complete the infusion of blinded study medication or were not subjected to any wean attempts. Narratives will include details of the cause of SE, the comorbid conditions, the adverse event(s), and reasons for non-completion of the infusion or failure to attempt weaning. This blinded narrative will be reviewed by the medical monitors and the patient adjudicated as MITT eligible or ineligible. Acceptable reasons for defining a subject as MITT ineligible include death or withdrawal of consent due to progression of the underlying cause of SE or comorbid conditions, unless the cause of death or progression of disease were thought by the investigator, sponsor, or DSMB to be related to study drug.

The **Per-Protocol (PP) Population** is defined as a subset of the MITT population but will exclude data from all subjects with significant protocol violations or deviations. Subjects will be classified according to actual treatment received. This data set will be used for sensitivity analyses to examine the robustness of results for the primary and key secondary efficacy endpoints.

The **Pharmacokinetics Population** is defined as all subjects who at least had an infusion of blinded SAGE-547 initiated and have at least one pharmacokinetic sample collected.

The **Pharmacogenetic Population** is defined all subjects who consent to being included in the pharmacogenetic assessment and provide a pharmacogenetic sample.

Summary statistics of all data collected will be presented for subjects who were QW successes.

### 13.1.3. General Aspects

Tabular displays of descriptive statistics will be provided for all variables. Summary tables will include n, mean, mean, standard deviation, minimum and maximum for continuous variable and frequency and percentage for categorical variables.

### 13.1.4. Analysis of Primary Endpoint

The analysis of response to treatment (see Section 11.1.1 for definition of primary endpoint) between SAGE-547 treated subjects and placebo treated subjects will be performed on the ITT population using a Cochran-Mantel-Haenszel (CMH) test with variables for treatment, concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior

to randomization (one vs two or more). The CMH general association statistic and its associated p-value will be presented. The comparison of treatment response rates will be conducted at the 5% level of significance. To confirm the CMH results, a permutation test will also be conducted.

An additional analysis of the primary endpoint will also be performed on the MITT population. In addition sensitivity analyses of the primary endpoint will be performed using the ITT population based on:

- the number of third-line agents (one, two, or three) subjects were administered post-randomization; and
- which third line agent was the subject of the first TW.

### **13.1.5. Analysis of Secondary Efficacy Endpoints**

Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section (Section 6). Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. The analysis of the secondary endpoints will also be performed on the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

### **13.1.6. Analysis of Other Endpoints**

Safety and “Other” endpoints will only be summarized by treatment group.

Summaries of safety endpoints will be based on the overall Safety Population.

### **13.1.7. Epilepsy and SRSE Status**

Diagnosis of epilepsy and recurrence of RSE or SRSE will be documented as the percentage of subjects by time point and overall. Kaplan-Meier curves may be plotted if sufficient data are available.

Utilization of AEDs during follow-up and during recurrence will be summarized.

### **13.1.8. Questionnaires**

The data collected from each questionnaire will be interpreted according to the standard methodology for that questionnaire. There will be no adjustment for missing values.

### **13.1.9. Pharmacokinetic Data Analysis**

Details of the pharmacokinetic data analysis will be described in detail in a separate Pharmacokinetic Analysis Plan.

### **13.1.10. Pharmacogenetic Data Analysis**

Any genotype data generated in this study will be stored within a secured database within Sage Therapeutics and / or a third party contracted to work with Sage Therapeutics to analyze the samples. Because the number of subjects agreeing to participate in the genetic research component of the study is unknown, it is not possible to establish, a priori, whether sufficient samples will be obtained to support formal statistical evaluation of data. As a consequence a Pharmacogenetic Analysis Plan will only be prepared where appropriate and the results obtained from any genetic research will be reported in a report separate from the main study CSR.

### **13.1.11. Open-Label Study Drug Subjects**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are treated with SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo.

### **13.1.12. EEG-Responders**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who are classified as EEG-responders/non-responders based on the independent assessment of the PAEEG. Summaries will be derived for the two randomized treatment groups.

### **13.1.13. QT/QTc Assessment**

An analysis of the correlation between changes in QT/QTc intervals and SAGE-547 plasma levels will be performed to investigate if there is a potential effect that SAGE-547 may have on QT/QTc interval. A detailed description of the QT/QTc assessment will be included in the SAP.

### **13.1.14. Quantitative EEG**

The nine EEG records for each subject may be subjected to exploratory quantitative EEG analysis, the details of which will be included in the EEG Analysis Plan. In summary the following comparisons may be made, SAGE-547 versus placebo: the QWEEG versus the TWEEG (main analysis); the CEEG versus PAEEG (subsidiary analysis); and TAEEG versus PAEEG (exploratory analysis).

## **13.2. Determination of Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between treatment groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

### **13.3. Statistical Analysis Plan**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.



## **14. ADVERSE EVENTS**

The safety procedures in this study will be detailed in a Safety Management Plan, which will be agreed and signed before the first subject is randomized in the study. [Section 14.1](#) summarizes Investigator responsibilities regarding the identification and documentation of AEs, the classification of AEs for relationship to study drug and severity, and the reporting of AE information to the Sponsor and the IRB.

[Section 14.2](#) summarizes Sponsor/Medical Monitor Responsibilities regarding monitoring of AE data and reporting relevant safety information to FDA.

[Section 14.3](#) lists important AE definitions.

### **14.1. Investigator Responsibilities**

#### **14.1.1. Identification and Documentation of Adverse Events by Investigator**

Subjects will be evaluated and questioned generally (if possible) to identify AEs during the course of the study. AEs will be collected from the signature of the consent form through Visit 12/12R. Adverse events that occur prior to completion of screening will be captured on the Medical History eCRF. Adverse events that occur after completion of screening will be recorded on the Adverse Event eCRF.

All AEs revealed by observation, other diagnostic procedures, or spontaneously reported by the subject and/or in response to an open question from study personnel will be recorded on the Adverse Event Form. Any clinically significant deterioration in laboratory assessments or other clinical findings are considered an AE and must be recorded on the Adverse Event Form, unless otherwise stated. AE information recorded will be entered into the database on an ongoing basis.

AEs with a relationship considered related to study drug (probable, possible) should be followed until the event is resolved or the Investigator determines the event is stable or no longer clinically significant. AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

For SAEs, an electronic Serious Adverse Event eCRF must be completed with as much information as possible and submitted in the time frame described below in [Section 14.1.3](#). When new significant information is obtained as well as when the outcome of an event is known, the electronic SAE eCRF should be updated within 24 hours. If the subject was an outpatient at the time of the SAE and was re-hospitalized due to the SAE, a copy of relevant hospital records (e.g., admission report, laboratory test results, discharge summary, etc.) may be requested to be included as part of the subject medical file.

All SAEs will be followed until resolved or until a stable status has been achieved.

**14.1.2. Adverse Event Classification****14.1.2.1. Relationship to Investigational Drug**

None:	No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state.
Possible:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject, but this is not known for sure.
Probable:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

**14.1.2.2. Severity**

Mild	Discomfort noticed, but no disruption to daily activity.  For subjects that are unconscious, this may be a slight or minor change in a lab result or clinical sign or symptom that does not require immediate corrective action.
Moderate	Discomfort sufficient to reduce or affect normal daily activity, but is not hazardous to health; prescription drug therapy may be employed to treat the AE.  For subjects that are unconscious, this may be a clinically meaningful change that may require immediate corrective action.
Severe	Inability to work or perform normal daily activity and represented a definite hazard to health; prescription drug therapy and/or hospitalization may be employed to treat the AE.  For unconscious subjects, this may be a significant clinical change that requires immediate corrective action.

**14.1.2.3. Action Taken with Investigational Drug**

None	Study medication was continued without change.
Discontinued	Study medication was terminated.
Dose adjusted	Study medication dose/infusion rate was changed and then continued per protocol.
Interrupted	Study medication was interrupted and then continued per protocol.
Unknown	The action taken with regard to study medication is unknown.
Not applicable	Administration of study medication was not ongoing.

**14.1.2.4. Assessment of Outcome**

Ongoing	At the end of the study, the event has not resolved or stabilized.
Ongoing and stable	The event is ongoing but has stabilized and is unlikely to change
Resolved	The event has resolved or the subject recovered without sequelae.
Resolved with sequelae	The event has at least one secondary outcome that may result in permanent disability and/or functional limitation.
Unknown	The status of the event is unknown.
Death	The subject has expired.

**14.1.3. Investigator Reporting to Sponsor and Sponsor Emergency Contact**

All new SAEs that come to the Investigator and/or Sponsor's notice during the course of the study (up to and including the last study visit) must be reported by the Investigator on the designated electronic report form within 24 hours of the point in time when the Investigator becomes aware of the SAE. As additional information becomes available, the designated electronic report form must be updated within 24 hours.

Investigators must report any SAE, whether or not considered drug related. The report must include an assessment of whether there is a reasonable possibility that the drug caused the event.

In a medical emergency (ie, an event that requires immediate attention regarding the treatment of a subject, operation of the clinical study, and/or the use of investigational drug), study site staff will apply appropriate medical intervention according to current standards of care, and contact the Medical Monitor.

**14.1.4. Medical Monitor and Emergency Contact Information**

[REDACTED], MD  
[REDACTED]

In a study related medical emergency situation, when the assigned Medical Monitor cannot be reached by a caller, an on-call Physician can be reached 24 hours per day, 7 days per week via an [REDACTED] Call-Center:

- Telephone: [REDACTED]  
(this is a chargeable telephone number allowing a global reach from both landlines and mobile phones)

- 

On this internet page a list of country-specific toll-free telephone numbers is provided. It should be noted that not all countries globally have access to toll-free numbers as indicated on the “24/7 Medical Help desk” index. Countries without toll-free numbers need to dial the chargeable number as indicated above. Furthermore, toll-free numbers are not available from mobile phones.

#### **14.1.5. SAE Reporting Contact Information**

Contact information and reporting instructions are provided in the Safety Management Plan.

#### **14.1.6. Reporting to Institutional Review Boards (IRBs)**

It is the responsibility of the Investigator to promptly notify the institution’s IRB of all serious and unexpected suspected adverse reactions (see [Section 14.3](#) for definitions).

### **14.2. Sponsor/Medical Monitor Responsibilities**

#### **14.2.1. Monitoring of Adverse Event Data**

The Medical Monitor will review any newly reported adverse events in an ongoing basis. If the aggregate assessment indicates that an event is occurring more frequently than would normally be expected in this population, or as previously observed, and the sponsor believes that the events are causally related to the administration of SAGE-547, the Sponsor will then report that information in an IND safety report.

#### **14.2.2. Data Safety Monitoring Board**

An independent DSMB will monitor the clinical, PK and PD data for safety signals throughout the study and will be asked to assess the placebo response rate at the time of the interim analysis to determine final sample size. In order to perform their monitoring function the DSMB will have access to un-blinded safety data as necessary.

The composition and procedures for the board will be described in a separate DSMB Charter.

#### **14.2.3. Reporting to FDA**

The Sponsor must report in an IND safety report any suspected adverse reaction to study treatment that is both serious and unexpected (21 CFR 312.32(c)(1)(i)). Before submitting an IND safety report, the Sponsor will ensure the event meets all three of the definitions: (1) suspected adverse reaction, (2) serious, (3) unexpected. If the AE does not meet all three of the definitions, it should not be submitted as an IND safety report. The Sponsor should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the adverse event and, therefore, that the event meets the definition of a suspected adverse reaction.

If there is a serious and unexpected suspected adverse reaction, the Sponsor will notify the appropriate regulatory agency(ies) and all appropriate parties on an expedited basis. In addition, Sponsors must submit expedited reports of an increased rate of occurrence or severity of serious suspected adverse reactions over that listed in the protocol or Investigational Brochure.

SUSARs will be unblinded prior to reporting to FDA. Unless it is necessary to unblind for the safety of the patient, the investigator will not be informed of the unblinding of the subject.

Under 21 CFR 312.32, Sponsors should identify in the protocol SAEs that it does not plan to report individually in an expedited manner, because they are known consequences of the disease or otherwise common in the study population. Given the grave condition and prognosis of SRSE being studied, individual occurrences of seizures or seizure activity will not be reported expeditiously in this study. Regardless of which events are reported in an expedited manner, all adverse events will be closely monitored throughout the study.

#### **14.2.4. Reporting to European Regulatory Authorities**

The Sponsor or its designee is responsible for SUSAR notification to the relevant regulatory authorities as outlined in the ICH Guidelines. All investigators participating in the study will also be informed as required by regulations.

Any SUSAR is subject to expedited reporting in the EU. The Sponsor or its designee, will report any single SUSAR to the appropriate National CAs and IECs within 7 days if the SUSAR is life-threatening or fatal (with the relevant follow-up information subsequently communicated within an additional eight days), and within 15 days if the SUSAR is neither life-threatening nor fatal. SUSARs reported will be those that have arisen in the present clinical trial and SUSARs that have arisen in other clinical trials conducted by the Sponsor with the same medicinal product.

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to competent authorities of the concerned Member States and to IEC(s)/IRBs as required by national laws.

### **14.3. Adverse Event Definitions**

#### **14.3.1. Adverse Event**

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

#### **14.3.2. Suspected Adverse Reaction**

Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

#### **14.3.3. Life-Threatening**

An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

**14.3.4. Serious**

An AE or suspected adverse reaction is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE – see definition above
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disability
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

**14.3.5. Unexpected**

An AE or suspected adverse reaction is considered “unexpected”:

- If it is not listed in the Investigational Brochure or is not listed at the specificity or severity that has been observed, or
- If an Investigational Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigational Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigational Brochure listed only cerebral vascular accidents.

“Unexpected,” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigational Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

**14.4. Emergency Identification of Study Medication**

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject’s treatment in the study via the IVRS; this normally requires prior approval by the medical monitor. However, if the subject is at immediate risk and the Investigator believes that immediate knowledge of the study treatment will alter medical management, discussion with the medical monitor may take place after unblinding. The Investigator will not unblind the medical monitor during that discussion. The process of unblinding will ensure that only the investigator is unblinded; the medical monitor, study management team, and data management team will not be made aware of the treatment allocation of an individual subject. All

cases of emergency unblinding will be fully documented in a way that does not unblind the medical monitor, study management team, and data management team.

## **15. STUDY ADMINISTRATIVE CONSIDERATIONS**

### **15.1. Quality Control and Quality Assurance**

The Investigators and institutions will permit trial related monitoring, audits, IRB review, and regulatory inspections as requested by FDA, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed informed consent forms, etc.) in addition to case report forms.

Quality assurance and quality control systems with written standard operating procedures (SOPs) will be followed to ensure this trial will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The site's dedicated study monitor will arrange to visit the Investigator at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be identified and resolved. The study monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality assurance officers named by Sage Therapeutics or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements, made by the Sponsor with the Investigator/institution and any other parties involved with the clinical trial, will be in writing in a separate agreement.

### **15.2. Data Handling and Recordkeeping**

#### **15.2.1. Data Handling**

Procedures for data handling (including electronic data) used in this protocol will be documented in a Data Management Plan.

#### **15.2.2. Case Report Form Completion**

eCRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of demographics, study drug administration, study procedures, AEs, questionnaire completion, efficacy assessments and subject status, including survival.

The Investigator will maintain copies of the eCRFs at the study site. For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate eCRF.

### **15.2.3. Retention of Study Records**

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval and until there are no pending or contemplated marketing applications or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to an appropriate person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

## **15.3. Confidentiality**

To maintain subject privacy, all eCRFs, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available trial registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by Sage Therapeutics to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

## **15.4. Publication Policy**

All information concerning SAGE-547 is considered confidential and shall remain the sole property of Sage Therapeutics. The Investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval from Sage Therapeutics. No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between Sage Therapeutics and the Investigator.

## **15.5. Protocol Amendments**

Changes to the conduct of the study should be prepared as a protocol amendment by the Sponsor. Protocol amendments should receive written IRB/IEC approval prior to implementation at the investigative site, except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the trial (eg, change of monitor, telephone numbers). In this case, Sage Therapeutics will amend and implement the protocol change



and subsequently notify the regulatory authorities and the Investigative sites who will notify the respective IRB, as appropriate.

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**APPENDIX 1. APPENDIX 1: FOUR SCORE****FOUR score****Full Outline of UnResponsiveness****Eye response**

- E4: eyelids open or opened, tracking, or blinking to command
- E3: eyelids open but not tracking
- E2: eyelids closed but open to loud voice
- E1: eyelids closed but open to pain
- E0: eyelids remain closed with pain

**Motor response**

- M4: thumbs-up, fist or peace sign
- M3: localizing to pain
- M2: flexion response to pain
- M1: extension response to pain
- M0: no response to pain or generalized myoclonus status

**Brainstem reflexes**

- B4: pupil and corneal reflexes present
- B3: one pupil wide and fixed
- B2: pupil or corneal reflexes absent
- B1: pupil and corneal reflexes absent
- B0: absent pupil, corneal and cough reflex

**Respiration pattern**

- R4: not intubated, regular breathing pattern
- R3: not intubated, Cheyne-Stokes breathing pattern
- R2: not intubated, irregular breathing
- R1: breathes above ventilatory rate
- R0: breathes at ventilator rate or apnea

Reference ([Iyer, Hoel et al. 2009](#)).

**APPENDIX 2. GLASGOW OUTCOME SCALE (GOS)****GLASGOW  
OUTCOME  
SCALE**

Patient Name: \_\_\_\_\_  
 Rater Name: \_\_\_\_\_  
 Date: \_\_\_\_\_

*Note:* The scale presented here is based on the original article by Jennett and Bond. It has become common practice in clinical trial administration, however, to use a modified version that places the scores in reverse order (i.e., "good recovery" = 1, "moderate disability" =2, etc.).

Score	Description
1	DEATH
2	PERSISTENT VEGETATIVE STATE Patient exhibits no <i>obvious cortical</i> function.
3	SEVERE DISABILITY (Conscious but disabled). Patient depends upon others for daily support due to mental or physical disability or both.
4	MODERATE DISABILITY (Disabled but independent). Patient is independent as far as daily life is concerned. The disabilities found include varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes.
5	GOOD RECOVERY Resumption of normal activities even though there may be minor neurological or psychological deficits.

**TOTAL (1-5):** \_\_\_\_\_

Reference ([Jennett and Bond 1975](#)).

## APPENDIX 3. SUPERVISION RATING SCALE (SRS)

### SUPERVISION RATING SCALE (SRS)

**Instructions:** Circle the rating that is closest to the amount of supervision that the patient *actually receives*. "Supervision" means that someone is responsible for being with the patient.

<u>Rating</u>	<u>Description</u>
<b>Level 1: INDEPENDENT</b>	
1	The patient lives alone or independently. Other persons can live with the patient, but they cannot take responsibility for supervision (for example, a child or elderly person).
2	The patient is unsupervised overnight. The patient lives with one or more persons who <i>could</i> be responsible for supervision (for example, a spouse or roommate), but they are <i>all</i> sometimes absent overnight.
<b>Level 2: OVERNIGHT SUPERVISION</b>	
3	The patient is only supervised overnight. One or more supervising persons are always present overnight but they are <i>all</i> sometimes absent for the rest of the day.
<b>Level 3: PART-TIME SUPERVISION</b>	
4	The patient is supervised overnight and part-time during waking hours, but is allowed on independent outings. One or more supervising persons are always present overnight and are also present during part of waking hours every day. However, the patient is sometimes allowed to leave the residence without being accompanied by someone who is responsible for supervision.
5	The patient is supervised overnight and part-time during waking hours, but is unsupervised during working hours. Supervising persons are <i>all</i> sometimes absent for enough time for them to work full-time outside the home.
6	The patient is supervised overnight and during most waking hours. Supervising persons are <i>all</i> sometimes absent for periods longer than one hour, but less than the time needed to hold a full-time job away from home.
7	The patient is supervised overnight and during almost all waking hours. Supervising persons are <i>all</i> sometimes absent for periods shorter than one hour.
<b>Level 4: FULL-TIME INDIRECT SUPERVISION</b>	
8	The patient is under full-time indirect supervision. At least one supervising person is <i>always</i> present, but the supervising person does not check on the patient more than once every 30 minutes.
9	Same as #8 plus requires overnight safety precautions (for example, a deadbolt on outside door).
<b>Level 5: FULL-TIME DIRECT SUPERVISION</b>	
10	The patient is under full-time direct supervision. At least one supervising person is always present and the supervising person checks on the patient more than once every thirty minutes.
11	The patient lives in a setting in which the exits are physically controlled by others (for example, a locked ward).
12	Same as #11 plus a supervising person is designated to provide full-time line-of-sight supervision (for example, an escape watch or suicide watch).
13	The patient is in physical restraints.

3/12/93

Corwin Boake, Ph.D., TIRR, 1333 Moursund, Houston, TX 77030-3405, 713/799-6990

## APPENDIX 4. MODIFIED RANKIN SCALE – LEVEL OF FUNCTION SURVEY (mRS-9Q)

1. Do you have any symptoms that are bothering you? (For example, trouble with reading or writing, trouble speaking, problems with vision, numbness, weakness, balance trouble, or problems with swallowing?)	YES <input type="radio"/>	NO <input type="radio"/>
2. Are you able to do the same work as before?	YES <input type="radio"/>	NO <input type="radio"/>
3. Are you able to keep up with your hobbies?	YES <input type="radio"/>	NO <input type="radio"/>
4. Have you maintained your ties to friends and family?	YES <input type="radio"/>	NO <input type="radio"/>
5. Do you need help making a simple meal, doing household chores, or balancing a checkbook?	YES <input type="radio"/>	NO <input type="radio"/>
6. Do you need help with shopping or traveling close to home?	YES <input type="radio"/>	NO <input type="radio"/>
7. Do you need another person to help you walk?	YES <input type="radio"/>	NO <input type="radio"/>
8. Do you need help with eating, going to the toilet, or bathing?	YES <input type="radio"/>	NO <input type="radio"/>
9. Do you stay in bed most of the day and need constant nursing care?	YES <input type="radio"/>	NO <input type="radio"/>

## APPENDIX 5. CLINICAL GLOBAL IMPRESSION (CGI)

### Clinical Global Impression (CGI)

#### 1. Severity of illness

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- |                             |   |
|-----------------------------|---|
| 0 = Not assessed            | 4 = Moderately ill                        |
| 1 = Normal, not at all ill  | 5 = Markedly ill                          |
| 2 = Borderline mentally ill | 6 = Severely ill                          |
| 3 = Mildly ill              | 7 = Among the most extremely ill patients |

#### 2. Global improvement: Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.

Compared to his condition at admission to the project, how much has he changed?

- |                        |                     |
|------------------------|---------------------|
| 0 = Not assessed       | 4 = No change       |
| 1 = Very much improved | 5 = Minimally worse |
| 2 = Much improved      | 6 = Much worse      |
| 3 = Minimally improved | 7 = Very much worse |

#### 3. Efficacy index: Rate this item on the basis of drug effect only.

Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.

EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect		Side effects			
		None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
<b>Marked</b>	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
<b>Moderate</b>	Decided improvement. Partial remission of symptoms	05	06	07	08
<b>Minimal</b>	Slight improvement which doesn't alter status of care of patient	09	10	11	12
<b>Unchanged or worse</b>		13	14	15	16
Not assessed = 00					

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare



**APPENDIX 6. STATUS EPILEPTICUS SEVERITY SCORE (STESS)**

Outcome Predictor	Feature	Score
Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type (prior to first treatment)	Simple-partial, complex-parial, absence, myoclonic (complicating idiopathic generalized epilepsy)	0
	Generalized-convulsive	1
	Nonconvulsive status epilepticus in coma	2
Age	< 65 years	0
	≥ 65 years	2
History of previous seizures	Yes	0
	No or unknown	1
Summed Total		

**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY  
TO EVALUATE THE EFFICACY AND SAFETY OF SAGE-547 INJECTION  
IN THE TREATMENT OF SUBJECTS WITH SUPER-REFRACTORY  
STATUS EPILEPTICUS**

**PROTOCOL NUMBER: 547-SSE-301  
ADULT ONLY VERSION**

**IND NUMBER: 117901**

**EudraCT Number: 2015-002142-31**

Product: SAGE-547 Injection (allopregnanolone)

Sponsor Contact: [REDACTED], MD  
Sage Therapeutics  
215 First Street  
Cambridge, MA 02142  
[REDACTED]

Medical Monitor: [REDACTED], MD  
[REDACTED]

Date of Protocol: 09 March 2015  
Date of Amendment One 27 May 2015  
Date of Amendment Two (Adults Only) 17 November 2015  
Date of Amendment Three (Adults Only) 22 April 2016  
[not implemented])  
Date of Amendment Four (Adults Only) 18 August 2016

**Confidentiality Statement**

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

**PROTOCOL NUMBER: 547-SSE-301**

Sponsor [REDACTED]:

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

CRO [REDACTED]:

[REDACTED]

## 1. SIGNATURE PAGE

Title of Protocol:

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus

Protocol No: 547-SSE-301

### Sponsor Approval

[Redacted Signature]

23 AUG 2016

[Redacted Signature] MD

Date (dd/mm/yyyy)

Sage Therapeutics

[Redacted Signature]

23 Aug 2016

[Redacted Signature] MPH

Date (dd/mm/yyyy)

Sage Therapeutics

[Redacted Signature]

23 Aug 2016

[Redacted Signature] MPH

Date (dd/mm/yyyy)

Sa [Redacted Signature]

23 AUG 2016

[Redacted Signature]

Date (dd/mm/yyyy)

Sage Therapeutics

**Investigator Agreement**

By signing this page I attest that I have read and understand the contents of Clinical Protocol 547-SSE-301 and any current amendments. I agree to adhere to the design, conduct, and reporting requirements of the study as stated in the clinical protocol and to my obligations to the Sponsor as described in the protocol and executed contracts between myself, my Institution, and the Sponsor. I also agree to adhere to any subsequent amendments to the clinical protocol.

Investigator's Signature: \_\_\_\_\_

Investigator's Name: \_\_\_\_\_

Institution: \_\_\_\_\_

Date: \_\_\_\_\_

## 2. SYNOPSIS

<b>Name of Sponsor:</b> Sage Therapeutics 215 First Street Cambridge, MA 02142		
<b>Protocol No.</b> 547-SSE-301	<b>Phase:</b> 3	
<b>Name of Investigational Product:</b> SAGE-547 Injection		
<b>Name of Active Ingredient:</b> Allopregnanolone		
<b>Title of the Protocol:</b> A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus		
<b>Dosing Regimen: SAGE-547 or Placebo Dosing Schedule</b>		
<b>Hour</b>	<b>Type and Duration of SAGE-547 Infusions</b>	<b>Dose</b>
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	90 µg/kg/h
H121 – H128	8 hour taper	65 µg/kg/h
H129 – H136	8 hour taper	45 µg/kg/h
H137 – H144	8 hour taper	25 µg/kg/h
<b>Dosing Regimen: SAGE-547 Open-Label Dosing Schedule</b>		
<b>Hour</b>	<b>Type and Duration of SAGE-547 Infusion</b>	<b>Dose</b>
H1	One hour loading infusion	300 µg/kg/h
H2 –H120	119 hour maintenance infusion	150 µg/kg/h
H121 – H126	6 hour taper	125 µg/kg/h
H127 – H132	6 hour taper	95 µg/kg/h
H133 – H138	6 hour taper	65 µg/kg/h
H139 – H144	6 hour taper	35 µg/kg/h
<b>Study Sites</b> Up to 180 sites in the USA, Israel, Europe, and Canada.		
<b>Number of Subjects</b>		

The study will randomize 140 subjects at up to 180 sites.

### Study Population

Subjects will be aged 17 years or more, in SRSE<sup>1</sup> (as defined in the Inclusion Criteria [Section 8.1](#)), and being managed in an intensive care setting.

### Duration of Subject Involvement

Individual subject participation will be up to 30 days.

### Study Design

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

Patients will follow one of three paths to entry to the study. The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst or seizure suppression with a third-line agent. These subjects will be consented for the study after admission to the intensive care unit, before or after any third-line agents are administered for burst or seizure suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their legally authorized representative (LAR). Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours. Once burst or seizure suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The second path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst or seizure suppression pattern on the EEG. These subjects may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst or seizure suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst or seizure suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst or seizure suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

<sup>1</sup> In this study, the term Super-Refractory Status Epilepticus or SRSE is equivalent to “Refractory Status Epilepticus (RSE) that has failed standard treatment” and the two terms are used interchangeably.

The third path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst or seizure suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These subjects may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 treatment or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within eight hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo).

The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that subjects, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as both the ability to wean the subject off all third-line agents before the end of the infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication infusion, and concurrent signs of physiologic brain activity as determined by EEG. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#) and [Table 2](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo will all subsequently be eligible to be administered SAGE-547 at the higher dose.

### Visit Schedule

The visit schedule and an overview of events at each visit is provided in [Table 1](#), [Table 2](#) and [Table 3](#) Schedule of Assessments.



**Study Objectives*****Primary objective:***

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult subjects with SRSE, and for the response to endure at least 24 hours after the end of the SAGE-547 or placebo infusion (primary response).

***Secondary objectives:***

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in the Clinical Global Impression scale (CGI) between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

***Safety objectives:***

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

***Other objectives:***

1. To evaluate the impact of treatment with a higher dose SAGE-547 infusion;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;

3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;
6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS).

## **Endpoints**

### ***Primary endpoint:***

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### ***Secondary endpoints:***

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### ***Safety endpoints:***

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.

**Other endpoints:**

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who are treated with a higher dose of SAGE-547.
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol<sup>®</sup> and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS).

**Inclusion Criteria**

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects 17 years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed zero or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst or seizure suppression pattern; or who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst or seizure suppression pattern.

**Exclusion Criteria**

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone or any excipients in SAGE-547.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy with highly malignant/malignant EEG features ([Westhall, Rosetti et al. 2016](#)).
4. Subjects who have any of the following:

- a. a GFR low enough to warrant dialysis but for whatever reason, dialysis that would adequately remove Captisol<sup>®</sup> is not planned;
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the opinion of the investigator, of less than 30 days.
5. Subjects who are being administered more than three third-line agents concomitantly or in whom the qualifying wean cannot be completed within 24 hours, or who are being administered a third-line agent for other indications such as management of raised intra-cranial pressure that would preclude weaning according to this protocol.
  6. Subjects with a living will that does not allow heroic measures.
  7. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
  8. Subjects who have been treated or randomized in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not have received study drug/placebo and then re-enroll).

### **Pharmacogenetic Research**

In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **Statistical Analysis**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

### **Interim Analysis**

When approximately 50% of the subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### **Analysis of Primary Endpoint**

The analysis of response to treatment between SAGE-547 treated subjects and placebo treated subjects will be performed using a Cochran-Mantel-Haenszel test with variables for treatment, concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). In this analysis, a treatment responder is a subject who is successfully weaned off all third-line agents and blinded study medication prior to the end of study treatment infusion.

and remains off third-line agents for at least 24 hours following cessation of the blinded study medication, and who has concurrent signs of physiologic brain activity as determined by EEG. The analysis will be based on the ITT Population. The comparison of treatment response rates will be conducted at the 5% level of significance.

### **Analysis of Secondary Efficacy Endpoints**

The primary analysis will be repeated for the MITT population. Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section. Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. Secondary analyses will be repeated for the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from Baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third-line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

Summaries of safety endpoints will be based on the overall Safety Population which is defined as all subjects who at least initiated the infusion with blinded study treatment.

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects are treated with a higher dose of SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo. Summary statistics will be presented for subjects who were QW successes.

### **Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

**Table 1: Schedule of Assessments for Protocol 547-SSE-301: One Infusion of Study Drug (blinded)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical/SE/Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X	X	X	X	X	X	X	X		X		
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X		X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X		X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X		X	X		X		X		X		
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X			
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>n</sup>											X
Modified Rankin Score (mRS)	X <sup>n</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV 3rd-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>o</sup>				
EEG	X	X				X		X	X			
Randomization		X										
Study Drug Administration <sup>p</sup>			X	X	X	X	X	X				
TW Outcome & Open-label Treatment Decision										X <sup>q</sup>		
Physiologic Brain Activity									X			
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

**Table 2: Schedule of Assessments for Protocol 547-SSE-301: Two Infusions of Study Drug (one blinded, one open-label)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V3R
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	0-24h
Eligibility Checklist	X										S
Informed Consent <sup>a</sup>	X										E
Inclusion/Exclusion Criteria	X										E
Demography <sup>b</sup>	X										
Medical and SE and Wean History <sup>c</sup>	X										T
Height	X										A
Weight <sup>d</sup>	X	X	X	X	X	X	X	X		X	B
Serum Pregnancy Test <sup>e</sup>	X										L
Hematology <sup>f</sup>	X		X	X		X		X		X	E
Serum Chemistry and GFR <sup>f</sup>	X		X	X		X		X		X	
Urinalysis <sup>h</sup>	X		X	X		X		X		X	E
Pharmacogenetic sample	X										X
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X	T
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X	E
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X		N
STESS	X										I
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	O
Glasgow Outcome Score (GOS)											N
Supervision Rating Scale (SRS)	X <sup>n</sup>										
Modified Rankin Score (mRS)	X <sup>n</sup>										
Epilepsy Status	X										N
Clinical Global Impression (CGI)	X										E
Continuous IV Third-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>o</sup>			X
EEG	X	X				X		X	X		T
Randomization		X									
Study Drug Administration <sup>p</sup>			X	X	X	X	X	X			
TW Outcome and Open-label Treatment Decision										X <sup>q</sup>	P
Physiologic Brain Activity									X		
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X	A
Concomitant Anti-Epileptic Drugs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	G
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	E
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X	
Pharmacoeconomic Data											
Mortality											

**Table 2 continued**

	V3R	V4R	V5R	V6R	V7R	V8R	V9R	V10R	V11R	V12R
	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3R+14d (±2d)	V3R+21d (±2d)
Weight <sup>d</sup>	X	X	X	X	X	X				
Serum Pregnancy Test <sup>e</sup>										
Hematology <sup>f</sup>	X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X	X		X		X		X		
Vital Signs <sup>i</sup>	X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>	X	X	X	X	X	X	X			
STESS										
FOUR Score <sup>m</sup>	X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)										X
Supervision Rating Scale (SRS)										X
Modified Rankin Score (mRS)										X
Epilepsy Status										X
Clinical Global Impression Scale (CGI)										X
Continuous IV Third-Line Agent(s)	X	X	Wean	Wean	Wean	Wean <sup>o</sup>				
EEG			X			X	X			
Randomization										
Study Drug Administration <sup>p</sup>	X	X	X	X	X	X				
TW Success and Physiologic Brain Activity							X			
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data										X
Mortality										X



**Table 3: Schedule of Assessments for Protocol 547-SSE-301: Qualifying Wean Successes**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical and SE and Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X											
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X											
Serum Chemistry and GFR <sup>f</sup>	X											
Urinalysis <sup>h</sup>	X											
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X											
ECG <sup>j</sup>	X											
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>n</sup>											X
Modified Rankin Score (mRS)	X <sup>n</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV Third-Line Agent(s)	X	Wean										
EEG	X	X										
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

<sup>a</sup> Written informed consent by proxy (LAR) will be obtained prior to starting any study-related procedures not considered standard of care.

<sup>b</sup> Demographic information will be obtained by proxy and confirmed by the subject when possible.

<sup>c</sup> Medical history will be obtained by proxy and confirmed by the subject when possible. All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Dosing changes with the third-line agent(s) that constitute a wean attempt will be marked as such on the CRF, and the start/stop dates and times of all wean attempts prior to V3 will be recorded, as well as the outcome of the wean attempt.

<sup>d</sup> Weight will be collected at Screening (V1) and prior to administration of the blinded study drug infusion at V2 and the open-label study drug infusion at V10. The weights at V2 and V10 will be used to determine the appropriate infusion rate of the blinded and open-label infusions respectively. If easily obtained (such as via a scale-bed), weight will also be recorded once during each subsequent 24 hour period of the initial study drug infusion period (V3-V8) and second infusion period (V3R-V8R, if applicable).

<sup>e</sup> Serum pregnancy test for females aged 17 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy.

<sup>f</sup> Blood samples will be taken for hematology and serum chemistry and GFR calculation at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will document whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

<sup>g</sup> Blood samples will be taken at V11 or V11R for serum chemistry (renal panel only).

<sup>h</sup> Urine samples will be taken for urinalysis and NAG at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will add a comment about whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

<sup>i</sup> Vital signs will be recorded at the following time points relative to the start of each infusion of study drug: Screening (V1), at 0, 30, 60 minutes ( $\pm 15$  minutes), at 2, 4, and 8 hours ( $\pm 30$  minutes), and at 24, 48, 72, 96, 120, 144, 168, and 192 hours ( $\pm 2$  hours).

<sup>j</sup> For the first 50 subjects randomized in the study, ECG (12-lead) should be performed at Screening (V1) and at the following times relative to the start of study drug infusion. For the blinded (first) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 128, 136, 144, 152, 160, and 192 hours ( $\pm 2$  hours). For the open-label SAGE-547 (second) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 126, 132, 138, 144, 152, 160, and 192 hours ( $\pm 2$  hours). Heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours. Following randomization of the first 50 subjects, subsequent subjects randomized in the study will have ECG collected at the following timepoints: Pre-dose and at 1, 12, 24, 48, 72, 96, 120, 144, and 192 hours after the start of the blinded (first) study drug infusion; and, Pre-dose and at 1, 12, 24, 48, 72, 96, 120, 144, and 192 hours after the start of the open-label (second) study drug infusion. It is not necessary to collect these ECGs with the PK samples at these timepoints and, apart from the 1 h ECG, there is  $\pm 2$  hour time window for these ECGs.

<sup>k</sup> Plasma will be collected to assay for study drug concentrations at the following time points relative to the start of each infusion of study drug: For the blinded (first) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion. For the open-label SAGE-547 (second) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open-label SAGE-547 study drug infusion. Pre-dose samples may be taken within two hours before starting the infusion of study drug; timepoints up to and including 1h will have a time window of  $\pm 5$  minutes; all other timepoints will have a window of  $\pm 15$  minutes.

<sup>m</sup> FOUR Score assessments will be performed at Screening (V1), 24, 48, 72, 96, 120, 144, 168, and 192 hours (all  $\pm 2$  hours) relative to the start of each infusion of study drug, and at V11 or V11R, and at V12 or V12R.

<sup>n</sup> SRS at V1 will be a retrospective assessment of the supervision required by the subject immediately prior to admission that includes the index episode of the SE, and mRS at V1 will be a retrospective assessment of the disability and dependence of the subject immediately prior to admission that includes the index episode of the SE.

<sup>o</sup> Target for complete wean of all continuous IV third-line agents by 144 hours at V8/V8R if not completed by 120 hours at V7/V7R.

<sup>p</sup> Study drug infusion is intended for IV administration only with a dedicated peripheral IV line using Sage-approved IV administration bags and lines.

<sup>q</sup> At V10 only a decision to re-treat at a higher dose of SAGE-547 will be made by the Investigator if the continuous IV third-line agent wean has failed or the third-line agent requires re-introduction during V9. Subjects who become eligible for open-label study drug at a higher dose of SAGE-547 will discontinue the planned visit schedule at V10, then repeat V3 (V3R) and all applicable subsequent visits.

<sup>r</sup> AEs will be collected from the time Informed Consent is obtained and prior to the start of study-specific screening procedures not considered standard of care. Collection of AEs will continue throughout the study from V1 through V12 or V12R.

<sup>s</sup> Subjects may enter the study on AEDs and Pressors and be administered AEDs and Pressors during the study. For all randomized and the first 50 QWS subjects, all Concomitant AEDs and Pressors must be recorded on the CRF with details including date and time of starting/stopping each AED and Pressor, the route of administration, changes in doses, and

frequency of administration. Details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the CRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”. For subsequent QWS subjects, after the detailed information on all concomitant AEDs and Pressors collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant AED and Pressor and the start and stop dates and times) from Visit 3 to Visit 12 will be recorded in the eCRF.

<sup>†</sup> All third-line agents administered since the diagnosis of SE will be recorded on the CRF. For all randomized and the first 50 QWS subjects, details will include the name of the drug, the start/stop dates and times, and, after consent, the doses with start/stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R. For subsequent QWS subjects, after the detailed information on all concomitant third-line agents collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant third-line agent and the start and stop dates and times) from Visit 3 to Visit 12 will be recorded in the eCRF.

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**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
AE	adverse event
AED	anti-epileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the time-concentration curve
AW	additional weans
BDZ	benzodiazepine
BIEEG	blinded infusion electroencephalogram
BUN	blood urea nitrogen
CBC	complete blood count
CEEG	consent electroencephalogram
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
C <sub>max</sub>	maximum plasma concentration
C <sub>min</sub>	minimum plasma concentration
CNS	central nervous system
CRF	case report form
CSR	clinical study report
CYP2C9	cytochrome P450 enzyme involved in drug metabolism
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EEG	electroencephalogram
EIND	Emergency Use Investigational New Drug Application
EP	European Pharmacopeia
ESETT	Established Status Epilepticus Treatment Trial
FDA	Food and Drug Administration
FOUR	Full Outline of UnResponsiveness
GABA	$\gamma$ -aminobutyric acid
GABA <sub>A</sub>	$\gamma$ -aminobutyric acid-gated chloride channel
GCP	Good Clinical Practice

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
GFR	glomerular filtration rate
GOS	Glasgow Outcome Scale
H	hour
HPLC	high performance liquid chromatography
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent to Treat
IV	intravenous
IVRS	Interactive Voice Randomization System
LAR	legally authorized representative
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent to Treat
mRS-9Q	Modified Rankin Score - 9Q
MS/MS	tandem mass spectrometry
nM	nanomolar
NMDA	n-methyl-D-aspartic acid
OW	other weans
PAEEG	primary endpoint electroencephalogram
PD	pharmacodynamics
PK	pharmacokinetic
QOL	quality of life
QW	qualifying wean
QWEEG	qualifying wean electroencephalogram
RBC	red blood cell
RSE	refractory status epilepticus

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
SAE	serious adverse event
SAP	Statistical Analysis Plan
SE	status epilepticus
SOP	standard operating procedure
SRS	Severity Rating Scale
SRSE	Super-refractory status epilepticus
SSRI	Selective serotonin re-uptake inhibitors
STESS	Status Epilepticus Severity Score
SUSAR	Suspected Unexpected Serious Adverse Reactions
SWFI	Sterile Water for Injection
TAEEG	taper electroencephalogram
T <sub>max</sub>	time at maximum plasma concentration
TW	terminal wean
TWEEG	terminal wean electroencephalogram
US	United States
USP	United States Pharmacopeia

### 3. INTRODUCTION AND RATIONALE

#### 3.1. Status Epilepticus

Status epilepticus (SE) is a life-threatening seizure condition in which the brain is in a state of persistent seizure triggered by neuronal hyperexcitability. The Neurocritical Care Society defines SE as one continuous unremitting seizure lasting longer than five minutes or recurrent seizures without regaining consciousness between seizures for greater than five minutes (Brophy, Bell et al. 2012). Common causes of SE include preexisting epilepsy, cerebrovascular disease (in adults), electrolyte and metabolic disturbances, anoxia, encephalopathies, head trauma, high fever (in children, especially in the first year of life) and drug or substance intoxication. SE is associated with substantial morbidity and mortality.

##### 3.1.1. Epidemiology of SE

Geography, sex, age, and race influence the epidemiology of SE, whose incidence has a bimodal distribution, peaking in infants/young children and the elderly (Hauser 1990; DeLorenzo, Pellock et al. 1995; Wu, Shek et al. 2002). The incidence of SE in the elderly population is at least twice that in the general population. Concurrent medical conditions often exist in the elderly population, which can complicate therapy and worsen the prognosis of SE (Chapman, Smith et al. 2001).

The annual incidence of SE in the US is generally quoted to be within the range of 18/100,000 to 61/100,000, based on a 19-year retrospective study in Rochester, Minnesota (Hesdorffer, Logroscino et al. 1998) and a 2-year prospective study in Richmond, Virginia (DeLorenzo, Pellock et al. 1995), respectively. Two studies from Europe give annual incidences of a similar magnitude, ranging between 9.9/100,000 and 15.8/100,000 (Coeytaux, Jallon et al. 2000; Knake, Rosenow et al. 2001). It is thus estimated that in the United States each year there are as many as 150,000 cases of SE (DeLorenzo, Pellock et al. 1995).

#### 3.2. Refractory SE

When a patient begins to seize, the emergency medical technician will administer a first-line intravenous (IV) benzodiazepine (BDZ), such as diazepam, lorazepam or midazolam (Silbergleit, Durkalski et al. 2012), which is done either at the scene of the seizure or in the ambulance. If this is unsuccessful at abating the seizure, additional doses of the first-line therapy will be administered in the emergency room. Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line therapy, which is an IV anti-epileptic drug (AED) such as phenytoin or valproic acid (Novy, Logroscino et al. 2010; Shorvon 2011; Hocker, Britton et al. 2013).

Approximately 20-30% of patients refractory to first-line treatment will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to approximately 70-80% of patients who receive second-line therapy refractory to that therapy.

If a patient's SE continues after administration of BDZs and AEDs, the subject is diagnosed as having refractory status epilepticus (RSE), which must be treated quickly to terminate the seizure activity, maintain the patient's airway, and prevent cerebral damage. RSE patients are immediately admitted to the Intensive Care Unit (ICU) and placed in a medically-induced coma to stop all seizure-related activity. The drugs used to induce coma are continuously-infused IV agents,

commonly propofol, midazolam, or pentobarbital, referred to as third-line agents (Brophy, Bell et al. 2012).

The RSE patient is continually monitored using electroencephalography (EEG) to ensure that seizure and/or burst suppression is achieved. Burst suppression is a pattern of brain waves seen on an EEG, characterized by periods of activity alternating with periods of little or no activity in the brain, informing medical personnel of the effectiveness of the medically-induced coma. The goal of burst suppression is to allow the brain and corresponding neuronal tissue to restore function and reset to normal pre-seizure levels.

### **3.2.1. Epidemiology of RSE**

Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line AED therapy. In turn, approximately 20 – 30% of these patients treated with AEDs will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to 28% of the total estimated SE patient population refractory to second-line therapy. Based on the previously-cited estimated incidence in the US, this means that there are up to 42,000 incident cases of RSE in the USA, annually (DeLorenzo, Pellock et al. 1995).

## **3.3. Super-refractory SE**

After 24 hours of burst or seizure suppression, the patient is weaned off of the third-line therapy. If the weaning is unsuccessful (neuronal activity has not returned to normal), the third-line agent is re-administered or a different third-line agent is started, and the patient is considered to be in super-refractory status epilepticus (SRSE) (Chapman, Smith et al. 2001; Shorvon 2011; Brophy, Bell et al. 2012). SAGE-547 is being developed as an adjunct to third-line therapy in patients in RSE who have failed standard treatment. In this protocol, the term “RSE that has failed standard treatment” is deemed to be equivalent to the term “SRSE” and the two may be used interchangeably.

### **3.3.1. Epidemiology of SRSE**

The incidence of SRSE is very poorly understood, mainly because the diagnostic codes used for SE do not generally differentiate its nature as responding or refractory to treatment. Based on the variable reporting of outcomes data, the incident cases of SRSE could represent between one and two-thirds of the RSE patients (Novy, Logroscino et al. 2010; Ferlisi and Shorvon 2012; Hocker, Britton et al. 2013; Sutter, Marsch et al. 2013). More detailed epidemiology studies are needed to better elucidate the proportion of RSE patients whose condition becomes super-refractory. A recent review of ICU discharge data in the USA suggests an annual incidence of approximately 35,000, based on patients who required at least three days in the ICU for SE [Sage data on file].

### **3.3.2. Outcomes of SRSE**

SE has varying degrees of mortality depending on the underlying etiologies. Table 4 outlines the acute mortality in patients with SE by etiology (Neligan and Shorvon 2010). The mortality rate of SRSE is estimated to be 30% to 50% using current standard of care.

The causes of death from SE (and therefore SRSE) are heterogeneous, resulting from neuronal cell death, complications of underlying medical conditions, or adverse effects of the current standard treatments. Prognosis worsens and mortality increases with longer duration of SE, i.e. with SE that develops into RSE or SRSE (Neligan and Shorvon 2010), and with longer duration of

medically-induced coma ([Ferlisi and Shorvon 2012](#)). There is an obvious unmet medical need to improve upon the current standard of care treatment regimens.

Morbidity is high and survivors have outcomes ranging from poor function to vegetative state ([Shorvon 2011](#)). Approximately one third of patients with RSE and SRSE will recover, but with chronic neurologic or other deficits ([Neligan and Shorvon 2010](#); [Hocker, Britton et al. 2013](#)). In all, it is estimated that less than 25-30% of all SRSE patients have a favorable functional outcome.

**Table 4: Approximate Mortality of Status Epilepticus in Different Etiologies**

Underlying Etiology	Associated Acute Mortality in Patients with SE (%)
Drug reduction/withdrawal, poor AED compliance, or low AED levels	0-10
Cerebrovascular Disease	20-60
Metabolic Disorders	10-35
Acute CNS Infection	0-30
Anoxia	60-100
Alcohol Abuse	0-10
Head Trauma	0-25
Drug Overdose/Toxicity	10-25
Brain Tumors	0-20
Cryptogenic/Idiopathic	5-20

### 3.3.3. Unmet Medical Need in Super-refractory Status Epilepticus

Treatment approaches for SRSE consist of diagnosis and treatment of underlying medical conditions, adding and changing anti-seizure drugs, and repeated attempts at weaning from IV anesthetic agents. Treatment of SRSE has three aims:

- to prevent excitotoxicity, which begins within 24 hours of SE onset;
- to prevent cerebral damage by initiating neuroprotective burst or seizure suppression;
- to prevent the complications of extended periods of anesthesia or unconsciousness ([Shorvon 2011](#)).

Currently, there are no therapies that have been specifically approved for RSE or SRSE. The primary drugs used to induce coma are continuously infused IV anesthetics such as propofol, midazolam, or pentobarbital/thiopental, known as third-line agents. Use of these drugs to control SRSE has only been studied in small retrospective reviews or small prospective studies without controls ([Hocker, Britton et al. 2013](#)) therefore there is no agreement on which drug is optimal nor on an optimal dosing regimen for the treatments that are used.

The most common adverse effect of the third-line agents is hemodynamic instability; in addition, they are not universally effective, with breakthrough seizures and withdrawal seizures requiring dose adjustments and changes in third-line agent(s). The drug thought to be most effective in SRSE, pentobarbital, is also associated with the most toxic adverse effect profile, comprising



decreased blood pressure and cardiorespiratory collapse (Claassen, Hirsch et al. 2002). The ability to wean patients successfully off the third-line agents as quickly as possible is therefore paramount, and an adjunct to SRSE treatment that enhances the success of the third-line agents and supports their successful weaning in a short timeframe would be an important addition to the therapeutic armamentarium. Preliminary clinical data show that SAGE-547 has been a successful adjunct to third-line therapy in this regard.

### 3.4. SAGE-547 Injection

Allopregnanolone is an endogenous, naturally occurring neuroactive steroid formed in the corpus luteum of the ovary, adrenal cortex and central nervous system (CNS) (Holzbauer, Birmingham et al. 1985; Paul and Purdy 1992; Ottander, Poromaa et al. 2005). It is a metabolite of progesterone created by the actions of 5- $\alpha$  reductase and 3- $\alpha$  hydroxy-steroid dehydrogenase. Allopregnanolone is a potent positive allosteric modulator of both synaptic and extra-synaptic GABA<sub>A</sub> receptors.

SAGE-547 Injection (allopregnanolone aqueous formulation in Captisol<sup>®</sup>) is being developed for the treatment of patients in RSE who have not responded to standard treatment. SAGE-547 Injection is a solution of 5 mg/mL allopregnanolone in Sterile Water for Injection (SWFI), USP and 250 mg/mL betadex sulfobutyl-ether sodium, NF. It is further diluted with Sterile Water for Injection, USP (SWFI) in IV bags to achieve an allopregnanolone concentration of approximately 1.67 mg/mL in an approximately isotonic solution and will be administered intravenously.

#### 3.4.1. Scientific Rationale for SAGE-547 in SRSE

Ineffective recruitment of inhibitory neurotransmission, together with excessive neuronal excitation, likely plays a role in the initiation and propagation of the electrical disturbance occurring in SE. GABA ( $\gamma$ -aminobutyric acid), the major inhibitory neurotransmitter in the central nervous system (CNS), is released from GABAergic neurons and binds to several types of GABA receptors (GABA<sub>A</sub>, GABA<sub>B</sub>, and GABA<sub>C</sub>) on target neurons. GABA<sub>A</sub> receptors are macromolecular proteins that form a chloride ion channel complex and contain specific binding sites for GABA and a number of allosteric regulators, including barbiturates, benzodiazepines, and some anesthetic agents. GABA receptor-mediated inhibition contributes significantly to the normal termination of a seizure (Kapur and Macdonald 1997). SAGE-547 is a positive allosteric modulator of the GABA<sub>A</sub> receptor.

The importance of terminating seizure activity as soon as possible is underpinned by a growing body of evidence from research and clinical observation that SE becomes more difficult to control as its duration increases. It has been postulated that this occurs due to a mechanistic shift from inadequate GABAergic inhibitory receptor-mediated transmission to excessive N-methyl-D-aspartic acid (NMDA) excitatory receptor-mediated transmission (Kapur and Macdonald 1997). As prolonged epileptiform bursting results in a reduction of GABA<sub>A</sub>-mediated synaptic inhibition, antiepileptic treatments which rely on enhancing intrasynaptic GABA<sub>A</sub> neurotransmission become less effective the longer SE continues.

Furthermore, the constitutive process of synaptic GABA<sub>A</sub> receptor internalization is accelerated by the increased neuronal activity associated with seizures. These findings suggest that the rate of GABA<sub>A</sub> receptor internalization is regulated by neuronal activity, and its acceleration contributes to the reduction of inhibitory transmission observed during prolonged seizures (Kapur and Macdonald 1997). Of note is that SAGE-547 binds to extrasynaptic as well as intrasynaptic GABA<sub>A</sub> receptors;

extrasynaptic receptors remain active with ongoing seizure activity, resulting in a putative mode of action for SAGE-547 in SRSE.

Status epilepticus induces cerebral damage that includes neuronal cell necrosis, gliosis, and network reorganization. The major cause of cell death in cerebral damage is excitotoxicity, which is initiated by glutaminergic receptor over-activation, causing calcium to flood the cell, thereby leading to apoptosis and necrosis. This process is initiated within a few hours of the start of seizure activity, and provides the medical imperative to terminate SE as quickly as possible. To prevent the consequences of the excitotoxicity cascade, it is recommended that anesthesia be initiated within 1-2 hours of onset of seizures at doses designed to induce EEG suppression patterns (Shorvon and Ferlisi 2011).

### **3.4.2. SAGE-547 Clinical Program in the Treatment of SRSE**

The current SAGE-547 development program includes:

- a completed Phase 2 open-label trial, Study 547-SSE-201;
- this proposed Phase 3 randomized, double-blind, placebo-controlled trial, Study 547-SSE-301;
- an ongoing open-label, expanded access protocol, Study 547-SSE-302;
- a number of EINDs for SAGE-547 in patients with SRSE.

The designs of these studies are all similar, with a five to six day infusion of SAGE-547 (or placebo), during which time attempts are made to wean the subject off all third-line agents. In the Phase 3 studies, those subjects who cannot be weaned off third-line agents while being administered SAGE-547 (or placebo) may be eligible for a second open-label infusion of SAGE-547 at a higher dose. Follow up of subjects is for 21 – 30 days after the first infusion of study medication.

### **3.4.3. Data from the SAGE-547 Development Program**

The data from 30 subjects included in the on-going clinical evaluation of SAGE-547 for the treatment of adults and children with SRSE clearly offers preliminary evidence that SAGE-547 could provide substantial and clinically significant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate. These subjects comprise 20 from the ongoing Phase 2 trial (71% success rate in 12/17 evaluable subjects) and 10 subjects who received EIND treatments (78% success rate in 7/9 evaluable subjects).

Successful therapy of SRSE has been defined as “the SE is completely controlled by the therapy, without breakthrough of withdrawal seizures, or discontinuation due to side effects or death during therapy,” (Ferlisi and Shorvon 2012). By this definition, which is in accord with the efficacy assessments used in the overall clinical evaluation of SAGE-547, 19 of the 26 (73%) subjects with SRSE who completed the SAGE-547 infusion were treatment successes. As data collection is ongoing, this information is preliminary and subject to change upon further monitoring.

Published reports on RSE and SRSE have stated mortality rate ranges from 35% to 65%. The underlying etiologies of SE in the 547-SAGE-201 study and EINDs are heterogeneous, and each one conveys a different risk of mortality and longer term morbidity. However, the death rate in subjects who have received SAGE-547, 6 out of 30 (20%) subjects, appears to be lower than the published rates. None of the deaths were considered related to SAGE-547: brain tumor, organophosphate toxicity, respiratory failure, respiratory arrest due to ventilator support withdrawal, and breast cancer.

In the Phase 2 study, 20 SAEs (15 non-fatal) have been reported in 13 (65%) subjects, and of these 3 events in 2 subjects (10%) were considered by the investigator to be related to SAGE-547: pulmonary emboli and tracheostomy dehiscence/infection. The Sponsor did not consider these events to be related to SAGE-547, rather to the underlying disease states. Four of the 20 subjects (20%) experienced AEs considered possibly related to SAGE-547 by the investigator, namely moderate myopathy and severe pulmonary emboli in 1 subject, moderate tracheostomy dehiscence and tracheostomy infection in 1 subject, moderate thrombocytosis in 1 subject and moderate BUN, ALT and AST elevation in 1 subject.

Review of the most current safety data from 547-SAGE-201 reveals that there were changes in serum chemistry, hematology, and urinalysis during the study, but that none of those changes were assessed as related to SAGE-547. There were also no SAGE-547-related changes to vital signs.

Despite the heterogeneity in the underlying causes of SE, the ages of the subject, comorbidities, which normally complicate the treatment of SE, and the fact that all subjects had failed current standard of care treatment, a large majority of subjects had a successful therapy outcome, with discontinuation of all third-line agents and resolution of SE.

Refer to the Investigational Brochure for further information on the pre-clinical and clinical data supporting the use of SAGE-547 in SRSE.

### **3.5. Study Rationale - SAGE-547 in SRSE**

#### **3.5.1. Justification for the Control Group**

Although SAGE-547 has demonstrated extremely promising activity in subjects with SRSE, both in the Phase 2 study and during the EINDs, these have been open-label investigations with no control data for comparison. Generally in the literature there are few data describing the success rates of wean attempts of third-line agents, and few comparative data on the effectiveness of the three main third-line agents, propofol, pentobarbital/thiopental, and midazolam.

Several options for a control group in Study 547-SSE-301 were considered:

- No control group was thought to be unacceptable since there are no reliable published data on success rates in this population that could be used for broad comparisons;
- An active control was considered but found to be impractical since none of the third-line agents are approved for their use in SRSE, no standardized dosing regimens or treatment guidelines have been adopted for the management of SRSE, and clinicians were unlikely to agree which of the available third-line agents would be reserved for the active control arm;
- Historical controls were considered but abandoned because of the practical difficulties of obtaining high quality data, the lack of ability to prospectively match cases, and a suspicion that clinical practice in the standard of care of SRSE is evolving, mandating the use of prospective, concurrent control data;
- Comparison to standard of care alone was considered as a feasible design. However, in a field where no widely adopted treatment guidelines exist, there was a concern that knowledge of the treatment group (SAGE-547 plus standard of care versus standard of care alone) would alter the behavior of the investigators such that they could be more aggressive with weaning in the SAGE-547 group;

- Placebo control is not without its challenges since the preliminary efficacy data for SAGE-547 show that the compound exerts central pharmacological effects and is associated with positive outcomes in around 70% of patients. There is therefore a potential ethical concern about administering placebo to desperately ill patients who have often exhausted all treatment options for SRSE. This concern has been addressed in two ways: firstly all patients receive current standard of care; secondly, all subjects who fail to be weaned from their third-line agents at the end of the blinded infusion of study drug will be administered open-label SAGE-547 without un-blinding their initial treatment allocation, so treatment with the investigational product is not denied, but delayed about a week in the setting of ongoing receipt of full current standard of care.

It was therefore decided that a blinded, placebo-controlled design was appropriate for Study 547-SSE-301.

### **3.5.2. Justification for the Dose Regimen**

The standard dose regimen has been studied in 19 subjects in the 547-SSE-201 Phase 2 trial; the average peak plasma concentration of SAGE-547 at the end of the loading dose was approximately 144 ng/ml. The average plasma concentration during the maintenance infusion was approximately 70 ng/ml. At these concentrations, there were no clear safety signals although two-thirds of subjects experienced an SAE and there were four deaths, all related to the underlying comorbid conditions. The standard dosing regimen was associated with an approximate 70% successful treatment outcome. For these reasons, the standard dosing regimen has been adopted for the initial SAGE-547 infusion to be compared in a blinded fashion to placebo.

In the 547-SSE-201 trial, three subjects have thus far received the higher dose regimen. This dose regimen has also been well tolerated. The average peak plasma concentrations at the end of the loading dose for both dosing regimens will be in the same range, as the loading dose is the same for both regimens. The average plasma concentrations observed during the higher maintenance dose are 102 ng/ml (n=2). The rationale for adopting the higher dose regimen as the open-label infusion of SAGE-547 for subjects who are retreated in this 547-SSE-301 trial is that those who fail on the standard SAGE-547 dose regimen are afforded the opportunity to have access to a higher dose. The justification to also administer the higher dose regimen to failures on placebo is that the regimen has thus far been well tolerated, and this methodology preserves the blind for the initial infusion.

A five-day dosing regimen with SAGE-547 was investigated in the Phase 2 study, 547-SSE-201. There were some cases when weaning off all third-line agents was not possible within 48 hours, but weaning was completed after the end of the infusion of SAGE-547. For this reason, the duration of dosing with SAGE-547 has been increased from 120 hours (five days) in Phase 2 to 144 hours (six days) in this Phase 3 study.

### **3.5.3. Rationale for Genetic Testing Sub-study**

Sage Therapeutics intends to perform genetic research in the SAGE-547 development program in order to explore how genetic variations may affect the metabolism and activity of SAGE-547. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials, and, possibly, to genetically-guided treatment strategies for optimizing decision making with respect to individual benefit:risk. Participation of subjects in genetic research as part of the overall clinical study is optional.

### **3.6. Benefit-Risk Evaluation of the Present Study**

Previous reports of human administration of exogenous allopregnanolone indicate that for exposures in men and women up to 150 nM, the most commonly reported AEs were sedation (recorded as sleepiness or tiredness), feelings of intoxication (like alcohol), flushing, and mild headache (Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007). No SAEs were reported (Navarro, Kaddouz et al. 2003; Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007; Kask, Backstrom et al. 2008; Kask, Backstrom et al. 2009; Timby, Hedstrom et al. 2011a). In view of the reduced consciousness and sedation of study subjects at entry into this protocol, none of these previously-reported events are likely to impact subjects in this study.

To date, in the SAGE-547 Phase 2 study and the EIND subjects, a majority of subjects demonstrated a successful therapy outcome (>70%). The majority in the clinical trial (65%) have also experienced SAEs, but none has been considered related to SAGE-547 by the Sponsor (SAEs in 2 subjects (10%) were considered possibly related by Investigator). Five deaths have been reported in 30 subjects (20%), all related to the underlying cause of SRSE and not related to SAGE-547 – this is in the context of published mortality rates between 35% and 65%. These preliminary data suggest that SAGE-547 has the potential to provide clinically relevant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate.

The underlying etiologies of SE are heterogeneous, and each one conveys a different risk of mortality. Subjects who survive SRSE still have a high risk of severe morbidity (Neligan and Shorvon 2010). The subjects treated with SAGE-547 in Study 547-SSE-201, are heterogeneous in factors such as age and etiology of SE, factors that usually complicate treatment and can increase morbidity and mortality. Even with this heterogeneity, the preliminary efficacy and safety data for SAGE-547 are very encouraging, and the mortality rate suggests that the risk to benefit assessment of this treatment rests on the side of benefit.

## **4. ETHICS**

### **4.1. Institutional Review Board or Independent Ethics Committee**

This protocol will be reviewed and approved by the Institutional Review Board (IRB) where the study is conducted. The IRB will meet all FDA requirements governing IRBs (CFR, Title 21, Part 56).

### **4.2. Ethical Conduct of the Study**

The Sponsor, the Medical Monitor, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable ICH and GCP guidelines, and must also conduct the study in accordance with local regulations.

### **4.3. Subject Information and Informed Consent**

Subjects prospectively enrolled in this study will be unable to give consent. Therefore, consent will be given by proxy by a legally authorized representative (LAR). Written informed consent is required for each subject prior to any testing under this protocol not considered standard of care, including screening tests and evaluations. Should a subject gain the ability to sufficiently

comprehend the situation and consent during the course of the study, written informed consent or verbal assent will be documented as required or recommended by the institution's IRB.

The form of consent to be obtained will depend on the condition of the subject as determined by the Principal Investigator. The informed consent form (ICF), as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50.

It is the responsibility of the Investigator to obtain consent and to provide the subject's LAR with a copy of the signed and dated informed consent form. The informed consent form for subject participation must also be available as part of the subject file for review by the site's dedicated study monitor or any authorized auditor of the Sponsor or regulatory authorities.

All ICFs used in this study must be approved by the appropriate IRB and by the Sponsor. The ICF must not be altered without the prior agreement of the relevant IRB and the Sponsor.

#### **4.4. Ethical and Regulatory Considerations for Pharmacogenetic Sub-study**

##### **4.4.1. Informed Consent for Pharmacogenetics**

The genetic component of this study is optional and subjects may participate in other components of the main study without having to agree to participate in the genetic component. If subject chooses to participate in the genetic component of the study, the subject or LAR must sign and date a specific consent form for the genetic component of the study in addition to the main study consent form. The principal investigator(s) is responsible for ensuring that consent is freely given and that the subject understands that they may discontinue from the genetic aspect of the study independent of their decision to remain within or withdrawal from the main study.

##### **4.4.2. Subject Data Protection Relative to Pharmacogenomics**

Sage Therapeutics will not provide individual genotype results to subjects, their family members, their general physician, their employer or any insurance company unless required to do so by law. While extra precautions will be taken to preserve confidentiality and to prevent genetic data from being linked to an individual's identity outside of a restricted access site, in certain exceptional situations (e.g. in case of a medical emergency or as a consequence of a specific regulatory need), certain individuals may see both genetic data and the personal identifiers of a subject; however in all cases a subject's medical information and genetic files will remain physically separated.

## **5. STUDY OBJECTIVES**

### **5.1. Primary Objective**

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult subjects with SRSE, and for the response to endure at least 24 hours after cessation of the SAGE-547 or placebo infusion (primary response).

## 5.2. Secondary Objectives

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in Clinical Global Impression Scale between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

## 5.3. Safety Objectives

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

## 5.4. Other Objectives

1. To evaluate the impact of retreatment with a higher dose of SAGE-547 infusion;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;

6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS).

## **6. ENDPOINTS**

### **6.1. Primary Endpoint**

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### **6.2. Secondary Endpoints**

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) and to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### **6.3. Safety Endpoints**

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.

### **6.4. Other Endpoints**

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who are treated with a higher dose of SAGE-547;



2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS).

## 7. INVESTIGATIONAL PLAN

### 7.1. Overview of Study Design

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

[Figure 1](#) provides an overview of the study design and [Figure 2](#) gives the details of treatment and follow-up on the active treatment arm. Patients will follow one of three paths to entry to the study. The first path is for patients who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst or seizure suppression with a third-line agent. These patients will be consented for the study after admission to the intensive care unit, before or after any third-line agents are administered for burst or seizure suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their LAR. Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours. Once burst or seizure suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned during the QW will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst or seizure suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The second path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst or seizure suppression pattern on the EEG. These patients may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst or seizure suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst or seizure suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst or seizure suppression has been achieved, the third-line agent or agents will

be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst or seizure suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The third path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst or seizure suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These patients may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst or seizure suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within eight hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third line agent wean attempts prior to randomization (one vs two or more).

The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

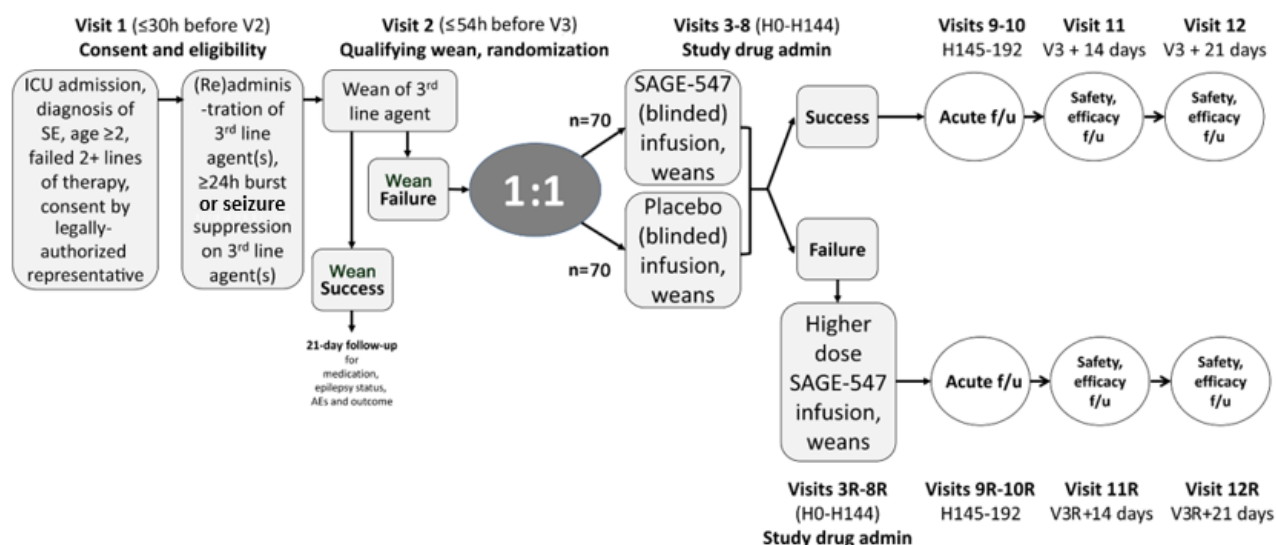
For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as the ability to wean the subject off all third-line agents before the end of the first infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication. Subjects must also have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) at the end of the primary endpoint assessment period as determined by EEG in order to be deemed a success. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#), [Table 2](#) and [Table 3](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion may be eligible to receive an open-label infusion of SAGE-547 at a dose higher than

that administered in the blinded part of the study. Eligibility for the open-label treatment must be confirmed in writing by the medical monitor prior to the open-label infusion starting. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo may all subsequently be eligible to be administered SAGE-547 at the higher dose.

**Figure 1: Study Design**



## 7.2. Trial Conduct

This study will be conducted according to the principles of the World Medical Association Declaration of Helsinki and most recent amendment, and in compliance with the protocol approved by the IRBs/Independent Ethics Committees (IECs), and in accordance with ICH Guidelines on GCP standards.

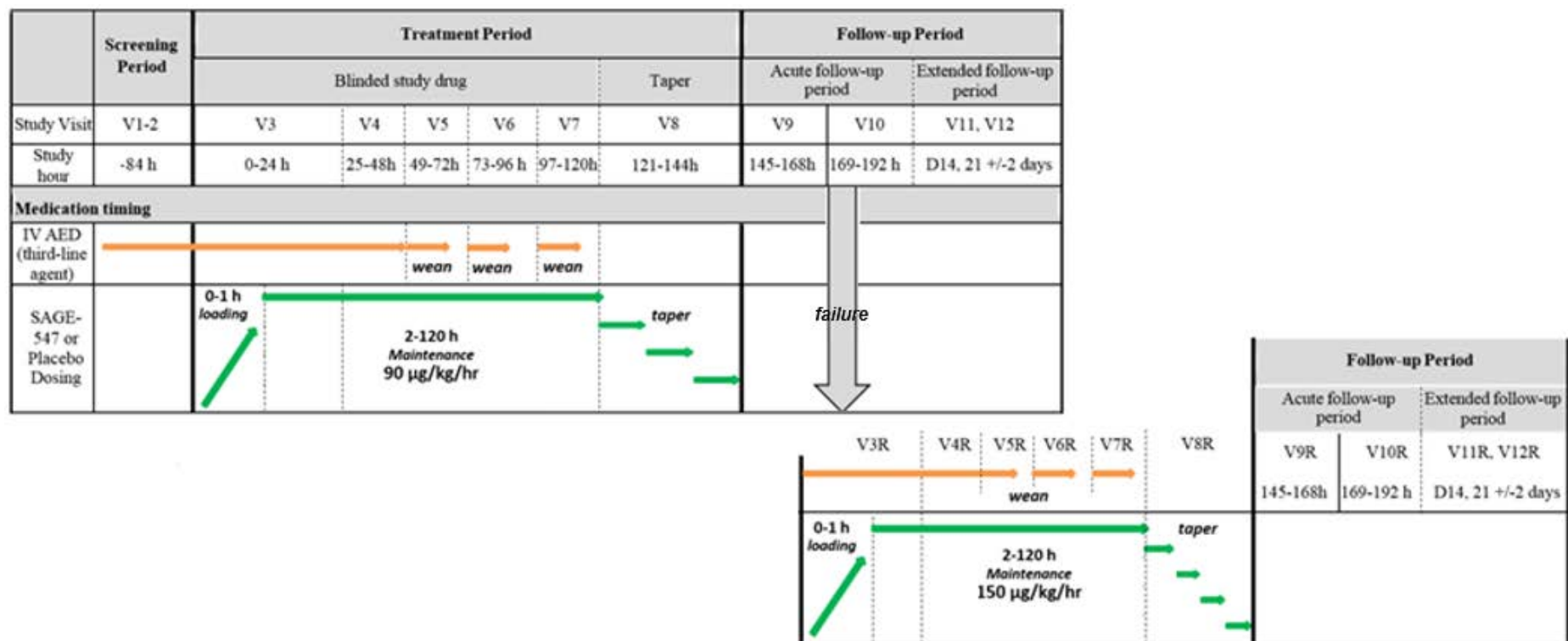
## 7.3. Blinding and Randomization

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo). Details of the dynamic randomization process will be included in the SAP.

The randomized portion of the study will be blinded, with the two treatment products (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

The second infusion of SAGE-547 will be administered on an open-label basis to subjects who meet the criteria for open-label treatment.

### Figure 2: Details of Treatment Administration and Follow-up



## 8. SELECTION AND WITHDRAWAL OF SUBJECTS

The study will randomize 140 patients at up to 180 sites. All subjects deemed eligible to enroll must have written Medical Monitor approval on a case-by-case basis prior to undertaking the qualifying wean.

### 8.1. Inclusion Criteria

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects 17 years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; *or* who have previously failed zero or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst or seizure suppression pattern; *or* who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst or seizure suppression pattern.

### 8.2. Exclusion Criteria

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy with highly malignant/malignant EEG features ([Westhall, Rosetti et al. 2016](#)).
4. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis but for whatever reason, dialysis that would adequately remove Captisol® is not planned;
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the experience of the investigator, is less than 30 days.
5. Subjects who are being administered more than three third-line agents concomitantly or for whom the qualifying wean cannot be completed within 24 hours or who are being

administered a third-line agent for indications such as raised intra-cranial pressure that would preclude weaning according to this protocol.

6. Subjects with a living will that does not allow heroic measure.
7. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
8. Subjects who have been treated or randomized in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not have received study drug/placebo and then re-enroll).

### **8.3. Selection and Consent of Subjects for Pharmacogenetic Substudy**

All subjects will be asked to participate in pharmacogenetic research; however, participation in research is voluntary and a subject can decide to decline his/her participation without penalty or loss of benefit. Participation or lack thereof will not be a cause for exclusion from any aspect of the main study. In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **8.4. Subject Withdrawal / Study Termination**

#### **8.4.1. Withdrawal/Discontinuation of Individual Subjects**

The reasons for study drug discontinuation and/or subject withdrawal from the study must be recorded in the subject's electronic case report form (eCRF). The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject has been discontinued/withdrawn due to an AE.

##### **8.4.1.1. Withdrawal from the Study**

Subjects or their LAR may withdraw subjects from the study at any time for any reason without compromising the subject's medical care. The Investigator will also withdraw subjects upon the request of Sage Therapeutics or upon termination of the study.

Subjects who withdraw from the study prior to Visit 10 (or 10R) should complete the procedures scheduled for the day of study drug taper (Hour 121-144; Visit8/8R) on the day of their withdrawal, including the SAGE-547 taper schedule, with the addition of the mortality assessment from Visit 12/12R. Subjects who withdraw from the study after Visit 10/10R should undergo study procedures as outlined for Visit 12/12R on the day of their withdrawal. In all cases, the reason for subject withdrawal will be recorded in the eCRF.

Withdrawal of subjects for any reason should be discussed with the Medical Monitor.

##### **8.4.1.2. Discontinuation of Study Drug**

If it is necessary to discontinue the study drug earlier than planned, subjects should continue to be followed per protocol to capture safety and efficacy assessments for the duration of the study period.

The investigator may withdraw the subject from the study drug for the following reasons:

- Upon subject's or LAR's request
- The subject or LAR is unwilling or unable to adhere to the protocol-specified visits
- The subject experiences an intolerable adverse event
- During the course of the study, the subject develops symptoms or conditions listed in the exclusion criteria.
- Other medical reason, at the discretion of the Investigator and/or the Medical Monitor

Subjects who discontinue the study due to an AE considered related to study drug should be followed until the event is resolved, considered stable, or the Investigator determines the event is no longer clinically significant. Study drug discontinuation due to AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

#### **8.4.2. Study Termination**

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of AEs or other findings suggesting unacceptable risk to subjects, administrative or operational reasons. In the event of study termination, Sage Therapeutics will provide written notification to the Investigator. Investigational sites must promptly notify their IRB and initiate withdrawal procedures for participating subjects.

## **9. INVESTIGATIONAL PRODUCT**

### **9.1. Identity of Investigational Product**

SAGE-547 Injection (allopregnanolone)

### **9.2. Clinical Supplies**

#### **9.2.1. SAGE-547**

Adequate supplies of SAGE-547 Injection and materials for intravenous administration will be provided to each site.

SAGE-547 Injection is a clear, colorless sterile solution of allopregnanolone intended for intravenous injection. SAGE-547 Injection is an aqueous solution of 5 mg/mL allopregnanolone in 250 mg/mL Captisol® (betadex sulfobutyl-ether sodium, NF). It is presented either un-buffered or buffered with 10 mM citrate at a pH of 6.0 in either 20 mL or 50 mL vials. SAGE-547 is further diluted according to the Pharmacy Manual to achieve an approximately isotonic solution and will be administered intravenously.

No preservatives are included in the drug product, which is intended to be used as a single-use vial. All inactive components (excipients) used in the formulation are compendial grade and conform to current USP/EP, and include sodium citrate, citric acid and betadex sulfobutyl-ether sodium (Captisol®).

#### **9.2.2. Placebo**

Placebo will be identical to SAGE-547 and presented in identical vials. Placebo will be manufactured in a similar way to SAGE-547 and comprises all excipients but no SAGE-547.



### **9.2.3. Blinding**

The vials of SAGE-547 and placebo will be identical in every way so that they are indistinguishable by the pharmacist, investigator, anyone treating or managing the patient, the monitors, and the sponsor. In this way the first infusion of study drug administered to each patient will be double-blind.

For the blinded study drug infusions, subject-specific dosing kits will be provided. These dosing kits will be pre-labelled with kit number for the first blinded infusion. For the second-infusion, open-label kits will be provided, which will require subject assignment by the pharmacy for reconciliation purposes. The study kits must be stored under refrigerated conditions (2-8 °C). IV administration bags and lines may be provided for the blinded and open-label infusions. Refer to the Pharmacy Manual for additional details.

The label for the SAGE-547 Injection vials will include standard product identification information according to the Code of Federal Regulations, 21CFR 312.6. All study labels will also contain the following statement:

Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use.

### **9.3. Preparation of SAGE-547 or Placebo Injection for Dosing**

The Pharmacy will be responsible for preparing the blinded and open-label study drug for subject dosing. The prepared admixture will be assigned a room temperature (20-25 °C) storage shelf life of 30 hours from time of compounding.

SAGE-547, which is hypertonic, will require dilution with SWFI to achieve an approximately isotonic solution according to the instructions provided in the Pharmacy Manual. Exactly the same procedures will be used to prepare the placebo admixture, so that all site staff remain blinded as to treatment allocation for the first infusion of study drug. SAGE-547 Injection is not intended to be administered to patients undiluted.

Refer to the Pharmacy Manual for specific instructions regarding infusion preparation.

### **9.4. Administration and Accountability**

The Pharmacy will maintain accurate records of all investigational product supplies. Accurate records will be kept regarding the volume of SAGE-547 Injection or placebo used for each IV preparation, as well as the required infusion rate or rates, and the date and time of preparation. Reasons for departure from the expected dosing regimen must also be recorded. To satisfy regulatory requirements regarding drug accountability, all study medication will be reconciled in full. Refer to the Pharmacy Manual for additional details.

## **10. TREATMENT OF SUBJECTS**

### **10.1. Dosing Schedule (Blinded Infusions)**

SAGE-547 Injection or placebo will be administered according to the dosing schedules in [Table 5](#). The infusion rates to accomplish these µg/kg/h doses will be calculated according to the weight of the subject obtained within the eight-hour window that follows the declaration of the QW failure at V2 and prior to dosing at V3. The infusion rates will be applied to blinded study drug for the first infusion of study medication.



**Table 5: SAGE-547 or Placebo Dosing Schedule**

Hour	Type and Duration of Study Drug Infusion	Description
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	90 µg/kg/h
H121 – H128	8 hour taper	65 µg/kg/h
H129 – H136	8 hour taper	45 µg/kg/h
H137 – H144	8 hour taper	25 µg/kg/h

## 10.2. Dosing Schedule (Open-Label Infusions)

Those subjects that qualify for the open-label study drug will be administered SAGE-547 Injection will be re-administered according to the dosing schedule in [Table 6](#). The dose will be administered on a µg/kg/h basis, and the subject's weight measured prior to dosing during V10 will be used to calculate the doses. These infusion rates will be applied to SAGE-547 treatment for the open-label second infusions of study medication.

**Table 6: SAGE-547 Open-Label Dosing Schedule**

Hour	Type and Duration of SAGE-547 Infusion	Description
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	150 µg/kg/h
H121 – H126	6 hour taper	125 µg/kg/h
H127 – H132	6 hour taper	95 µg/kg/h
H133 – H138	6 hour taper	65 µg/kg/h
H139 – H144	6 hour taper	35 µg/kg/h

## 10.3. Route of Administration

SAGE-547 Injection is intended for IV administration only. The compatibility of SAGE-547 with other drugs is unknown, and the product should be administered via a dedicated peripheral IV line using any Sage-supplied study-specific IV administration bags and lines. In order to preserve blinding, these instructions also apply to the blinded placebo infusions.

## 10.4. Treatment Period

The treatment period with double-blind SAGE-547 or placebo is six 24-hour periods (144 hours), which may encompass 6-7 calendar days. The open-label study drug treatment period is of identical duration.

## 10.5. Concomitant Medications, Procedures and Treatments

Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. For all randomized and the first 50 qualifying wean success (QWS) subjects, detailed information on all concomitant medications (concomitant AEDs, third-line agents, pressors, and other concomitant medications), procedures, and treatments should

be documented throughout the study from Screening through Visit 12/12R, as described below, and recorded on the eCRF. For subsequent QWS subjects, after the detailed information on all concomitant AEDs, pressors, third-line agents, procedures, and treatments collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant AED or pressor, third-line agent, procedure, and/or treatment, and the start and stop dates and times) from Visit 3 through Visit 12 will be recorded in the eCRF. For subsequent QWS subjects, after the detailed information on all concomitant medications collected during the screening period (Visits 1 and 2) has been recorded, only minimal information, to include the name of the concomitant medications and indication only will be recorded from Visit 3 through Visit 12.

SAGE-547 has demonstrated inhibitory effects on cytochrome P450 isoenzyme 2C9 (CYP2C9). Therefore, AEDs such as phenytoin and phenobarbital that are primarily metabolized by CYP2C9 should be closely monitored during SAGE-547 administration to ensure target exposures are maintained.

#### **10.5.1. Concomitant AEDs**

Subjects may enter the study on AEDs, and be administered AEDs during the study. All of these must be recorded on the eCRF with details including date and time of starting and stopping each AED, the route of administration, changes in doses, and frequency of administration. In addition, details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the eCRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.

#### **10.5.2. Concomitant Third-Line Agents**

All third-line agents (as defined in [Section 8](#)) administered since the diagnosis of SE will be recorded on the eCRF, whatever path the patient took for entry into the study. Details will include the name of the drug, the start and stop dates and times, and, after consent, the doses with start and stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

In addition, those changes in dose that constitute a wean attempt will be marked as such on the eCRF. In this way the start and stop dates and times of all wean attempts (see [Section 11](#) for definitions) will be recorded, as will the type of wean (QW, OW, or TW) and the outcome of the wean attempt (successful, failed and dose of this third-line agent increased or failed and this third-line agent stopped and another third-line agent started). Those wean attempts that occur after the TW up to and including Visit 12/12R will be marked “AW”.

Some third-line agents (such as propofol) are also used to induce sedation to facilitate a subject’s ability to tolerate the ventilator. For subjects requiring such sedation, propofol is the preferred agent unless there are contraindications. The eCRF will make clear from the indication for the third-line agent when it is being used for burst or seizure suppression and when it is being used as ventilator support or for another purpose. The investigator will add a note to the eCRF to justify that the doses used are appropriate for sedation and not for seizure or burst suppression. The doses used for ventilator support and other similar uses are usually much lower than those used for seizure or burst suppression, and use of these third-line agents for these other purposes does not constitute a wean failure under this protocol.

### **10.5.3. Concomitant Pressors**

The start and stop dates and times of all pressors will be recorded as well as the start and stop dates and times of all dose changes.

### **10.5.4. Other Concomitant Medications**

All other concomitant medications must be recorded on the eCRF with details including date and time of starting and stopping, the route of administration, dose, and frequency of administration.

## **11. STUDY ASSESSMENTS**

### **11.1. Efficacy Assessments**

#### **11.1.1. Primary Efficacy**

Success or failure will be determined, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo infusion and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the blinded (first) infusion of SAGE-547 or placebo. In addition, subjects must have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) to be deemed to be successes. All subjects who fail to complete their infusion of randomized treatment or do not have at least one attempt during study treatment to wean off all third-line agents will be considered as “failures” for the primary endpoint.

##### **11.1.1.1. Weaning**

Third-line agents are anesthetic agents that are administered in order to reach a seizure or burst suppression EEG pattern. For the purposes of this study, third-line agents are defined as continuous intravenous infusions of pentobarbital/thiopental, midazolam, propofol, and ketamine at maintenance doses alone or in combination sufficient to produce a burst or seizure suppression pattern on the EEG. The following are considered to be minimum maintenance doses of these agents that may be expected alone or in combination to achieve EEG burst suppression. If subjects are on lower doses than these and are not in EEG burst suppression for the first 12 hours of the blinded study drug infusion, they will be considered to be protocol violators and will exit the study.

- Pentobarbital: 1 mg/kg/hour
- Thiopental: 3mg/kg/hour
- Midazolam: 0.1 mg/kg/hour
- Propofol: 3 mg/kg/hour
- Ketamine 1.2 mg/kg/hour

The timing and nature of the third-line agent weans will be guided by the Clinical Standardization Guidelines for the study, and the clinical judgment of the investigator, and will always be primarily done in the best medical interests of the subject. Advice about weaning may be sought from the Clinical Standardization Team, a group of fellow investigators with experience of performing clinical trials in subjects with SRSE. The Clinical Standardization Team will be able to discuss EEGs in real time related to key study timepoints (terminal wean and the period after the end of the

blinded study drug infusion if the terminal wean was successful) in a timely manner in order to provide advice about compliance with the Clinical Standardization Guidelines.

The following guidance for weaning applies to all weans of third-line agents undertaken during the study. Continued determined efforts to liberate subjects from sedation must be undertaken for the entire duration of the blinded study drug infusion. Each failed wean from third-line agents should be followed by a 6-24 hour period of suppression and then another wean attempt, with further optimization of the AED regimen.

Weans include the qualifying wean (QW); the terminal wean (TW), which is the wean of the third-line agent if the subject is on only one third-line agent or the wean of the last third-line agent if the subject is on more than one third-line agent; the other weans (OW), which are the weans of the third-line agents other than the TW if the subject is on more than one third-line agent. The guidance also applies to additional weans (AW), which are the weans from third-line agents that take place after the TW for the first blinded study drug infusion or the second open-label study drug infusion.

### **QW Guidance**

- Wean to be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace that third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Investigators should allow 24 hours to lapse after the end of a “successful” qualifying wean before finally declaring the QW a success. If a third-line agent needs to be re-instituted within that 24 hours, the QW is a failure, and the subject may then be randomized in the study.

### **OW Guidance**

- First OW should not begin before H49 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- If the subject is on two third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the TW. However the OW may be completed over a shorter or longer time period and may overlap if clinically indicated with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- If the subject is on three third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the wean of the second agent. The second agent should be weaned over 24 hours and that wean completed before starting the TW. However the OWs may be completed over a shorter or longer time period and may overlap if clinically indicated with each other and with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the

dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.

- All OWs should be completed before H96 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **TW Guidance**

- The TW is defined as the wean of the last third-line agent.
- If the subject is on one third-line agent, the TW should not begin before H49 and should begin no later than H97 after starting administration of study drug or starting the open-label infusion of SAGE-547. If the subject has had one or more OWs, the TW should ideally begin as soon as the last OW is complete but in any case not later than H97 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- The TW must be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace this third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Every effort must be made to complete the TW before H120 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547, but the TW must be complete before H144 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **AW Guidance**

- AWs will take place when medically indicated in the opinion of the investigator.
- Ideally the AW should take place over 24 hours, but completion may be over a shorter or longer time period than this. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.

#### **11.1.1.2. EEG**

Electroencephalographs (EEGs) that are representative of the intermittent or continuous EEG being used to support key investigator decisions will be collected at the following time points:

- A 24-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst or seizure suppression for the second path to eligibility, and a variable pattern for the third path to eligibility. This EEG also aims to capture the burst or seizure suppression pattern during the 24 hours that precede the QW. If the CEEG does not capture the 24 hours that precede the QW, additional EEG data collected as standard of care prior to the CEEG and prior to the

QW may be collected to assess the depth of burst or seizure suppression in the 24 hour period prior to the QW.

- EEG will be performed to cover the qualifying wean (QWEEG). EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for up to 24 hours after the end of the QW. The duration of the QWEEG will be up to 48.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s), the decision to re-institute a third-line agent(s) at doses intended to induce burst or seizure suppression, and the decision that the QW is a success.
- EEG will be performed from three hours prior to the start of the blinded infusion to 12 hours after the start of the blinded infusion. This will be called the BIEEG. The intent of this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG and to assess the depth of burst suppression in the first 12 hours of blinded study drug infusion.
- EEG will be performed to cover the final or terminal wean of third-line agent (TWEEG). The TW is the wean of the final third-line agent during the blinded administration of study drug or the open-label infusion of SAGE-547; if the subject was on one third-line agent, the TW is the wean of that agent. If the subject was on three third-line agents, the TW is the wean of the third and final agent. EEG recording will start 30 minutes prior to the start of the TW, continue for up to 24 hours during the TW, and then continue for the one hour after the end of the TW. The duration of the TWEEG will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the final third-line agent or the decision to re-institute a third-line agent at doses intended to induce burst or seizure suppression because any seizure activity could not be managed using intermittent bolus doses of AEDs.
- EEG will be performed during the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 (TAEED). The TAEED is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the start of the taper (at Hour 119.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours during the taper, and then continue for the one hour after the end of the taper (to Hour 145 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547). The duration of the TAEED will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst or seizure suppression because any seizure activity seen during the taper could not be managed using intermittent bolus doses of AEDs.
- EEG will be obtained to cover the end of the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 and the ensuing 24-hour period, during which the primary endpoint is assessed (PAEED). The PAEED is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the end of taper (at Hour 143.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours after the end of the blinded administration of study treatment or the open-label infusion of SAGE-547, and then continue for the one hour after the end of the 24-hour assessment period (to Hour 169 after starting the blinded administration of study

treatment or after starting the open-label infusion of SAGE-547). The duration of the PAEEG will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst or seizure suppression because any seizure activity seen in the 24 hours following the end of the blinded administration of study treatment or the open-label infusion of SAGE-547 that could not be managed using intermittent bolus doses of AEDs.

In practice, most subjects are on continuous EEG monitoring or long periods of intermittent EEG monitoring. However, this protocol does not mandate continuous EEG monitoring and breaks from EEG monitoring to provide relief to the scalp from the irritating effects of the electrodes are advised, according to local practice. If a break in EEG monitoring is mandated by local practice guidelines at a time when one of the protocolled EEG segments is to be collected, the break in EEG monitoring will take precedence, with the reason for missing the EEG reading noted on the eCRF. The EEGs obtained for the study are therefore part of the existing EEG record rather than being obtained de-novo at each timepoint. For timepoints where there might be some ambiguity, such as the TWEEG, the final EEG record is that of the final attempt to wean the last third-line agent, even if earlier attempts to wean that agent took place. In some cases (the TAEED and PAEEG, for instance), the EEG records will overlap, but different cuts are taken to service the different EEG record requirements.

The electronic EEG file will be de-identified, the date and time of the start and stop of the EEG and the subject number will be attached to the file, and the study time point will be indicated (CEEG, QWEEG, BIEEG, TWEEG, TAEED, and PAEEG). The PI will indicate on the eCRF what the EEG shows, as follows:

- For the CEEG, the PI will describe the EEG pattern that determined which path to eligibility the subject was on.
- For the QWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure or success on the qualifying wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst or seizure suppression during the qualifying wean constitutes a failure); the QWEEG will extend to cover the 24 hours after the end of third line agents in order to confirm that the QW was a success.
- For the BIEEG, the PI will note the date and time of the start of the EEG and the pattern seen on the EEG.
- For the TWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure on the terminal wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst or seizure suppression during the terminal wean).
- For the TAEED, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst or seizure suppression before the end of the SAGE-547 infusion).
- For the PAEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary

endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst or seizure suppression in the 24 hours following the end of the SAGE-547 infusion).

A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm the depth of burst or seizure suppression prior to the QW and during the first 12 hours of the blinded study drug infusion, the PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period (average EEG power at the end of Visit 9 of more than two microvolts):

- All subjects will have the CEEG and QWEEG collected and stored, and the CEEG and QWEEG read;
- Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;
- Those subjects randomized who are not administered the open-label study drug will have the QWEEG, BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the BIEEG, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read;
- Those subjects randomized who later undergo the open-label infusion will have the QWEEG, BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion and the TWEEG, TAEED, and PAEEG related to the open-label study drug infusion collected and stored, and the BIEEG, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read.

All EEG records may be subject to quantitative EEG analysis.

### **11.1.2. Secondary Efficacy**

#### **11.1.2.1. Clinical Global Impression Scale (CGI)**

The clinical global impression scales are often utilized in clinical trials to allow clinicians to integrate several sources of information into a single rating of the subject's condition. Both the CGI-Severity (Question 1, CGI-S) and the CGI-Improvement (Question 2, CGI-I) employ a 7-point Likert scale measuring severity of the disease state in the subject and improvement, respectively. All severity assessments after initiation of SAGE-547 treatment should consider the general state of the subject over the preceding week. The third question on the scale will not be employed in this trial, and where the scale states "mental illness", this means "physical illness" in this trial.

The CGI-S will be evaluated at Visit 1 and at the last visit, Visit 12 or 12R. The CGI-I will be evaluated at Visit 12 or 12R.

#### **11.1.2.2. Epilepsy Status**

At Visit 1, the diagnosis of epilepsy will be documented as a no/yes question. If there was a previous diagnosis of epilepsy, further details will be documented, including:

- Date of diagnosis;
- Details of anti-epileptic drugs currently being taken;



- Type of epilepsy;
- Seizure frequency in the past month.

Information about the current (index) episode of status epilepticus will be obtained at Visit 1:

- Date of onset
- Date of failure to respond to first line agent(s) and the name(s) of the agent(s)
- Date of failure to respond to second line agent(s) and the name(s) of the agent(s)
- Any previous treatment with third line agents and the response to those agents (details of the third line agent drugs and previous wean attempts will be recorded on the Third Line Agent Medication CRF)
- The cause of the index episode of status epilepticus
- If the subject was transferred from another hospital or from within the hospital, the reason for the transfer will be recorded (such as for study enrollment, due to lack of medical options at original hospital or unit, due to lack of beds at the original hospital or unit, family request, other)

Previous (non-index) diagnosis of status epilepticus will be documented as a no/yes question. If SE did occur in the past 12 months, further information will be gathered, including:

- SE, RSE, or SRSE diagnosis, whichever was the most severe diagnosis for each episode;
- Cause;
- Treatment, including experimental treatments and need for intubation/ventilation;
- Dates of onset and duration.

At Visit 12 or Visit 12R, the following information will be gathered:

- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of SE up to and including Visit 12 or Visit 12R;
- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of seizures (convulsive and non-convulsive) up to and including Visit 12 or Visit 12R;
- Number of separate episodes of SE after H144 at the end of Visit 8 or Visit 8R (no/yes); if yes,
  - SE, RSE, or SRSE diagnosis;
  - Cause;
  - Treatment, including experimental treatments and need for intubation/ventilation;
  - Dates of onset and duration.

Note that a separate episode of SE is defined as an episode of SE separated from other periods of status epilepticus by at least 24 hours.

- Diagnosis of epilepsy since Visit 11 or Visit 11R will be documented as a no/yes question. If a diagnosis of epilepsy has been made, further details will be documented, including:

- Status as ongoing or new epilepsy since Visit 11 or Visit 11R after initiation of SAGE-547 treatment;
- Details of anti-epileptic drugs currently being taken;
- Type of epilepsy and seizure frequency in the past week.

## **11.2. Safety Assessments**

The safety and tolerability of SAGE-547 will be assessed using adverse events, clinical laboratory measures, vital signs, ECG intervals and morphology, and mortality. All safety assessments should be performed per hospital standard of care and will be collected periodically throughout the study according to [Table 1](#), [Table 2](#), and [Table 3](#) (Schedules of Assessments).

### **11.2.1. Adverse Events**

AEs will be collected after informed consent has been signed and prior to study-specific screening procedures not considered standard of care, during subject preparation for SAGE-547 administration and through Visit 12 or Visit 12R. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™) coding system (current version). See [Section 14](#) for additional details.

### **11.2.2. Clinical Laboratory Tests**

Blood samples will be taken for hematology, and serum chemistry and GFR will be calculated at:

- Visit 1 and then at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.
- Blood samples will be taken at Visit 11 or Visit 11R for serum chemistry (renal panel only).

Urine samples (20 ml) will be taken for urinalysis and urine NAG analysis at:

- Visit 1 and at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.

These samples will be analyzed at a central laboratory; hour-to-hour medical decisions will be based on sampling for laboratory testing done outside the protocol as part of normal standard of care. GFR will be calculated by the central laboratory.

Any out-of-range values will be flagged by the laboratory; the investigator will add a comment about whether the abnormality is clinically significant. Clinical significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

#### **11.2.2.1. Hematology and Serum Chemistry**

Hematology will include complete blood count (CBC) white blood cell count with differential, platelet count and red blood cell (RBC) count, hemoglobin and hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatine kinase,

lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose. In addition triglycerides will be measured in serum chemistry samples (to aid assessment of lipemia in pharmacokinetic samples).

#### **11.2.2.2. Pregnancy Test**

Females of child-bearing potential will be tested for pregnancy by serum pregnancy test at Visit 1. In this study, since an accurate history of menstruation in girls and menopause in older women may not be available at Visit 1, “child-bearing potential” is taken to mean any female aged 17 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy. Female subjects with a positive pregnancy test will be ineligible for study participation.

#### **11.2.2.3. Urinalysis**

Urinalysis will include assessment of protein, blood, leukocytes, glucose, ketones, urobilinogen, pH, and specific gravity.

#### **11.2.3. Vital Signs**

Blood pressure, heart rate, and temperature will be recorded at the following time points relative to the first infusion of study drug, and to the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547:

- Visit 1;
- At 0, +30, +60 minutes (+/-15 minutes) and +2, +4 and +8 hours (+/- 30 minutes) after the start of the infusion;
- At +24, +48, +72, +96, +120, +144, +168, and +192 hours (+/- 2 hours) after the start of the infusion.

#### **11.2.4. Weight and Height**

Weight and height will be measured at Visit 1. Weight will also be obtained at V2, within the eight hour window that follows the declaration of the QW failure and prior to the initiation of the blinded infusion loading dose at H0 of V3, and will be used to calculate the infusion rates throughout the entire blinded treatment course. If a subject qualifies for open-label study drug, the infusion rates for the open-label infusion will be calculated using the subject’s weight measured prior to dosing during V10.

If it is not possible to obtain the actual weight at the above-referenced timepoints, permission from the Clinical Monitor must be obtained to use another method to obtain the subject’s weight (such as information from the LAR or estimating using an established local protocol).

In addition, a daily weight will be obtained and recorded if this is easily obtained, such as the use of a scale bed.

#### **11.2.5. ECG**

For the first 50 subjects randomized in the study, 12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours. If it is not possible to

perform ECG immediately after the collection of PK samples up to 160 hours, ECG must be performed within 15 minutes prior to the collection of PK samples up to 160 hours; at other times the allowed time window for ECGs is +/- 2 hours:

- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +128, +136, +144, +152, +160, and +192 hours after the start of the blinded (first) study drug infusion
- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +126, +132, +138, +144, +152, +160, and +192 hours after the start of the open-label (second) study drug

The heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm.

For the subsequent subjects randomized in the study, the following timepoints for ECG will be used:

- pre-dose and at +1, +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the blinded (first) study drug infusion
- pre-dose and at +1, +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the open-label (second) study drug infusion

It is not necessary to collect these ECGs with the PK samples at these timepoints and, apart from the +1h ECG, there is +/- 2 hour time window for these ECGs.

#### **11.2.6. Mortality**

Mortality will be recorded on the Visit 12 or Visit 12R case report form. If the subject has died, the following information will be collected:

- Date of death;
- Cause of death.

As accurate as possible cause of death will be collected, which will be further categorized as due to one of the following causes:

- SE;
- complications of long term intubation and third-line agent infusions;
- underlying cause of qualifying SE;
- co-morbidity existing at the time of the qualifying SE;
- new co-morbidity or trauma;
- study drug;
- other (specify).

#### **11.2.7. Pharmacogenetic Samples**

If a subject's LAR consents to pharmacogenetic sampling, a blood sample for genetic research will be collected at Visit 1 in order to avoid the possible introduction of bias through the exclusion of patients who may withdraw from study due to an AE (a subject population that may be of specific interest for subsequent genetic analysis). If for any reason a sample cannot be taken prior to treatment, a sample can be drawn at any point prior to completion with the restriction that no more than one genetic sample be taken per subject.

The objective of this research is to collect and store blood samples for possible DNA extraction and exploratory research into how genes or specific genetic variation may influence response (i.e. distribution, safety, tolerability, and efficacy) to SAGE-547. Specific genetic variations of interest include but are not limited to: classes of metabolizing enzymes (e.g. Cytochrome P450 supra-family genes), genes encoding enzymes involved in the production and metabolism of allopregnanolone (e.g. AKR1C4 (3 $\alpha$ -hydroxysteroid dehydrogenase)), genes associated with the GABA receptor (e.g. GABRA1-A6, GABRB1-B3, GABRD, GABRE, GABRG1-3) and genes associated with the production and degradation of GABA.

Future research may suggest other genes or gene categories as candidates for influencing not only response to SAGE-547 but also susceptibility to disorders for which SAGE-547 is being evaluated. Thus, the genetic research may involve study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.

#### **11.2.7.1. Biological Sampling and Coding Procedures (Pharmacogenetics)**

To ensure patient confidentiality, utmost care will be taken in the coding and storage of pharmacogenetic samples.

*Extraction and coding:* DNA will be extracted from the blood sample and the DNA sample will be assigned a unique number replacing information from sampling tube. The assigned DNA number will be used to identify the sample and its corresponding information within Sage Therapeutics or at any designated contract laboratory for the purpose of sequencing of other DNA specific analysis. No personal details sufficient for individual identification will be available to any person (internal or external to Sage Therapeutics) working with the DNA.

*Genotype/Phenotype Analysis:* Samples and data from genetic analysis will be coded. The link between subject enrollment / randomization code and DNA number will be maintained and stored in a secure environment with restricted access. The established link will be used to identify relevant DNA samples for analysis, facilitated correlation of genotype results with clinical data, allow regulatory audit, and to trace samples for destruction in case of withdrawal of consent.

#### **11.2.7.2. Retention of Biological Samples for Pharmacogenetic Analysis**

Extracted DNA is a finite research that is destroyed in the process of being analyzed. Primary blood samples from which DNA can be extracted will be stored and used until no further analyses are possible, a maximum storage period of 25 years from time of last subject last visit has been reached, or an individual or LAR withdraws his/her or their consent.

### **11.2.8. Other Outcomes**

#### **11.2.8.1. Pharmacokinetic Data**

Formal plasma analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS)). In addition, all samples will be analyzed for important SAGE-547 metabolites (if and when these are identified) and Captisol<sup>®</sup> concentrations.

#### Plasma Analysis

Plasma will be collected to assay for SAGE-547 concentrations at the following time points relative to the start of each infusion of study drug:

- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion.
- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open-label SAGE-547 study drug infusion.
- All samples will also be analyzed for plasma concentrations of important metabolites of SAGE-547 if and when these are identified.
- All samples from the first 50 subjects randomized will also be analyzed for plasma concentrations of Captisol®.

The plasma samples will be drawn from the arm contralateral to that used for drug administration. Drawing samples from peripheral arterial or venous lines or from a central line is permissible. PK collection times should be adhered to as strictly as possible. The allowed time window for all samples is: pre-dose in the two hours prior to starting the infusion of study drug; samples up to and including 1h, +/- 5 minutes; subsequent samples, +/- 15 minutes. Subject-specific PK kits for sampling including instructions on collection and processing methods, and storage and shipping conditions, will be provided separately. To maintain the blind, all subjects will have samples taken as outlined above: subjects receiving SAGE-547 will have all samples analyzed for all analytes. Subjects on placebo may have samples analyzed to investigate endogenous allopregnanolone and metabolite concentrations, as well as Captisol® concentrations; experience with the plasma concentration data will determine if and which placebo samples are analyzed.

Each blood sample will be 3 ml in volume for subjects weighing 30 kg or more, and 1 ml in volume for subjects weighing less than 30 kg. Separate aliquots will be obtained from each sample to service the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum blood draw for PK analysis for a subject having two infusions of study drug will be 99 ml (33 ml for subjects weighing less than 30 kg).

Plasma PK parameters for SAGE-547 will be calculated where appropriate (e.g.,  $C_{max}$ ,  $C_{min}$ ,  $t_{max}$ ,  $AUC_{last}$ ,  $AUC_{\infty}$ ,  $CL_s$ ). In addition, similar PK parameters will be calculated for Captisol®. PK parameters for important metabolites of SAGE-547 may be calculated. An evaluation will be made of the feasibility of adopting a population-PK approach to assess drug-drug-interactions with SAGE-547 as victim of AEDs.

In addition, the Visit 9 sample may be analyzed for plasma concentrations of third-line agents.

#### Other Analysis

If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations. The minimum volume of cerebrospinal fluid for analysis is 100 microlitres.

Full details of all pharmacokinetic analyses will be described in the Pharmacokinetic Analysis Plan.

**11.2.8.2. Correlation of QT/QTc Changes and Plasma Concentrations of SAGE-547**

An analysis will be performed to determine whether there is any correlation between changes in QT/QTc interval and plasma concentrations of SAGE-547, in order to investigate any effect that SAGE-547 may have on QT/QTc interval.

**11.2.8.3. Pharmacoeconomic Data**

At Visit 12 or Visit 12R, the following information will be collected: number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital. If the subject dies before Visit 12 or Visit 12R, data will be collected up to the date of death. The definition of “hospital” is the institution that the subject was initially treated in. If the subject is transferred to another hospital, that hospital would be the “discharge destination from the hospital” and the “number of days in hospital” would be the number of days in the initial treating hospital.

For those subjects discharged from hospital before Visit 12/12R, the following questions will be asked:

- On what study day was the subject discharged from hospital?
- What type of facility was the subject discharged to (another hospital, a rehabilitation center, a supported care facility, home, other)?
- How many days did the subject stay in this facility?

The following questions will be answered regarding the stay in the ICU and hospital:

- Was the subject still in the ICU at the end of Visit 10/10R?
- If the FOUR Score was  $\geq 12$  at Visit 10/10R and the subject was in the ICU at Visit 10/10R, what was the reason for the subject not being discharged from the ICU (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, other)?
- Was the subject still an in-patient in the hospital at the end of Visit 12/12R?
- If the FOUR Score was  $\geq 15$  at Visit 12/12R and the subject was in the hospital at Visit 12/12R, what was the reason for the subject not being discharged from the hospital (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, unsuitable home circumstances, other)?

**11.2.8.4. STESS**

The STESS will be assessed during Visit 1 in order to assess the severity of the status epilepticus.

**11.2.8.5. FOUR Score**

The Full Outline of UnResponsiveness or FOUR Score is designed to assess conscious level and unlike other scores, is suitable for subjects who are intubated. It assesses four domains of neurological function (eye responses, motor responses, brainstem reflexes, and breathing pattern).

The FOUR Score will be collected at the following time points relative to each infusion of study drug (the initial blinded infusion and the second open-label infusion if this is administered):

- baseline, +24, +48, +72, +96, +120, +144, +168, and +192 hours (all +/- 2 hours) after the start of the infusion, and at Visit 11/11R and Visit 12/12R.

#### **11.2.8.6. Glasgow Outcome Scale (GOS)**

The GOS is a relatively common assessment scale used to standardize descriptions of the objective degree of recovery from brain injury such as cerebral trauma, or in this case SRSE. It was first used in 1975 ([Jennett and Bond 1975](#)) and allows a prediction of the long-term course of rehabilitation to return to work and everyday life. The scale classifies subjects into 5 groups:

- Death
- Persistent vegetative state
- Severe disability
- Moderate disability
- Good recovery

The GOS will be assessed at Visit 12 or Visit 12R.

#### **11.2.8.7. Supervision Rating Scale (SRS)**

The Supervision Rating (SRS) measures the level of supervision that a patient/subject receives from caregivers. The SRS rates level of supervision on a 13-point ordinal scale that can optionally be grouped into five ranked categories (Independent, Overnight Supervision, Part-Time Supervision, Full-Time Indirect Supervision, and Full-Time Direct Supervision). The SRS was designed to be rated by a clinician based on interviews with the subject and an informant who has observed at first hand the level of supervision received by the subject ([Boake 2000](#)). Scoring is a one-step procedure in which the clinician assigns the rating that is closest to the subject's level. Ratings are based on the level of supervision received, not on how much supervision a subject is judged or predicted to need.

The SRS will be assessed at Visit 1 and Visit 12 or Visit 12R. The Visit 1 assessment will be a retrospective assessment of the supervision required by the subject immediately prior to the admission that included the index episode of status epilepticus.

#### **11.2.8.8. Modified Rankin Scale – 9Q (mRS-9Q)**

The Modified Rankin Scale (mRS) is a commonly used scale to determine disability and functional dependence due to neurological insult such as stroke in adults. The 7-point scale (0 – 6) denotes functional capacity from no symptoms (0) to severe disability (5) and death (6). The Modified Rankin Scale – 9Q is a shortened version consisting of 9 questions that reliably determines the mRS score and was developed to both simplify the assessment and expand the rater base to non- medically trained personnel ([Patel, Rao et al. 2012](#)). The assessment is a web-based tool in the public domain with automatic score calculation and error checking found at [www.modifiedrankin.com](http://www.modifiedrankin.com).

The mRS will be assessed at Visit 1 and at Visit 12 or Visit 12R. The baseline assessment will be a retrospective assessment of the disability and dependence of the subject immediately prior to the admission that included the index episode of status epilepticus.



## 12. STUDY PROCEDURES

The study procedures listed below by study day reflect the required data collection times for this protocol. When a time window is necessary, this is specified below. If no time window is specified, the test may be performed at any time within the specified 24-hour period.

### 12.1. Visit 1 (V2-≤30h)

The baseline period will be up to approximately 84 hours prior to starting blinded study treatment and should include the assessments/procedures listed below and summarized in [Table 1 and Table 2 \(for open-label treatment\)](#), the Schedules of Events.

- Informed consent
- Eligibility checklist
- Verification of inclusion/exclusion criteria.
- Demographic information and medical history obtained by proxy and confirmed by the subject when possible.
- SE and wean history
- Blood will be collected from female subjects 17 years to 55 years for a serum pregnancy test unless they are known to be pre-menstrual or post-menopausal or to have had a hysterectomy.
- Blood and urine samples collected for clinical laboratory testing.
- Pharmacogenetic sample will be collected from consenting/eligible subjects.
- Vital signs
- Height
- Weight
- An ECG reading taken.
- Administration of the STESS.
- Administration of the FOUR Score.
- Administration of SRS.
- Administration of the mRS-9Q assessment.
- Assessment of the CGI scale.
- Evaluation of epilepsy status.
- Administration of continuous IV third-line agents.
- Perform EEG.
- Recording of adverse events.
- Recording of previous and concomitant anti-epileptic drugs.
- Recording of previous and concomitant third-line agents.
- Recording of concomitant pressors.

- Recording of other concomitant medications, procedures, and treatments.

## **12.2. Visit 2 (V3-≤54h)**

- Recording of adverse events.
- Recording of concomitant anti-epileptic drugs.
- Recording of concomitant third-line agents.
- Recording of concomitant pressors.
- Recording of other concomitant medications, procedures, and treatments.
- Wean of continuous third-line agent (QW):
  - If wean is successful, subject is followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (these subjects are Qualifying Wean Success subjects or QWS subjects);
  - If wean is not successful, there is ongoing intravenous administration of at least one continuous IV third-line agent and EEG is performed and the subject is randomized.
- Weight
  - Subject weight will be obtained within the eight-hour period from the declaration of failure of QW and prior to the initiation of the blinded infusion loading dose at H0 of V3. This weight will be the dosing weight used to determine the infusion rate for the entire blinded infusion treatment course.

## **12.3. SAGE-547 Treatment Period**

### **12.3.1. Visit 3/3R (0-24 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs will be recorded at:
  - 0, +30, +60 minutes (+/-15 minutes) and +2, +4, +8 (+/- 30 minutes) and +24 hours (+/- 2 hours) after the start of the infusion
- For the first 50 subjects randomized in the study, ECG readings will be recorded immediately after PK sampling, or within 15 minutes prior to PK sampling, at the following time points:
  - 0 (pre-dose) and at +0.5, +1, +3, +6, +12, and +24 hours after the start of the blinded study drug infusion.
  - Subsequent subjects randomized in the study will have ECG readings recorded at 0 (pre-dose) and +1, +12, and +24 hours after the start of the study drug infusion, it will not be necessary to collect these ECGs with PK samples at these timepoints and, apart from the +1 h ECG, there is +/- 2 hour time window for these ECGs
- A blood sample for PK analysis should be collected at the following time points (all +/- 15 minutes except where otherwise stated):

0 (pre-dose, within two hours of the start of the infusion) and at +0.5, +1 (+/- 5 minutes), +3, +6, +12, and +24 hours after the start of the study drug infusion.

- Completion of the FOUR Score
  - +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the final declaration of QW success)
- Ongoing intravenous administration of a continuous IV third-line agent.
- Study drug administration in loading (Hour 0-1) and maintenance infusions (at completion of Hour 1).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.2. Visit 4/4R (25-48 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +48 hours (+/- 2 hours) after the start of the infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +48 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +48 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +48 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +48 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent.
- Ongoing study drug maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.3. Visit 5/5R (49-72 hours)**

- Weight if easily obtained

- Vital signs should be recorded at:
  - +72 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +72 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +72 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +72 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +72 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.4. Visit 6/6R (73-96 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +96 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +96 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +96 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +96 hours (+/- 15 minutes) after the start of study drug infusion.

- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +96 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Perform EEG.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.5. Visit 7/7R (97-120 hours)**

- Weight if easily obtained
- Vital signs should be recorded at:
  - +120 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +120 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +120 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +120 hours (+/- 15 minutes) after the start of study drug infusion, immediately prior to the end of the maintenance infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +120 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled. Complete wean by 120 hours if at all possible.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## 12.4. SAGE-547 Taper Period

### 12.4.1. Visit 8/8R (121-144 hours)

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +144 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after each PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +128, +136 hours and +144 hours after the start of the blinded study drug infusion
  - +126, +132, +138 hours and +144 hours after the start of the open-label study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +144 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected (+/- 15 minutes unless otherwise stated):
  - +128 (immediately prior to the end of the first taper step), +136 hours (+/- 5 minutes, immediately prior to the end of the second taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of study drug infusion.
  - During the open-label study drug phase of the study PK blood draws at: +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 hours (+/- 5 minutes, immediately prior to the end of the third taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of the study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +144 hours (+/- 2 hours) after the start of the infusion
- Complete wean of third line agents by H144 if not completed by H120.
- Perform EEG.
- Taper of SAGE-547 infusion begins at hour 121.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## **12.5. Follow-up Period**

### **12.5.1. Visit 9/9R (145-168 hours)**

- Vital signs should be recorded at:
  - +168 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +152, +160 hours (+/- 2 hours) after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +152 and +160 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +168 hours (+/- 2 hours) after the start of the infusion
- Perform EEG.
- Assessment of the presence of physiologic brain activity using EEG.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.5.2. Visit 10/10R (169-192 hours)**

- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +192 hours (+/- 2 hours) after the start of the infusion
- At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine eligibility for the open-label treatment with the higher dose of study drug. This determination may occur at any point during Visit 10: the higher dose open-label infusion must begin within the Visit 10 window. All patients receiving the higher dose open-label treatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.
- Weight if the subject qualifies for the open-label study drug (Visit 10 only, not Visit 10R).
- Recording of adverse events (QWS subjects also).

- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.3. Visit 11/11R (Visit 3/3R + 14d (±2))**

- Blood samples collected for clinical laboratory testing (renal panel only).
- Completion of the FOUR Score (QWS subjects also).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.4. Visit 12/12R (Visit 3/3R + 21d (±2))**

All assessments also performed for QWS subjects.

- Completion of the FOUR Score.
- Administration of the GOS.
- Administration of the SRS.
- Administration of the mRS-9Q assessment.
- Evaluation of epilepsy status (see [Section 11.1.2.2](#) for details).
- Assessment of the CGI Scale.
- Recording of adverse events.
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications.
- Collection of pharmacoeconomic data.
- Mortality will be assessed throughout the study period.

## **13. STATISTICS**

### **13.1. Statistical Plan**

Complete details for the analysis and reporting of data from this study will be contained in the Statistical Analysis Plan (SAP).

#### **13.1.1. Interim Analysis**

When approximately 50% of subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.



### 13.1.2. Study Populations

The **Safety Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to actual treatment. This analysis population will be used for all safety analyses.

The **Intent to Treat Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to randomized treatment. This analysis population will be used for all efficacy analyses.

The **Modified Intent to Treat Population** is defined as all subjects who:

1. complete their initial course of blinded SAGE-547 or placebo treatment unless the non-completion was due a drug-related adverse event; and
2. have at least one attempt to wean from third-line agents prior to the end of blinded study treatment infusion unless the failure to wean was because seizures were not controlled.

Subjects will be classified according to randomized treatment. This analysis population will be used for sensitivity analyses of the primary endpoint and select secondary efficacy endpoints.

Narratives will be prepared for all subjects who do not complete the infusion of blinded study medication or were not subjected to any wean attempts. Narratives will include details of the cause of SE, the comorbid conditions, the adverse event(s), and reasons for non-completion of the infusion or failure to attempt weaning. This blinded narrative will be reviewed by the medical monitors and the patient adjudicated as MITT eligible or ineligible. Acceptable reasons for defining a subject as MITT ineligible include death or withdrawal of consent due to progression of the underlying cause of SE or comorbid conditions, unless the cause of death or progression of disease were thought by the investigator, sponsor, or DSMB to be related to study drug.

The **Per-Protocol (PP) Population** is defined as a subset of the MITT population but will exclude data from all subjects with significant protocol violations or deviations. Subjects will be classified according to actual treatment received. This data set will be used for sensitivity analyses to examine the robustness of results for the primary and key secondary efficacy endpoints.

The **Pharmacokinetics Population** is defined as all subjects who at least had an infusion of blinded SAGE-547 initiated and have at least one pharmacokinetic sample collected.

The **Pharmacogenetic Population** is defined all subjects who consent to being included in the pharmacogenetic assessment and provide a pharmacogenetic sample.

Summary statistics of all data collected will be presented for subjects who were QW successes.

### 13.1.3. General Aspects

Tabular displays of descriptive statistics will be provided for all variables. Summary tables will include n, mean, mean, standard deviation, minimum and maximum for continuous variable and frequency and percentage for categorical variables.

### 13.1.4. Analysis of Primary Endpoint

The analysis of response to treatment (see [Section 11.1.1](#) for definition of primary endpoint) between SAGE-547 treated subjects and placebo treated subjects will be performed on the ITT population using a Cochran-Mantel-Haenszel (CMH) test with variables for treatment, concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior

to randomization (one vs two or more). The CMH general association statistic and its associated p-value will be presented. The comparison of treatment response rates will be conducted at the 5% level of significance. To confirm the CMH results, a permutation test will also be conducted.

An additional analysis of the primary endpoint will also be performed on the MITT population. In addition sensitivity analyses of the primary endpoint will be performed using the ITT population based on:

- the number of third-line agents (one, two, or three) subjects were administered post-randomization; and
- which third line agent was the subject of the first TW.

### **13.1.5. Analysis of Secondary Efficacy Endpoints**

Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section ([Section 6](#)). Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. The analysis of the secondary endpoints will also be performed on the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

### **13.1.6. Analysis of Other Endpoints**

Safety and “Other” endpoints will only be summarized by treatment group.

Summaries of safety endpoints will be based on the overall Safety Population.

### **13.1.7. Epilepsy and SRSE Status**

Diagnosis of epilepsy and recurrence of RSE or SRSE will be documented as the percentage of subjects by time point and overall. Kaplan-Meier curves may be plotted if sufficient data are available.

Utilization of AEDs during follow-up and during recurrence will be summarized.

### **13.1.8. Questionnaires**

The data collected from each questionnaire will be interpreted according to the standard methodology for that questionnaire. There will be no adjustment for missing values.

### **13.1.9. Pharmacokinetic Data Analysis**

Details of the pharmacokinetic data analysis will be described in detail in a separate Pharmacokinetic Analysis Plan.

### **13.1.10. Pharmacogenetic Data Analysis**

Any genotype data generated in this study will be stored within a secured database within Sage Therapeutics and / or a third party contracted to work with Sage Therapeutics to analyze the samples. Because the number of subjects agreeing to participate in the genetic research component of the study is unknown, it is not possible to establish, a priori, whether sufficient samples will be obtained to support formal statistical evaluation of data. As a consequence a Pharmacogenetic Analysis Plan will only be prepared where appropriate and the results obtained from any genetic research will be reported in a report separate from the main study CSR.

### **13.1.11. Open-Label Study Drug Subjects**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are treated with SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo.

### **13.1.12. EEG-Responders**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who are classified as EEG-responders/non-responders based on the independent assessment of the PAEEG. Summaries will be derived for the two randomized treatment groups.

### **13.1.13. QT/QTc Assessment**

An analysis of the correlation between changes in QT/QTc intervals and SAGE-547 plasma levels will be performed to investigate if there is a potential effect that SAGE-547 may have on QT/QTc interval. A detailed description of the QT/QTc assessment will be included in the SAP.

### **13.1.14. Quantitative EEG**

The nine EEG records for each subject may be subjected to exploratory quantitative EEG analysis, the details of which will be included in the EEG Analysis Plan. In summary the following comparisons may be made, SAGE-547 versus placebo: the QWEEG versus the TWEEG (main analysis); the CEEG versus PAEEG (subsidiary analysis); and TAEEG versus PAEEG (exploratory analysis).

## **13.2. Determination of Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between treatment groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

### **13.3. Statistical Analysis Plan**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

## **14. ADVERSE EVENTS**

The safety procedures in this study will be detailed in a Safety Management Plan, which will be agreed and signed before the first subject is randomized in the study. [Section 14.1](#) summarizes Investigator responsibilities regarding the identification and documentation of AEs, the classification of AEs for relationship to study drug and severity, and the reporting of AE information to the Sponsor and the IRB.

[Section 14.2](#) summarizes Sponsor/Medical Monitor Responsibilities regarding monitoring of AE data and reporting relevant safety information to FDA.

[Section 14.3](#) lists important AE definitions.

### **14.1. Investigator Responsibilities**

#### **14.1.1. Identification and Documentation of Adverse Events by Investigator**

Subjects will be evaluated and questioned generally (if possible) to identify AEs during the course of the study. AEs will be collected from the signature of the consent form through Visit 12/12R. Adverse events that occur prior to completion of screening will be captured on the Medical History eCRF. Adverse events that occur after completion of screening will be recorded on the Adverse Event eCRF.

All AEs revealed by observation, other diagnostic procedures, or spontaneously reported by the subject and/or in response to an open question from study personnel will be recorded on the Adverse Event Form. Any clinically significant deterioration in laboratory assessments or other clinical findings are considered an AE and must be recorded on the Adverse Event Form, unless otherwise stated. AE information recorded will be entered into the database on an ongoing basis.

AEs with a relationship considered related to study drug (probable, possible) should be followed until the event is resolved or the Investigator determines the event is stable or no longer clinically significant. AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

For SAEs, an electronic Serious Adverse Event eCRF must be completed with as much information as possible and submitted in the time frame described below in [Section 14.1.3](#). When new significant information is obtained as well as when the outcome of an event is known, the electronic SAE eCRF should be updated within 24 hours. If the subject was an outpatient at the time of the SAE and was re-hospitalized due to the SAE, a copy of relevant hospital records (e.g., admission report, laboratory test results, discharge summary, etc.) may be requested to be included as part of the subject medical file.

All SAEs will be followed until resolved or until a stable status has been achieved.

**14.1.2. Adverse Event Classification****14.1.2.1. Relationship to Investigational Drug**

None:	No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state.
Possible:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject, but this is not known for sure.
Probable:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

**14.1.2.2. Severity**

Mild	Discomfort noticed, but no disruption to daily activity.  For subjects that are unconscious, this may be a slight or minor change in a lab result or clinical sign or symptom that does not require immediate corrective action.
Moderate	Discomfort sufficient to reduce or affect normal daily activity, but is not hazardous to health; prescription drug therapy may be employed to treat the AE.  For subjects that are unconscious, this may be a clinically meaningful change that may require immediate corrective action.
Severe	Inability to work or perform normal daily activity and represented a definite hazard to health; prescription drug therapy and/or hospitalization may be employed to treat the AE.  For unconscious subjects, this may be a significant clinical change that requires immediate corrective action.

**14.1.2.3. Action Taken with Investigational Drug**

None	Study medication was continued without change.
Discontinued	Study medication was terminated.
Dose adjusted	Study medication dose/infusion rate was changed and then continued per protocol.
Interrupted	Study medication was interrupted and then continued per protocol.
Unknown	The action taken with regard to study medication is unknown.
Not applicable	Administration of study medication was not ongoing.

**14.1.2.4. Assessment of Outcome**

Ongoing	At the end of the study, the event has not resolved or stabilized.
Ongoing and stable	The event is ongoing but has stabilized and is unlikely to change
Resolved	The event has resolved or the subject recovered without sequelae.
Resolved with sequelae	The event has at least one secondary outcome that may result in permanent disability and/or functional limitation.
Unknown	The status of the event is unknown.
Death	The subject has expired.

**14.1.3. Investigator Reporting to Sponsor and Sponsor Emergency Contact**

All new SAEs that come to the Investigator and/or Sponsor's notice during the course of the study (up to and including the last study visit) must be reported by the Investigator on the designated electronic report form within 24 hours of the point in time when the Investigator becomes aware of the SAE. As additional information becomes available, the designated electronic report form must be updated within 24 hours.

Investigators must report any SAE, whether or not considered drug related. The report must include an assessment of whether there is a reasonable possibility that the drug caused the event.

In a medical emergency (ie, an event that requires immediate attention regarding the treatment of a subject, operation of the clinical study, and/or the use of investigational drug), study site staff will apply appropriate medical intervention according to current standards of care, and contact the Medical Monitor.

**14.1.4. Medical Monitor and Emergency Contact Information**

[REDACTED], MD  
[REDACTED]

In a study related medical emergency situation, when the assigned Medical Monitor cannot be reached by a caller, an on-call Physician can be reached 24 hours per day, 7 days per week via an [REDACTED] Call-Center:

- Telephone: [REDACTED]  
(this is a chargeable telephone number allowing a global reach from both landlines and mobile phones)

- 

On this internet page a list of country-specific toll-free telephone numbers is provided. It should be noted that not all countries globally have access to toll-free numbers as indicated on the “24/7 Medical Help desk” index. Countries without toll-free numbers need to dial the chargeable number as indicated above. Furthermore, toll-free numbers are not available from mobile phones.

#### **14.1.5. SAE Reporting Contact Information**

Contact information and reporting instructions are provided in the Safety Management Plan.

#### **14.1.6. Reporting to Institutional Review Boards (IRBs)**

It is the responsibility of the Investigator to promptly notify the institution’s IRB of all serious and unexpected suspected adverse reactions (see [Section 14.3](#) for definitions).

### **14.2. Sponsor/Medical Monitor Responsibilities**

#### **14.2.1. Monitoring of Adverse Event Data**

The Medical Monitor will review any newly reported adverse events in an ongoing basis. If the aggregate assessment indicates that an event is occurring more frequently than would normally be expected in this population, or as previously observed, and the sponsor believes that the events are causally related to the administration of SAGE-547, the Sponsor will then report that information in an IND safety report.

#### **14.2.2. Data Safety Monitoring Board**

An independent DSMB will monitor the clinical, PK and PD data for safety signals throughout the study and will be asked to assess the placebo response rate at the time of the interim analysis to determine final sample size. In order to perform their monitoring function the DSMB will have access to un-blinded safety data as necessary.

The composition and procedures for the board will be described in a separate DSMB Charter.

#### **14.2.3. Reporting to FDA**

The Sponsor must report in an IND safety report any suspected adverse reaction to study treatment that is both serious and unexpected (21 CFR 312.32(c)(1)(i)). Before submitting an IND safety report, the Sponsor will ensure the event meets all three of the definitions: (1) suspected adverse reaction, (2) serious, (3) unexpected. If the AE does not meet all three of the definitions, it should not be submitted as an IND safety report. The Sponsor should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the adverse event and, therefore, that the event meets the definition of a suspected adverse reaction.

If there is a serious and unexpected suspected adverse reaction, the Sponsor will notify the appropriate regulatory agency(ies) and all appropriate parties on an expedited basis. In addition, Sponsors must submit expedited reports of an increased rate of occurrence or severity of serious suspected adverse reactions over that listed in the protocol or Investigational Brochure.



SUSARs will be unblinded prior to reporting to FDA. Unless it is necessary to unblind for the safety of the patient, the investigator will not be informed of the unblinding of the subject.

Under 21 CFR 312.32, Sponsors should identify in the protocol SAEs that it does not plan to report individually in an expedited manner, because they are known consequences of the disease or otherwise common in the study population. Given the grave condition and prognosis of SRSE being studied, individual occurrences of seizures or seizure activity will not be reported expeditiously in this study. Regardless of which events are reported in an expedited manner, all adverse events will be closely monitored throughout the study.

#### **14.2.4. Reporting to European Regulatory Authorities**

The Sponsor or its designee is responsible for SUSAR notification to the relevant regulatory authorities as outlined in the ICH Guidelines. All investigators participating in the study will also be informed as required by regulations.

Any SUSAR is subject to expedited reporting in the EU. The Sponsor or its designee, will report any single SUSAR to the appropriate National CAs and IECs within 7 days if the SUSAR is life-threatening or fatal (with the relevant follow-up information subsequently communicated within an additional eight days), and within 15 days if the SUSAR is neither life-threatening nor fatal. SUSARs reported will be those that have arisen in the present clinical trial and SUSARs that have arisen in other clinical trials conducted by the Sponsor with the same medicinal product.

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to competent authorities of the concerned Member States and to IEC(s)/IRBs as required by national laws.

### **14.3. Adverse Event Definitions**

#### **14.3.1. Adverse Event**

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

#### **14.3.2. Suspected Adverse Reaction**

Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

#### **14.3.3. Life-Threatening**

An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

**14.3.4. Serious**

An AE or suspected adverse reaction is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE – see definition above
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disability
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

**14.3.5. Unexpected**

An AE or suspected adverse reaction is considered “unexpected”:

- If it is not listed in the Investigational Brochure or is not listed at the specificity or severity that has been observed, or
- If an Investigational Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigational Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigational Brochure listed only cerebral vascular accidents.

“Unexpected,” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigational Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

**14.4. Emergency Identification of Study Medication**

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject’s treatment in the study via the IVRS; this normally requires prior approval by the medical monitor. However, if the subject is at immediate risk and the Investigator believes that immediate knowledge of the study treatment will alter medical management, discussion with the medical monitor may take place after unblinding. The Investigator will not unblind the medical monitor during that discussion. The process of unblinding will ensure that only the investigator is unblinded; the medical monitor, study management team, and data management team will not be made aware of the treatment allocation of an individual subject. All

cases of emergency unblinding will be fully documented in a way that does not unblind the medical monitor, study management team, and data management team.

## **15. STUDY ADMINISTRATIVE CONSIDERATIONS**

### **15.1. Quality Control and Quality Assurance**

The Investigators and institutions will permit trial related monitoring, audits, IRB review, and regulatory inspections as requested by FDA, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed informed consent forms, etc.) in addition to case report forms.

Quality assurance and quality control systems with written standard operating procedures (SOPs) will be followed to ensure this trial will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The site's dedicated study monitor will arrange to visit the Investigator at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be identified and resolved. The study monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality assurance officers named by Sage Therapeutics or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements, made by the Sponsor with the Investigator/institution and any other parties involved with the clinical trial, will be in writing in a separate agreement.

### **15.2. Data Handling and Recordkeeping**

#### **15.2.1. Data Handling**

Procedures for data handling (including electronic data) used in this protocol will be documented in a Data Management Plan.

#### **15.2.2. Case Report Form Completion**

eCRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of demographics, study drug administration, study procedures, AEs, questionnaire completion, efficacy assessments and subject status, including survival.

The Investigator will maintain copies of the eCRFs at the study site. For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate eCRF.

### **15.2.3. Retention of Study Records**

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval and until there are no pending or contemplated marketing applications or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to an appropriate person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

## **15.3. Confidentiality**

To maintain subject privacy, all eCRFs, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available trial registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by Sage Therapeutics to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

## **15.4. Publication Policy**

All information concerning SAGE-547 is considered confidential and shall remain the sole property of Sage Therapeutics. The Investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval from Sage Therapeutics. No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between Sage Therapeutics and the Investigator.

## **15.5. Protocol Amendments**

Changes to the conduct of the study should be prepared as a protocol amendment by the Sponsor. Protocol amendments should receive written IRB/IEC approval prior to implementation at the investigative site, except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the trial (eg, change of monitor, telephone numbers). In this case, Sage Therapeutics will amend and implement the protocol change

and subsequently notify the regulatory authorities and the Investigative sites who will notify the respective IRB, as appropriate.

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**APPENDIX 1. APPENDIX 1: FOUR SCORE****FOUR score****Full Outline of UnResponsiveness****Eye response**

- E4: eyelids open or opened, tracking, or blinking to command
- E3: eyelids open but not tracking
- E2: eyelids closed but open to loud voice
- E1: eyelids closed but open to pain
- E0: eyelids remain closed with pain

**Motor response**

- M4: thumbs-up, fist or peace sign
- M3: localizing to pain
- M2: flexion response to pain
- M1: extension response to pain
- M0: no response to pain or generalized myoclonus status

**Brainstem reflexes**

- B4: pupil and corneal reflexes present
- B3: one pupil wide and fixed
- B2: pupil or corneal reflexes absent
- B1: pupil and corneal reflexes absent
- B0: absent pupil, corneal and cough reflex

**Respiration pattern**

- R4: not intubated, regular breathing pattern
- R3: not intubated, Cheyne-Stokes breathing pattern
- R2: not intubated, irregular breathing
- R1: breathes above ventilatory rate
- R0: breathes at ventilator rate or apnea

Reference ([Iyer, Hoel et al. 2009](#)).



**APPENDIX 2. GLASGOW OUTCOME SCALE (GOS)****GLASGOW  
OUTCOME  
SCALE**

Patient Name: \_\_\_\_\_  
 Rater Name: \_\_\_\_\_  
 Date: \_\_\_\_\_

*Note:* The scale presented here is based on the original article by Jennett and Bond. It has become common practice in clinical trial administration, however, to use a modified version that places the scores in reverse order (i.e., "good recovery" = 1, "moderate disability" =2, etc.).

Score	Description
1	DEATH
2	PERSISTENT VEGETATIVE STATE Patient exhibits no <i>obvious cortical</i> function.
3	SEVERE DISABILITY (Conscious but disabled). Patient depends upon others for daily support due to mental or physical disability or both.
4	MODERATE DISABILITY (Disabled but independent). Patient is independent as far as daily life is concerned. The disabilities found include varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes.
5	GOOD RECOVERY Resumption of normal activities even though there may be minor neurological or psychological deficits.

**TOTAL (1-5):** \_\_\_\_\_

Reference ([Jennett and Bond 1975](#)).

## APPENDIX 3. SUPERVISION RATING SCALE (SRS)

### SUPERVISION RATING SCALE (SRS)

**Instructions:** Circle the rating that is closest to the amount of supervision that the patient *actually receives*. "Supervision" means that someone is responsible for being with the patient.

<u>Rating</u>	<u>Description</u>
<u>Level 1: INDEPENDENT</u>	
1	The patient lives alone or independently. Other persons can live with the patient, but they cannot take responsibility for supervision (for example, a child or elderly person).
2	The patient is unsupervised overnight. The patient lives with one or more persons who <i>could</i> be responsible for supervision (for example, a spouse or roommate), but they are <i>all</i> sometimes absent overnight.
<u>Level 2: OVERNIGHT SUPERVISION</u>	
3	The patient is only supervised overnight. One or more supervising persons are always present overnight but they are <i>all</i> sometimes absent for the rest of the day.
<u>Level 3: PART-TIME SUPERVISION</u>	
4	The patient is supervised overnight and part-time during waking hours, but is allowed on independent outings. One or more supervising persons are always present overnight and are also present during part of waking hours every day. However, the patient is sometimes allowed to leave the residence without being accompanied by someone who is responsible for supervision.
5	The patient is supervised overnight and part-time during waking hours, but is unsupervised during working hours. Supervising persons are <i>all</i> sometimes absent for enough time for them to work full-time outside the home.
6	The patient is supervised overnight and during most waking hours. Supervising persons are <i>all</i> sometimes absent for periods longer than one hour, but less than the time needed to hold a full-time job away from home.
7	The patient is supervised overnight and during almost all waking hours. Supervising persons are <i>all</i> sometimes absent for periods shorter than one hour.
<u>Level 4: FULL-TIME INDIRECT SUPERVISION</u>	
8	The patient is under full-time indirect supervision. At least one supervising person is <i>always</i> present, but the supervising person does not check on the patient more than once every 30 minutes.
9	Same as #8 plus requires overnight safety precautions (for example, a deadbolt on outside door).
<u>Level 5: FULL-TIME DIRECT SUPERVISION</u>	
10	The patient is under full-time direct supervision. At least one supervising person is always present and the supervising person checks on the patient more than once every thirty minutes.
11	The patient lives in a setting in which the exits are physically controlled by others (for example, a locked ward).
12	Same as #11 plus a supervising person is designated to provide full-time line-of-sight supervision (for example, an escape watch or suicide watch).
13	The patient is in physical restraints.

3/12/93

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## APPENDIX 4. MODIFIED RANKIN SCALE – LEVEL OF FUNCTION SURVEY (mRS-9Q)

1. Do you have any symptoms that are bothering you? (For example, trouble with reading or writing, trouble speaking, problems with vision, numbness, weakness, balance trouble, or problems with swallowing?)	YES <input type="radio"/>	NO <input type="radio"/>
2. Are you able to do the same work as before?	YES <input type="radio"/>	NO <input type="radio"/>
3. Are you able to keep up with your hobbies?	YES <input type="radio"/>	NO <input type="radio"/>
4. Have you maintained your ties to friends and family?	YES <input type="radio"/>	NO <input type="radio"/>
5. Do you need help making a simple meal, doing household chores, or balancing a checkbook?	YES <input type="radio"/>	NO <input type="radio"/>
6. Do you need help with shopping or traveling close to home?	YES <input type="radio"/>	NO <input type="radio"/>
7. Do you need another person to help you walk?	YES <input type="radio"/>	NO <input type="radio"/>
8. Do you need help with eating, going to the toilet, or bathing?	YES <input type="radio"/>	NO <input type="radio"/>
9. Do you stay in bed most of the day and need constant nursing care?	YES <input type="radio"/>	NO <input type="radio"/>

## APPENDIX 5. CLINICAL GLOBAL IMPRESSION (CGI)

### Clinical Global Impression (CGI)

#### 1. Severity of illness

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- |                             |   |
|-----------------------------|---|
| 0 = Not assessed            | 4 = Moderately ill                        |
| 1 = Normal, not at all ill  | 5 = Markedly ill                          |
| 2 = Borderline mentally ill | 6 = Severely ill                          |
| 3 = Mildly ill              | 7 = Among the most extremely ill patients |

#### 2. Global improvement: Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.

Compared to his condition at admission to the project, how much has he changed?

- |                        |                     |
|------------------------|---------------------|
| 0 = Not assessed       | 4 = No change       |
| 1 = Very much improved | 5 = Minimally worse |
| 2 = Much improved      | 6 = Much worse      |
| 3 = Minimally improved | 7 = Very much worse |

#### 3. Efficacy index: Rate this item on the basis of drug effect only.

Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.

EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect		Side effects			
		None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
<b>Marked</b>	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
<b>Moderate</b>	Decided improvement. Partial remission of symptoms	05	06	07	08
<b>Minimal</b>	Slight improvement which doesn't alter status of care of patient	09	10	11	12
<b>Unchanged or worse</b>		13	14	15	16
Not assessed = 00					

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

**APPENDIX 6. STATUS EPILEPTICUS SEVERITY SCORE (STESS)**

Outcome Predictor	Feature	Score
Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type (prior to first treatment)	Simple-partial, complex-parial, absence, myoclonic (complicating idiopathic generalized epilepsy)	0
	Generalized-convulsive	1
	Nonconvulsive status epilepticus in coma	2
Age	< 65 years	0
	≥ 65 years	2
History of previous seizures	Yes	0
	No or unknown	1
Summed Total		

**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY  
TO EVALUATE THE EFFICACY AND SAFETY OF SAGE-547 INJECTION  
IN THE TREATMENT OF SUBJECTS WITH SUPER-REFRACTORY  
STATUS EPILEPTICUS**

**PROTOCOL NUMBER: 547-SSE-301  
ADULT ONLY VERSION**

**IND NUMBER: 117901**

**EudraCT Number: 2015-002142-31**

Product: SAGE-547 Injection (allopregnanolone)

Sponsor Contact: [REDACTED], MD  
Sage Therapeutics  
215 First Street  
Cambridge, MA 02142  
[REDACTED]

Medical Monitor: [REDACTED], MD  
[REDACTED]

Date of Protocol: 09 March 2015  
Date of Amendment One 27 May 2015  
Date of Amendment Two (Adults Only) 17 November 2015  
Date of Amendment Three (Adults Only) 22 April 2016  
[not implemented])  
Date of Amendment Four (Adults Only) 18 August 2016

**Confidentiality Statement**

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

**PROTOCOL NUMBER: 547-SSE-301**

Sponsor [REDACTED]:

[REDACTED]  
[REDACTED]  
Sage Therapeutics  
215 First Street, Cambridge, MA 02142  
[REDACTED]

Sponsor [REDACTED]  
[REDACTED]

[REDACTED]  
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Sage Therapeutics  
215 First Street, Cambridge, MA 02142  
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Sponsor [REDACTED]  
[REDACTED]

[REDACTED]  
[REDACTED]  
Sage Therapeutics  
215 First Street, Cambridge, MA 02142  
[REDACTED]

CRO [REDACTED]:

[REDACTED]

## 1. SIGNATURE PAGE

Title of Protocol:

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus

Protocol No: 547-SSE-301

### Sponsor Approval

[Redacted Signature]

23 AUG 2016

[Redacted Signature] MD  
Sage Therapeutics

Date (dd/mm/yyyy)

[Redacted Signature]

23 Aug 2016

[Redacted Signature] MPH  
Sage Therapeutics

Date (dd/mm/yyyy)

[Redacted Signature]

23 Aug 2016

[Redacted Signature] MPH  
Sa

Date (dd/mm/yyyy)

[Redacted Signature]

23 AUG 2016

[Redacted Signature]  
Sage Therapeutics

Date (dd/mm/yyyy)



**Investigator Agreement**

By signing this page I attest that I have read and understand the contents of Clinical Protocol 547-SSE-301 and any current amendments. I agree to adhere to the design, conduct, and reporting requirements of the study as stated in the clinical protocol and to my obligations to the Sponsor as described in the protocol and executed contracts between myself, my Institution, and the Sponsor. I also agree to adhere to any subsequent amendments to the clinical protocol.

Investigator's Signature: \_\_\_\_\_

Investigator's Name: \_\_\_\_\_

Institution: \_\_\_\_\_

Date: \_\_\_\_\_

## 2. SYNOPSIS

<b>Name of Sponsor:</b> Sage Therapeutics 215 First Street Cambridge, MA 02142		
<b>Protocol No.</b> 547-SSE-301	<b>Phase:</b> 3	
<b>Name of Investigational Product:</b> SAGE-547 Injection		
<b>Name of Active Ingredient:</b> Allopregnanolone		
<b>Title of the Protocol:</b> A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus		
<b>Dosing Regimen: SAGE-547 or Placebo Dosing Schedule</b>		
<b>Hour</b>	<b>Type and Duration of SAGE-547 Infusions</b>	<b>Dose</b>
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	90 µg/kg/h
H121 – H128	8 hour taper	65 µg/kg/h
H129 – H136	8 hour taper	45 µg/kg/h
H137 – H144	8 hour taper	25 µg/kg/h
<b>Dosing Regimen: SAGE-547 Open-Label Dosing Schedule</b>		
<b>Hour</b>	<b>Type and Duration of SAGE-547 Infusion</b>	<b>Dose</b>
H1	One hour loading infusion	300 µg/kg/h
H2 –H120	119 hour maintenance infusion	150 µg/kg/h
H121 – H126	6 hour taper	125 µg/kg/h
H127 – H132	6 hour taper	95 µg/kg/h
H133 – H138	6 hour taper	65 µg/kg/h
H139 – H144	6 hour taper	35 µg/kg/h
<b>Study Sites</b> Up to 180 sites in the USA, Israel, Europe, and Canada.		
<b>Number of Subjects</b>		

The study will randomize 140 subjects at up to 180 sites.

### Study Population

Subjects will be aged 18 years or more, in SRSE<sup>1</sup> (as defined in the Inclusion Criteria [Section 8.1](#)), and being managed in an intensive care setting.

### Duration of Subject Involvement

Individual subject participation will be up to 30 days.

### Study Design

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

Patients will follow one of three paths to entry to the study. The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst or seizure suppression with a third-line agent. These subjects will be consented for the study after admission to the intensive care unit, before or after any third-line agents are administered for burst or seizure suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their legally authorized representative (LAR). Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours. Once burst or seizure suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The second path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst or seizure suppression pattern on the EEG. These subjects may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst or seizure suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst or seizure suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst or seizure suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

<sup>1</sup> In this study, the term Super-Refractory Status Epilepticus or SRSE is equivalent to “Refractory Status Epilepticus (RSE) that has failed standard treatment” and the two terms are used interchangeably.

The third path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst or seizure suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These subjects may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 treatment or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within eight hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo).

The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that subjects, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as both the ability to wean the subject off all third-line agents before the end of the infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication infusion, and concurrent signs of physiologic brain activity as determined by EEG. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#) and [Table 2](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo will all subsequently be eligible to be administered SAGE-547 at the higher dose.

### Visit Schedule

The visit schedule and an overview of events at each visit is provided in [Table 1](#), [Table 2](#) and [Table 3](#) Schedule of Assessments.

**Study Objectives*****Primary objective:***

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult subjects with SRSE, and for the response to endure at least 24 hours after the end of the SAGE-547 or placebo infusion (primary response).

***Secondary objectives:***

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in the Clinical Global Impression scale (CGI) between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

***Safety objectives:***

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

***Other objectives:***

1. To evaluate the impact of treatment with a higher dose SAGE-547 infusion;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;

3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;
6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS).

## Endpoints

### *Primary endpoint:*

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### *Secondary endpoints:*

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### *Safety endpoints:*

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.

**Other endpoints:**

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who are treated with a higher dose of SAGE-547.
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS).

**Inclusion Criteria**

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects 18 years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed zero or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst or seizure suppression pattern; or who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst or seizure suppression pattern.

**Exclusion Criteria**

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone or any excipients in SAGE-547.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy with highly malignant/malignant EEG features ([Westhall, Rosetti et al. 2016](#)).
4. Subjects who have any of the following:

- a. a GFR low enough to warrant dialysis but for whatever reason, dialysis that would adequately remove Captisol<sup>®</sup> is not planned;
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the opinion of the investigator, of less than 30 days.
5. Subjects who are being administered more than three third-line agents concomitantly or in whom the qualifying wean cannot be completed within 24 hours, or who are being administered a third-line agent for other indications such as management of raised intra-cranial pressure that would preclude weaning according to this protocol.
  6. Subjects with a living will that does not allow heroic measures.
  7. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
  8. Subjects who have been treated or randomized in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not have received study drug/placebo and then re-enroll).

### **Pharmacogenetic Research**

In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **Statistical Analysis**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

### **Interim Analysis**

When approximately 50% of the subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### **Analysis of Primary Endpoint**

The analysis of response to treatment between SAGE-547 treated subjects and placebo treated subjects will be performed using a Cochran-Mantel-Haenszel test with variables for treatment, concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). In this analysis, a treatment responder is a subject who is successfully weaned off all third-line agents and blinded study medication prior to the end of study treatment infusion.



and remains off third-line agents for at least 24 hours following cessation of the blinded study medication, and who has concurrent signs of physiologic brain activity as determined by EEG. The analysis will be based on the ITT Population. The comparison of treatment response rates will be conducted at the 5% level of significance.

### **Analysis of Secondary Efficacy Endpoints**

The primary analysis will be repeated for the MITT population. Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section. Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. Secondary analyses will be repeated for the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from Baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third-line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

Summaries of safety endpoints will be based on the overall Safety Population which is defined as all subjects who at least initiated the infusion with blinded study treatment.

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects are treated with a higher dose of SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo. Summary statistics will be presented for subjects who were QW successes.

### **Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

**Table 1: Schedule of Assessments for Protocol 547-SSE-301: One Infusion of Study Drug (blinded)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical/SE/Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X	X	X	X	X	X	X	X		X		
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X		X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X		X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X		X	X		X		X		X		
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X			
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>n</sup>											X
Modified Rankin Score (mRS)	X <sup>n</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV 3rd-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>o</sup>				
EEG	X	X				X		X	X			
Randomization		X										
Study Drug Administration <sup>p</sup>			X	X	X	X	X	X				
TW Outcome & Open-label Treatment Decision										X <sup>q</sup>		
Physiologic Brain Activity									X			
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

**Table 2: Schedule of Assessments for Protocol 547-SSE-301: Two Infusions of Study Drug (one blinded, one open-label)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V3R
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	0-24h
Eligibility Checklist	X										S
Informed Consent <sup>a</sup>	X										E
Inclusion/Exclusion Criteria	X										E
Demography <sup>b</sup>	X										
Medical and SE and Wean History <sup>c</sup>	X										T
Height	X										A
Weight <sup>d</sup>	X	X	X	X	X	X	X	X		X	B
Serum Pregnancy Test <sup>e</sup>	X										L
Hematology <sup>f</sup>	X		X	X		X		X		X	E
Serum Chemistry and GFR <sup>f</sup>	X		X	X		X		X		X	
Urinalysis <sup>h</sup>	X		X	X		X		X		X	E
Pharmacogenetic sample	X										X
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X	T
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X	E
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X		N
STESS	X										I
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	O
Glasgow Outcome Score (GOS)											N
Supervision Rating Scale (SRS)	X <sup>n</sup>										
Modified Rankin Score (mRS)	X <sup>n</sup>										
Epilepsy Status	X										N
Clinical Global Impression (CGI)	X										E
Continuous IV Third-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>o</sup>			X
EEG	X	X				X		X	X		T
Randomization		X									
Study Drug Administration <sup>p</sup>			X	X	X	X	X	X			
TW Outcome and Open-label Treatment Decision										X <sup>q</sup>	P
Physiologic Brain Activity									X		
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X	A
Concomitant Anti-Epileptic Drugs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	G
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	E
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X	
Pharmacoeconomic Data											
Mortality											

**Table 2 continued**

	V3R	V4R	V5R	V6R	V7R	V8R	V9R	V10R	V11R	V12R
	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3R+14d (±2d)	V3R+21d (±2d)
Weight <sup>d</sup>	X	X	X	X	X	X				
Serum Pregnancy Test <sup>e</sup>										
Hematology <sup>f</sup>	X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X	X		X		X		X		
Vital Signs <sup>i</sup>	X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>	X	X	X	X	X	X	X			
STESS										
FOUR Score <sup>m</sup>	X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)										X
Supervision Rating Scale (SRS)										X
Modified Rankin Score (mRS)										X
Epilepsy Status										X
Clinical Global Impression Scale (CGI)										X
Continuous IV Third-Line Agent(s)	X	X	Wean	Wean	Wean	Wean <sup>o</sup>				
EEG			X			X	X			
Randomization										
Study Drug Administration <sup>p</sup>	X	X	X	X	X	X				
TW Success and Physiologic Brain Activity							X			
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data										X
Mortality										X

**Table 3: Schedule of Assessments for Protocol 547-SSE-301: Qualifying Wean Successes**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical and SE and Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X											
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X											
Serum Chemistry and GFR <sup>f</sup>	X											
Urinalysis <sup>h</sup>	X											
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X											
ECG <sup>j</sup>	X											
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>n</sup>											X
Modified Rankin Score (mRS)	X <sup>n</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV Third-Line Agent(s)	X	Wean										
EEG	X	X										
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

<sup>a</sup> Written informed consent by proxy (LAR) will be obtained prior to starting any study-related procedures not considered standard of care.

<sup>b</sup> Demographic information will be obtained by proxy and confirmed by the subject when possible.

<sup>c</sup> Medical history will be obtained by proxy and confirmed by the subject when possible. All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Dosing changes with the third-line agent(s) that constitute a wean attempt will be marked as such on the CRF, and the start/stop dates and times of all wean attempts prior to V3 will be recorded, as well as the outcome of the wean attempt.

<sup>d</sup> Weight will be collected at Screening (V1) and prior to administration of the blinded study drug infusion at V2 and the open-label study drug infusion at V10. The weights at V2 and V10 will be used to determine the appropriate infusion rate of the blinded and open-label infusions respectively. If easily obtained (such as via a scale-bed), weight will also be recorded once during each subsequent 24 hour period of the initial study drug infusion period (V3-V8) and second infusion period (V3R-V8R, if applicable).

<sup>e</sup> Serum pregnancy test for females aged 17 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy.

<sup>f</sup> Blood samples will be taken for hematology and serum chemistry and GFR calculation at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will document whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

<sup>g</sup> Blood samples will be taken at V11 or V11R for serum chemistry (renal panel only).

<sup>h</sup> Urine samples will be taken for urinalysis and NAG at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will add a comment about whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

<sup>i</sup> Vital signs will be recorded at the following time points relative to the start of each infusion of study drug: Screening (V1), at 0, 30, 60 minutes ( $\pm 15$  minutes), at 2, 4, and 8 hours ( $\pm 30$  minutes), and at 24, 48, 72, 96, 120, 144, 168, and 192 hours ( $\pm 2$  hours).

<sup>j</sup> For the first 50 subjects randomized in the study, ECG (12-lead) should be performed at Screening (V1) and at the following times relative to the start of study drug infusion. For the blinded (first) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 128, 136, 144, 152, 160, and 192 hours ( $\pm 2$  hours). For the open-label SAGE-547 (second) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 126, 132, 138, 144, 152, 160, and 192 hours ( $\pm 2$  hours). Heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours. Following randomization of the first 50 subjects, subsequent subjects randomized in the study will have ECG collected at the following timepoints: Pre-dose and at 1, 12, 24, 48, 72, 96, 120, 144, and 192 hours after the start of the blinded (first) study drug infusion; and, Pre-dose and at 1, 12, 24, 48, 72, 96, 120, 144, and 192 hours after the start of the open-label (second) study drug infusion. It is not necessary to collect these ECGs with the PK samples at these timepoints and, apart from the 1 h ECG, there is  $\pm 2$  hour time window for these ECGs.

<sup>k</sup> Plasma will be collected to assay for study drug concentrations at the following time points relative to the start of each infusion of study drug: For the blinded (first) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion. For the open-label SAGE-547 (second) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open-label SAGE-547 study drug infusion. Pre-dose samples may be taken within two hours before starting the infusion of study drug; timepoints up to and including 1h will have a time window of  $\pm 5$  minutes; all other timepoints will have a window of  $\pm 15$  minutes.

<sup>m</sup> FOUR Score assessments will be performed at Screening (V1), 24, 48, 72, 96, 120, 144, 168, and 192 hours (all  $\pm 2$  hours) relative to the start of each infusion of study drug, and at V11 or V11R, and at V12 or V12R.

<sup>n</sup> SRS at V1 will be a retrospective assessment of the supervision required by the subject immediately prior to admission that includes the index episode of the SE, and mRS at V1 will be a retrospective assessment of the disability and dependence of the subject immediately prior to admission that includes the index episode of the SE.

<sup>o</sup> Target for complete wean of all continuous IV third-line agents by 144 hours at V8/V8R if not completed by 120 hours at V7/V7R.

<sup>p</sup> Study drug infusion is intended for IV administration only with a dedicated peripheral IV line using Sage-approved IV administration bags and lines.

<sup>q</sup> At V10 only a decision to re-treat at a higher dose of SAGE-547 will be made by the Investigator if the continuous IV third-line agent wean has failed or the third-line agent requires re-introduction during V9. Subjects who become eligible for open-label study drug at a higher dose of SAGE-547 will discontinue the planned visit schedule at V10, then repeat V3 (V3R) and all applicable subsequent visits.

<sup>r</sup> AEs will be collected from the time Informed Consent is obtained and prior to the start of study-specific screening procedures not considered standard of care. Collection of AEs will continue throughout the study from V1 through V12 or V12R.

<sup>s</sup> Subjects may enter the study on AEDs and Pressors and be administered AEDs and Pressors during the study. For all randomized and the first 50 QWS subjects, all Concomitant AEDs and Pressors must be recorded on the CRF with details including date and time of starting/stopping each AED and Pressor, the route of administration, changes in doses, and

frequency of administration. Details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the CRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”. For subsequent QWS subjects, after the detailed information on all concomitant AEDs and Pressors collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant AED and Pressor and the start and stop dates and times) from Visit 3 to Visit 12 will be recorded in the eCRF.

<sup>†</sup> All third-line agents administered since the diagnosis of SE will be recorded on the CRF. For all randomized and the first 50 QWS subjects, details will include the name of the drug, the start/stop dates and times, and, after consent, the doses with start/stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R. For subsequent QWS subjects, after the detailed information on all concomitant third-line agents collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant third-line agent and the start and stop dates and times) from Visit 3 to Visit 12 will be recorded in the eCRF.

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**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
AE	adverse event
AED	anti-epileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the time-concentration curve
AW	additional weans
BDZ	benzodiazepine
BIEEG	blinded infusion electroencephalogram
BUN	blood urea nitrogen
CBC	complete blood count
CEEG	consent electroencephalogram
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
C <sub>max</sub>	maximum plasma concentration
C <sub>min</sub>	minimum plasma concentration
CNS	central nervous system
CRF	case report form
CSR	clinical study report
CYP2C9	cytochrome P450 enzyme involved in drug metabolism
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EEG	electroencephalogram
EIND	Emergency Use Investigational New Drug Application
EP	European Pharmacopeia
ESETT	Established Status Epilepticus Treatment Trial
FDA	Food and Drug Administration
FOUR	Full Outline of UnResponsiveness
GABA	$\gamma$ -aminobutyric acid
GABA <sub>A</sub>	$\gamma$ -aminobutyric acid-gated chloride channel
GCP	Good Clinical Practice

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
GFR	glomerular filtration rate
GOS	Glasgow Outcome Scale
H	hour
HPLC	high performance liquid chromatography
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent to Treat
IV	intravenous
IVRS	Interactive Voice Randomization System
LAR	legally authorized representative
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent to Treat
mRS-9Q	Modified Rankin Score - 9Q
MS/MS	tandem mass spectrometry
nM	nanomolar
NMDA	n-methyl-D-aspartic acid
OW	other weans
PAEEG	primary endpoint electroencephalogram
PD	pharmacodynamics
PK	pharmacokinetic
QOL	quality of life
QW	qualifying wean
QWEEG	qualifying wean electroencephalogram
RBC	red blood cell
RSE	refractory status epilepticus



<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
SAE	serious adverse event
SAP	Statistical Analysis Plan
SE	status epilepticus
SOP	standard operating procedure
SRS	Severity Rating Scale
SRSE	Super-refractory status epilepticus
SSRI	Selective serotonin re-uptake inhibitors
STESS	Status Epilepticus Severity Score
SUSAR	Suspected Unexpected Serious Adverse Reactions
SWFI	Sterile Water for Injection
TAEEG	taper electroencephalogram
T <sub>max</sub>	time at maximum plasma concentration
TW	terminal wean
TWEEG	terminal wean electroencephalogram
US	United States
USP	United States Pharmacopeia

### 3. INTRODUCTION AND RATIONALE

#### 3.1. Status Epilepticus

Status epilepticus (SE) is a life-threatening seizure condition in which the brain is in a state of persistent seizure triggered by neuronal hyperexcitability. The Neurocritical Care Society defines SE as one continuous unremitting seizure lasting longer than five minutes or recurrent seizures without regaining consciousness between seizures for greater than five minutes (Brophy, Bell et al. 2012). Common causes of SE include preexisting epilepsy, cerebrovascular disease (in adults), electrolyte and metabolic disturbances, anoxia, encephalopathies, head trauma, high fever (in children, especially in the first year of life) and drug or substance intoxication. SE is associated with substantial morbidity and mortality.

##### 3.1.1. Epidemiology of SE

Geography, sex, age, and race influence the epidemiology of SE, whose incidence has a bimodal distribution, peaking in infants/young children and the elderly (Hauser 1990; DeLorenzo, Pellock et al. 1995; Wu, Shek et al. 2002). The incidence of SE in the elderly population is at least twice that in the general population. Concurrent medical conditions often exist in the elderly population, which can complicate therapy and worsen the prognosis of SE (Chapman, Smith et al. 2001).

The annual incidence of SE in the US is generally quoted to be within the range of 18/100,000 to 61/100,000, based on a 19-year retrospective study in Rochester, Minnesota (Hesdorffer, Logroscino et al. 1998) and a 2-year prospective study in Richmond, Virginia (DeLorenzo, Pellock et al. 1995), respectively. Two studies from Europe give annual incidences of a similar magnitude, ranging between 9.9/100,000 and 15.8/100,000 (Coeytaux, Jallon et al. 2000; Knake, Rosenow et al. 2001). It is thus estimated that in the United States each year there are as many as 150,000 cases of SE (DeLorenzo, Pellock et al. 1995).

#### 3.2. Refractory SE

When a patient begins to seize, the emergency medical technician will administer a first-line intravenous (IV) benzodiazepine (BDZ), such as diazepam, lorazepam or midazolam (Silbergleit, Durkalski et al. 2012), which is done either at the scene of the seizure or in the ambulance. If this is unsuccessful at abating the seizure, additional doses of the first-line therapy will be administered in the emergency room. Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line therapy, which is an IV anti-epileptic drug (AED) such as phenytoin or valproic acid (Novy, Logroscino et al. 2010; Shorvon 2011; Hocker, Britton et al. 2013).

Approximately 20-30% of patients refractory to first-line treatment will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to approximately 70-80% of patients who receive second-line therapy refractory to that therapy.

If a patient's SE continues after administration of BDZs and AEDs, the subject is diagnosed as having refractory status epilepticus (RSE), which must be treated quickly to terminate the seizure activity, maintain the patient's airway, and prevent cerebral damage. RSE patients are immediately admitted to the Intensive Care Unit (ICU) and placed in a medically-induced coma to stop all seizure-related activity. The drugs used to induce coma are continuously-infused IV agents,

commonly propofol, midazolam, or pentobarbital/thiopental, referred to as third-line agents (Brophy, Bell et al. 2012).

The RSE patient is continually monitored using electroencephalography (EEG) to ensure that seizure and/or burst suppression is achieved. Burst suppression is a pattern of brain waves seen on an EEG, characterized by periods of activity alternating with periods of little or no activity in the brain, informing medical personnel of the effectiveness of the medically-induced coma. The goal of burst suppression is to allow the brain and corresponding neuronal tissue to restore function and reset to normal pre-seizure levels.

### **3.2.1. Epidemiology of RSE**

Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line AED therapy. In turn, approximately 20 – 30% of these patients treated with AEDs will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to 28% of the total estimated SE patient population refractory to second-line therapy. Based on the previously-cited estimated incidence in the US, this means that there are up to 42,000 incident cases of RSE in the USA, annually (DeLorenzo, Pellock et al. 1995).

## **3.3. Super-refractory SE**

After 24 hours of burst or seizure suppression, the patient is weaned off of the third-line therapy. If the weaning is unsuccessful (neuronal activity has not returned to normal), the third-line agent is re-administered or a different third-line agent is started, and the patient is considered to be in super-refractory status epilepticus (SRSE) (Chapman, Smith et al. 2001; Shorvon 2011; Brophy, Bell et al. 2012). SAGE-547 is being developed as an adjunct to third-line therapy in patients in RSE who have failed standard treatment. In this protocol, the term “RSE that has failed standard treatment” is deemed to be equivalent to the term “SRSE” and the two may be used interchangeably.

### **3.3.1. Epidemiology of SRSE**

The incidence of SRSE is very poorly understood, mainly because the diagnostic codes used for SE do not generally differentiate its nature as responding or refractory to treatment. Based on the variable reporting of outcomes data, the incident cases of SRSE could represent between one and two-thirds of the RSE patients (Novy, Logroscino et al. 2010; Ferlisi and Shorvon 2012; Hocker, Britton et al. 2013; Sutter, Marsch et al. 2013). More detailed epidemiology studies are needed to better elucidate the proportion of RSE patients whose condition becomes super-refractory. A recent review of ICU discharge data in the USA suggests an annual incidence of approximately 35,000, based on patients who required at least three days in the ICU for SE [Sage data on file].

### **3.3.2. Outcomes of SRSE**

SE has varying degrees of mortality depending on the underlying etiologies. Table 4 outlines the acute mortality in patients with SE by etiology (Neligan and Shorvon 2010). The mortality rate of SRSE is estimated to be 30% to 50% using current standard of care.

The causes of death from SE (and therefore SRSE) are heterogeneous, resulting from neuronal cell death, complications of underlying medical conditions, or adverse effects of the current standard treatments. Prognosis worsens and mortality increases with longer duration of SE, i.e. with SE that develops into RSE or SRSE (Neligan and Shorvon 2010), and with longer duration of

medically-induced coma ([Ferlisi and Shorvon 2012](#)). There is an obvious unmet medical need to improve upon the current standard of care treatment regimens.

Morbidity is high and survivors have outcomes ranging from poor function to vegetative state ([Shorvon 2011](#)). Approximately one third of patients with RSE and SRSE will recover, but with chronic neurologic or other deficits ([Neligan and Shorvon 2010](#); [Hocker, Britton et al. 2013](#)). In all, it is estimated that less than 25-30% of all SRSE patients have a favorable functional outcome.

**Table 4: Approximate Mortality of Status Epilepticus in Different Etiologies**

Underlying Etiology	Associated Acute Mortality in Patients with SE (%)
Drug reduction/withdrawal, poor AED compliance, or low AED levels	0-10
Cerebrovascular Disease	20-60
Metabolic Disorders	10-35
Acute CNS Infection	0-30
Anoxia	60-100
Alcohol Abuse	0-10
Head Trauma	0-25
Drug Overdose/Toxicity	10-25
Brain Tumors	0-20
Cryptogenic/Idiopathic	5-20

### 3.3.3. Unmet Medical Need in Super-refractory Status Epilepticus

Treatment approaches for SRSE consist of diagnosis and treatment of underlying medical conditions, adding and changing anti-seizure drugs, and repeated attempts at weaning from IV anesthetic agents. Treatment of SRSE has three aims:

- to prevent excitotoxicity, which begins within 24 hours of SE onset;
- to prevent cerebral damage by initiating neuroprotective burst or seizure suppression;
- to prevent the complications of extended periods of anesthesia or unconsciousness ([Shorvon 2011](#)).

Currently, there are no therapies that have been specifically approved for RSE or SRSE. The primary drugs used to induce coma are continuously infused IV anesthetics such as propofol, midazolam, or pentobarbital/thiopental, known as third-line agents. Use of these drugs to control SRSE has only been studied in small retrospective reviews or small prospective studies without controls ([Hocker, Britton et al. 2013](#)) therefore there is no agreement on which drug is optimal nor on an optimal dosing regimen for the treatments that are used.

The most common adverse effect of the third-line agents is hemodynamic instability; in addition, they are not universally effective, with breakthrough seizures and withdrawal seizures requiring dose adjustments and changes in third-line agent(s). The drug thought to be most effective in SRSE, pentobarbital, is also associated with the most toxic adverse effect profile, comprising

decreased blood pressure and cardiorespiratory collapse (Claassen, Hirsch et al. 2002). The ability to wean patients successfully off the third-line agents as quickly as possible is therefore paramount, and an adjunct to SRSE treatment that enhances the success of the third-line agents and supports their successful weaning in a short timeframe would be an important addition to the therapeutic armamentarium. Preliminary clinical data show that SAGE-547 has been a successful adjunct to third-line therapy in this regard.

### 3.4. SAGE-547 Injection

Allopregnanolone is an endogenous, naturally occurring neuroactive steroid formed in the corpus luteum of the ovary, adrenal cortex and central nervous system (CNS) (Holzbauer, Birmingham et al. 1985; Paul and Purdy 1992; Ottander, Poromaa et al. 2005). It is a metabolite of progesterone created by the actions of 5- $\alpha$  reductase and 3- $\alpha$  hydroxy-steroid dehydrogenase. Allopregnanolone is a potent positive allosteric modulator of both synaptic and extra-synaptic GABA<sub>A</sub> receptors.

SAGE-547 Injection (allopregnanolone aqueous formulation in Captisol<sup>®</sup>) is being developed for the treatment of patients in RSE who have not responded to standard treatment. SAGE-547 Injection is a solution of 5 mg/mL allopregnanolone in Sterile Water for Injection (SWFI), USP and 250 mg/mL betadex sulfobutyl-ether sodium, NF. It is further diluted with Sterile Water for Injection, USP (SWFI) in IV bags to achieve an allopregnanolone concentration of approximately 1.67 mg/mL in an approximately isotonic solution and will be administered intravenously.

#### 3.4.1. Scientific Rationale for SAGE-547 in SRSE

Ineffective recruitment of inhibitory neurotransmission, together with excessive neuronal excitation, likely plays a role in the initiation and propagation of the electrical disturbance occurring in SE. GABA ( $\gamma$ -aminobutyric acid), the major inhibitory neurotransmitter in the central nervous system (CNS), is released from GABAergic neurons and binds to several types of GABA receptors (GABA<sub>A</sub>, GABA<sub>B</sub>, and GABA<sub>C</sub>) on target neurons. GABA<sub>A</sub> receptors are macromolecular proteins that form a chloride ion channel complex and contain specific binding sites for GABA and a number of allosteric regulators, including barbiturates, benzodiazepines, and some anesthetic agents. GABA receptor-mediated inhibition contributes significantly to the normal termination of a seizure (Kapur and Macdonald 1997). SAGE-547 is a positive allosteric modulator of the GABA<sub>A</sub> receptor.

The importance of terminating seizure activity as soon as possible is underpinned by a growing body of evidence from research and clinical observation that SE becomes more difficult to control as its duration increases. It has been postulated that this occurs due to a mechanistic shift from inadequate GABAergic inhibitory receptor-mediated transmission to excessive N-methyl-D-aspartic acid (NMDA) excitatory receptor-mediated transmission (Kapur and Macdonald 1997). As prolonged epileptiform bursting results in a reduction of GABA<sub>A</sub>-mediated synaptic inhibition, antiepileptic treatments which rely on enhancing intrasynaptic GABA<sub>A</sub> neurotransmission become less effective the longer SE continues.

Furthermore, the constitutive process of synaptic GABA<sub>A</sub> receptor internalization is accelerated by the increased neuronal activity associated with seizures. These findings suggest that the rate of GABA<sub>A</sub> receptor internalization is regulated by neuronal activity, and its acceleration contributes to the reduction of inhibitory transmission observed during prolonged seizures (Kapur and Macdonald 1997). Of note is that SAGE-547 binds to extrasynaptic as well as intrasynaptic GABA<sub>A</sub> receptors;

extrasynaptic receptors remain active with ongoing seizure activity, resulting in a putative mode of action for SAGE-547 in SRSE.

Status epilepticus induces cerebral damage that includes neuronal cell necrosis, gliosis, and network reorganization. The major cause of cell death in cerebral damage is excitotoxicity, which is initiated by glutaminergic receptor over-activation, causing calcium to flood the cell, thereby leading to apoptosis and necrosis. This process is initiated within a few hours of the start of seizure activity, and provides the medical imperative to terminate SE as quickly as possible. To prevent the consequences of the excitotoxicity cascade, it is recommended that anesthesia be initiated within 1-2 hours of onset of seizures at doses designed to induce EEG suppression patterns (Shorvon and Ferlisi 2011).

### **3.4.2. SAGE-547 Clinical Program in the Treatment of SRSE**

The current SAGE-547 development program includes:

- a completed Phase 2 open-label trial, Study 547-SSE-201;
- this proposed Phase 3 randomized, double-blind, placebo-controlled trial, Study 547-SSE-301;
- an ongoing open-label, expanded access protocol, Study 547-SSE-302;
- a number of EINDs for SAGE-547 in patients with SRSE.

The designs of these studies are all similar, with a five to six day infusion of SAGE-547 (or placebo), during which time attempts are made to wean the subject off all third-line agents. In the Phase 3 studies, those subjects who cannot be weaned off third-line agents while being administered SAGE-547 (or placebo) may be eligible for a second open-label infusion of SAGE-547 at a higher dose. Follow up of subjects is for 21 – 30 days after the first infusion of study medication.

### **3.4.3. Data from the SAGE-547 Development Program**

The data from 30 subjects included in the on-going clinical evaluation of SAGE-547 for the treatment of adults and children with SRSE clearly offers preliminary evidence that SAGE-547 could provide substantial and clinically significant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate. These subjects comprise 20 from the ongoing Phase 2 trial (71% success rate in 12/17 evaluable subjects) and 10 subjects who received EIND treatments (78% success rate in 7/9 evaluable subjects).

Successful therapy of SRSE has been defined as “the SE is completely controlled by the therapy, without breakthrough of withdrawal seizures, or discontinuation due to side effects or death during therapy,” (Ferlisi and Shorvon 2012). By this definition, which is in accord with the efficacy assessments used in the overall clinical evaluation of SAGE-547, 19 of the 26 (73%) subjects with SRSE who completed the SAGE-547 infusion were treatment successes. As data collection is ongoing, this information is preliminary and subject to change upon further monitoring.

Published reports on RSE and SRSE have stated mortality rate ranges from 35% to 65%. The underlying etiologies of SE in the 547-SAGE-201 study and EINDs are heterogeneous, and each one conveys a different risk of mortality and longer term morbidity. However, the death rate in subjects who have received SAGE-547, 6 out of 30 (20%) subjects, appears to be lower than the published rates. None of the deaths were considered related to SAGE-547: brain tumor, organophosphate toxicity, respiratory failure, respiratory arrest due to ventilator support withdrawal, and breast cancer.

In the Phase 2 study, 20 SAEs (15 non-fatal) have been reported in 13 (65%) subjects, and of these 3 events in 2 subjects (10%) were considered by the investigator to be related to SAGE-547: pulmonary emboli and tracheostomy dehiscence/infection. The Sponsor did not consider these events to be related to SAGE-547, rather to the underlying disease states. Four of the 20 subjects (20%) experienced AEs considered possibly related to SAGE-547 by the investigator, namely moderate myopathy and severe pulmonary emboli in 1 subject, moderate tracheostomy dehiscence and tracheostomy infection in 1 subject, moderate thrombocytosis in 1 subject and moderate BUN, ALT and AST elevation in 1 subject.

Review of the most current safety data from 547-SAGE-201 reveals that there were changes in serum chemistry, hematology, and urinalysis during the study, but that none of those changes were assessed as related to SAGE-547. There were also no SAGE-547-related changes to vital signs.

Despite the heterogeneity in the underlying causes of SE, the ages of the subject, comorbidities, which normally complicate the treatment of SE, and the fact that all subjects had failed current standard of care treatment, a large majority of subjects had a successful therapy outcome, with discontinuation of all third-line agents and resolution of SE.

Refer to the Investigational Brochure for further information on the pre-clinical and clinical data supporting the use of SAGE-547 in SRSE.

### **3.5. Study Rationale - SAGE-547 in SRSE**

#### **3.5.1. Justification for the Control Group**

Although SAGE-547 has demonstrated extremely promising activity in subjects with SRSE, both in the Phase 2 study and during the EINDs, these have been open-label investigations with no control data for comparison. Generally in the literature there are few data describing the success rates of wean attempts of third-line agents, and few comparative data on the effectiveness of the three main third-line agents, propofol, pentobarbital/thiopental, and midazolam.

Several options for a control group in Study 547-SSE-301 were considered:

- No control group was thought to be unacceptable since there are no reliable published data on success rates in this population that could be used for broad comparisons;
- An active control was considered but found to be impractical since none of the third-line agents are approved for their use in SRSE, no standardized dosing regimens or treatment guidelines have been adopted for the management of SRSE, and clinicians were unlikely to agree which of the available third-line agents would be reserved for the active control arm;
- Historical controls were considered but abandoned because of the practical difficulties of obtaining high quality data, the lack of ability to prospectively match cases, and a suspicion that clinical practice in the standard of care of SRSE is evolving, mandating the use of prospective, concurrent control data;
- Comparison to standard of care alone was considered as a feasible design. However, in a field where no widely adopted treatment guidelines exist, there was a concern that knowledge of the treatment group (SAGE-547 plus standard of care versus standard of care alone) would alter the behavior of the investigators such that they could be more aggressive with weaning in the SAGE-547 group;



- Placebo control is not without its challenges since the preliminary efficacy data for SAGE-547 show that the compound exerts central pharmacological effects and is associated with positive outcomes in around 70% of patients. There is therefore a potential ethical concern about administering placebo to desperately ill patients who have often exhausted all treatment options for SRSE. This concern has been addressed in two ways: firstly all patients receive current standard of care; secondly, all subjects who fail to be weaned from their third-line agents at the end of the blinded infusion of study drug will be administered open-label SAGE-547 without un-blinding their initial treatment allocation, so treatment with the investigational product is not denied, but delayed about a week in the setting of ongoing receipt of full current standard of care.

It was therefore decided that a blinded, placebo-controlled design was appropriate for Study 547-SSE-301.

### **3.5.2. Justification for the Dose Regimen**

The standard dose regimen has been studied in 19 subjects in the 547-SSE-201 Phase 2 trial; the average peak plasma concentration of SAGE-547 at the end of the loading dose was approximately 144 ng/ml. The average plasma concentration during the maintenance infusion was approximately 70 ng/ml. At these concentrations, there were no clear safety signals although two-thirds of subjects experienced an SAE and there were four deaths, all related to the underlying comorbid conditions. The standard dosing regimen was associated with an approximate 70% successful treatment outcome. For these reasons, the standard dosing regimen has been adopted for the initial SAGE-547 infusion to be compared in a blinded fashion to placebo.

In the 547-SSE-201 trial, three subjects have thus far received the higher dose regimen. This dose regimen has also been well tolerated. The average peak plasma concentrations at the end of the loading dose for both dosing regimens will be in the same range, as the loading dose is the same for both regimens. The average plasma concentrations observed during the higher maintenance dose are 102 ng/ml (n=2). The rationale for adopting the higher dose regimen as the open-label infusion of SAGE-547 for subjects who are retreated in this 547-SSE-301 trial is that those who fail on the standard SAGE-547 dose regimen are afforded the opportunity to have access to a higher dose. The justification to also administer the higher dose regimen to failures on placebo is that the regimen has thus far been well tolerated, and this methodology preserves the blind for the initial infusion.

A five-day dosing regimen with SAGE-547 was investigated in the Phase 2 study, 547-SSE-201. There were some cases when weaning off all third-line agents was not possible within 48 hours, but weaning was completed after the end of the infusion of SAGE-547. For this reason, the duration of dosing with SAGE-547 has been increased from 120 hours (five days) in Phase 2 to 144 hours (six days) in this Phase 3 study.

### **3.5.3. Rationale for Genetic Testing Sub-study**

Sage Therapeutics intends to perform genetic research in the SAGE-547 development program in order to explore how genetic variations may affect the metabolism and activity of SAGE-547. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials, and, possibly, to genetically-guided treatment strategies for optimizing decision making with respect to individual benefit:risk. Participation of subjects in genetic research as part of the overall clinical study is optional.



### **3.6. Benefit-Risk Evaluation of the Present Study**

Previous reports of human administration of exogenous allopregnanolone indicate that for exposures in men and women up to 150 nM, the most commonly reported AEs were sedation (recorded as sleepiness or tiredness), feelings of intoxication (like alcohol), flushing, and mild headache (Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007). No SAEs were reported (Navarro, Kaddouz et al. 2003; Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007; Kask, Backstrom et al. 2008; Kask, Backstrom et al. 2009; Timby, Hedstrom et al. 2011a). In view of the reduced consciousness and sedation of study subjects at entry into this protocol, none of these previously-reported events are likely to impact subjects in this study.

To date, in the SAGE-547 Phase 2 study and the EIND subjects, a majority of subjects demonstrated a successful therapy outcome (>70%). The majority in the clinical trial (65%) have also experienced SAEs, but none has been considered related to SAGE-547 by the Sponsor (SAEs in 2 subjects (10%) were considered possibly related by Investigator). Five deaths have been reported in 30 subjects (20%), all related to the underlying cause of SRSE and not related to SAGE-547 – this is in the context of published mortality rates between 35% and 65%. These preliminary data suggest that SAGE-547 has the potential to provide clinically relevant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate.

The underlying etiologies of SE are heterogeneous, and each one conveys a different risk of mortality. Subjects who survive SRSE still have a high risk of severe morbidity (Neligan and Shorvon 2010). The subjects treated with SAGE-547 in Study 547-SSE-201, are heterogeneous in factors such as age and etiology of SE, factors that usually complicate treatment and can increase morbidity and mortality. Even with this heterogeneity, the preliminary efficacy and safety data for SAGE-547 are very encouraging, and the mortality rate suggests that the risk to benefit assessment of this treatment rests on the side of benefit.

## **4. ETHICS**

### **4.1. Institutional Review Board or Independent Ethics Committee**

This protocol will be reviewed and approved by the Institutional Review Board (IRB) where the study is conducted. The IRB will meet all FDA requirements governing IRBs (CFR, Title 21, Part 56).

### **4.2. Ethical Conduct of the Study**

The Sponsor, the Medical Monitor, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable ICH and GCP guidelines, and must also conduct the study in accordance with local regulations.

### **4.3. Subject Information and Informed Consent**

Subjects prospectively enrolled in this study will be unable to give consent. Therefore, consent will be given by proxy by a legally authorized representative (LAR). Written informed consent is required for each subject prior to any testing under this protocol not considered standard of care, including screening tests and evaluations. Should a subject gain the ability to sufficiently

comprehend the situation and consent during the course of the study, written informed consent or verbal assent will be documented as required or recommended by the institution's IRB.

The form of consent to be obtained will depend on the condition of the subject as determined by the Principal Investigator. The informed consent form (ICF), as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50.

It is the responsibility of the Investigator to obtain consent and to provide the subject's LAR with a copy of the signed and dated informed consent form. The informed consent form for subject participation must also be available as part of the subject file for review by the site's dedicated study monitor or any authorized auditor of the Sponsor or regulatory authorities.

All ICFs used in this study must be approved by the appropriate IRB and by the Sponsor. The ICF must not be altered without the prior agreement of the relevant IRB and the Sponsor.

#### **4.4. Ethical and Regulatory Considerations for Pharmacogenetic Sub-study**

##### **4.4.1. Informed Consent for Pharmacogenetics**

The genetic component of this study is optional and subjects may participate in other components of the main study without having to agree to participate in the genetic component. If subject chooses to participate in the genetic component of the study, the subject or LAR must sign and date a specific consent form for the genetic component of the study in addition to the main study consent form. The principal investigator(s) is responsible for ensuring that consent is freely given and that the subject understands that they may discontinue from the genetic aspect of the study independent of their decision to remain within or withdrawal from the main study.

##### **4.4.2. Subject Data Protection Relative to Pharmacogenomics**

Sage Therapeutics will not provide individual genotype results to subjects, their family members, their general physician, their employer or any insurance company unless required to do so by law. While extra precautions will be taken to preserve confidentiality and to prevent genetic data from being linked to an individual's identity outside of a restricted access site, in certain exceptional situations (e.g. in case of a medical emergency or as a consequence of a specific regulatory need), certain individuals may see both genetic data and the personal identifiers of a subject; however in all cases a subject's medical information and genetic files will remain physically separated.

## **5. STUDY OBJECTIVES**

### **5.1. Primary Objective**

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult subjects with SRSE, and for the response to endure at least 24 hours after cessation of the SAGE-547 or placebo infusion (primary response).

## 5.2. Secondary Objectives

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in Clinical Global Impression Scale between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

## 5.3. Safety Objectives

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

## 5.4. Other Objectives

1. To evaluate the impact of retreatment with a higher dose of SAGE-547 infusion;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;

6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS).

## **6. ENDPOINTS**

### **6.1. Primary Endpoint**

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### **6.2. Secondary Endpoints**

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) and to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### **6.3. Safety Endpoints**

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.

### **6.4. Other Endpoints**

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who are treated with a higher dose of SAGE-547;

2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS).

## 7. INVESTIGATIONAL PLAN

### 7.1. Overview of Study Design

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

[Figure 1](#) provides an overview of the study design and [Figure 2](#) gives the details of treatment and follow-up on the active treatment arm. Patients will follow one of three paths to entry to the study. The first path is for patients who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst or seizure suppression with a third-line agent. These patients will be consented for the study after admission to the intensive care unit, before or after any third-line agents are administered for burst or seizure suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their LAR. Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours. Once burst or seizure suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned during the QW will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst or seizure suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The second path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst or seizure suppression pattern on the EEG. These patients may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst or seizure suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst or seizure suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst or seizure suppression has been achieved, the third-line agent or agents will

be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst or seizure suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The third path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst or seizure suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These patients may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst or seizure suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within eight hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third line agent wean attempts prior to randomization (one vs two or more).

The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

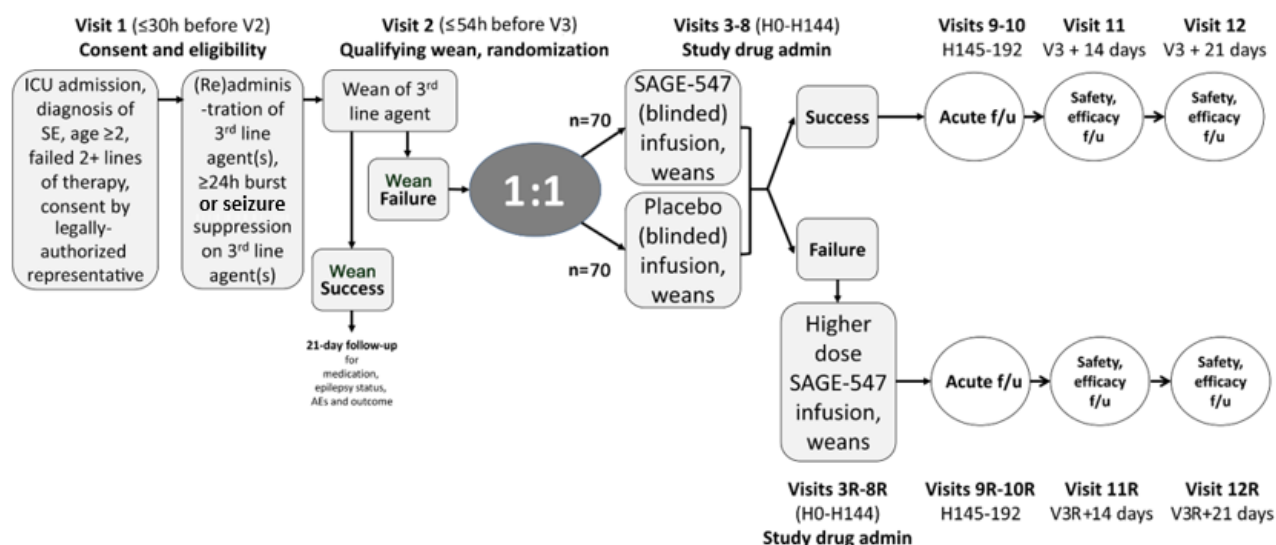
For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as the ability to wean the subject off all third-line agents before the end of the first infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication. Subjects must also have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) at the end of the primary endpoint assessment period as determined by EEG in order to be deemed a success. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#), [Table 2](#) and [Table 3](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion may be eligible to receive an open-label infusion of SAGE-547 at a dose higher than

that administered in the blinded part of the study. Eligibility for the open-label treatment must be confirmed in writing by the medical monitor prior to the open-label infusion starting. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo may all subsequently be eligible to be administered SAGE-547 at the higher dose.

**Figure 1: Study Design**



## 7.2. Trial Conduct

This study will be conducted according to the principles of the World Medical Association Declaration of Helsinki and most recent amendment, and in compliance with the protocol approved by the IRBs/Independent Ethics Committees (IECs), and in accordance with ICH Guidelines on GCP standards.

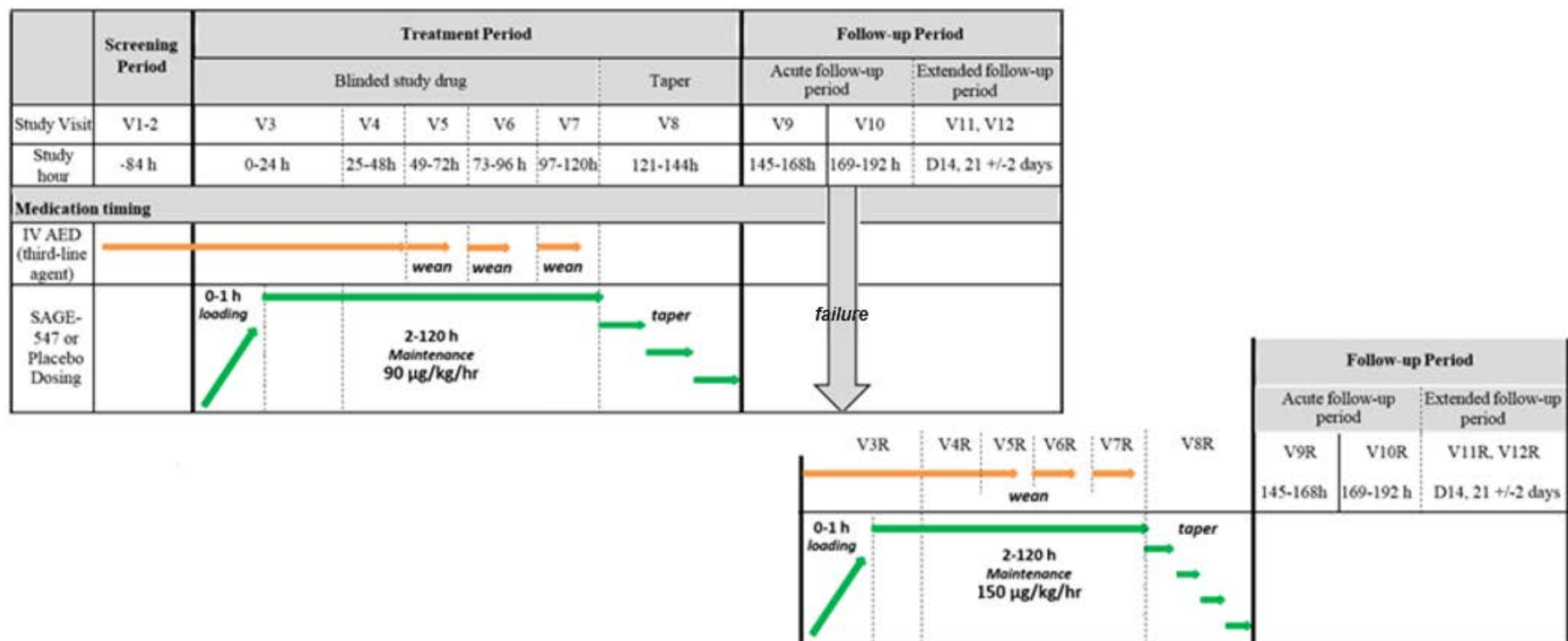
## 7.3. Blinding and Randomization

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo). Details of the dynamic randomization process will be included in the SAP.

The randomized portion of the study will be blinded, with the two treatment products (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

The second infusion of SAGE-547 will be administered on an open-label basis to subjects who meet the criteria for open-label treatment.

### Figure 2: Details of Treatment Administration and Follow-up





## 8. SELECTION AND WITHDRAWAL OF SUBJECTS

The study will randomize 140 patients at up to 180 sites. All subjects deemed eligible to enroll must have written Medical Monitor approval on a case-by-case basis prior to undertaking the qualifying wean.

### 8.1. Inclusion Criteria

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects 18 years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; *or* who have previously failed zero or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst or seizure suppression pattern; *or* who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst or seizure suppression pattern.

### 8.2. Exclusion Criteria

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy with highly malignant/malignant EEG features ([Westhall, Rosetti et al. 2016](#)).
4. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis but for whatever reason, dialysis that would adequately remove Captisol® is not planned;
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the experience of the investigator, is less than 30 days.
5. Subjects who are being administered more than three third-line agents concomitantly or for whom the qualifying wean cannot be completed within 24 hours or who are being

administered a third-line agent for indications such as raised intra-cranial pressure that would preclude weaning according to this protocol.

6. Subjects with a living will that does not allow heroic measure.
7. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
8. Subjects who have been treated or randomized in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not have received study drug/placebo and then re-enroll).

### **8.3. Selection and Consent of Subjects for Pharmacogenetic Substudy**

All subjects will be asked to participate in pharmacogenetic research; however, participation in research is voluntary and a subject can decide to decline his/her participation without penalty or loss of benefit. Participation or lack thereof will not be a cause for exclusion from any aspect of the main study. In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **8.4. Subject Withdrawal / Study Termination**

#### **8.4.1. Withdrawal/Discontinuation of Individual Subjects**

The reasons for study drug discontinuation and/or subject withdrawal from the study must be recorded in the subject's electronic case report form (eCRF). The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject has been discontinued/withdrawn due to an AE.

##### **8.4.1.1. Withdrawal from the Study**

Subjects or their LAR may withdraw subjects from the study at any time for any reason without compromising the subject's medical care. The Investigator will also withdraw subjects upon the request of Sage Therapeutics or upon termination of the study.

Subjects who withdraw from the study prior to Visit 10 (or 10R) should complete the procedures scheduled for the day of study drug taper (Hour 121-144; Visit8/8R) on the day of their withdrawal, including the SAGE-547 taper schedule, with the addition of the mortality assessment from Visit 12/12R. Subjects who withdraw from the study after Visit 10/10R should undergo study procedures as outlined for Visit 12/12R on the day of their withdrawal. In all cases, the reason for subject withdrawal will be recorded in the eCRF.

Withdrawal of subjects for any reason should be discussed with the Medical Monitor.

##### **8.4.1.2. Discontinuation of Study Drug**

If it is necessary to discontinue the study drug earlier than planned, subjects should continue to be followed per protocol to capture safety and efficacy assessments for the duration of the study period.

The investigator may withdraw the subject from the study drug for the following reasons:

- Upon subject's or LAR's request
- The subject or LAR is unwilling or unable to adhere to the protocol-specified visits
- The subject experiences an intolerable adverse event
- During the course of the study, the subject develops symptoms or conditions listed in the exclusion criteria.
- Other medical reason, at the discretion of the Investigator and/or the Medical Monitor

Subjects who discontinue the study due to an AE considered related to study drug should be followed until the event is resolved, considered stable, or the Investigator determines the event is no longer clinically significant. Study drug discontinuation due to AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

#### **8.4.2. Study Termination**

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of AEs or other findings suggesting unacceptable risk to subjects, administrative or operational reasons. In the event of study termination, Sage Therapeutics will provide written notification to the Investigator. Investigational sites must promptly notify their IRB and initiate withdrawal procedures for participating subjects.

## **9. INVESTIGATIONAL PRODUCT**

### **9.1. Identity of Investigational Product**

SAGE-547 Injection (allopregnanolone)

### **9.2. Clinical Supplies**

#### **9.2.1. SAGE-547**

Adequate supplies of SAGE-547 Injection and materials for intravenous administration will be provided to each site.

SAGE-547 Injection is a clear, colorless sterile solution of allopregnanolone intended for intravenous injection. SAGE-547 Injection is an aqueous solution of 5 mg/mL allopregnanolone in 250 mg/mL Captisol® (betadex sulfobutyl-ether sodium, NF). It is presented either un-buffered or buffered with 10 mM citrate at a pH of 6.0 in either 20 mL or 50 mL vials. SAGE-547 is further diluted according to the Pharmacy Manual to achieve an approximately isotonic solution and will be administered intravenously.

No preservatives are included in the drug product, which is intended to be used as a single-use vial. All inactive components (excipients) used in the formulation are compendial grade and conform to current USP/EP, and include sodium citrate, citric acid and betadex sulfobutyl-ether sodium (Captisol®).

#### **9.2.2. Placebo**

Placebo will be identical to SAGE-547 and presented in identical vials. Placebo will be manufactured in a similar way to SAGE-547 and comprises all excipients but no SAGE-547.

### 9.2.3. Blinding

The vials of SAGE-547 and placebo will be identical in every way so that they are indistinguishable by the pharmacist, investigator, anyone treating or managing the patient, the monitors, and the sponsor. In this way the first infusion of study drug administered to each patient will be double-blind.

For the blinded study drug infusions, subject-specific dosing kits will be provided. These dosing kits will be pre-labelled with kit number for the first blinded infusion. For the second-infusion, open-label kits will be provided, which will require subject assignment by the pharmacy for reconciliation purposes. The study kits must be stored under refrigerated conditions (2-8 °C). IV administration bags and lines may be provided for the blinded and open-label infusions. Refer to the Pharmacy Manual for additional details.

The label for the SAGE-547 Injection vials will include standard product identification information according to the Code of Federal Regulations, 21CFR 312.6. All study labels will also contain the following statement:

Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use.

### 9.3. Preparation of SAGE-547 or Placebo Injection for Dosing

The Pharmacy will be responsible for preparing the blinded and open-label study drug for subject dosing. The prepared admixture will be assigned a room temperature (20-25 °C) storage shelf life of 30 hours from time of compounding.

SAGE-547, which is hypertonic, will require dilution with SWFI to achieve an approximately isotonic solution according to the instructions provided in the Pharmacy Manual. Exactly the same procedures will be used to prepare the placebo admixture, so that all site staff remain blinded as to treatment allocation for the first infusion of study drug. SAGE-547 Injection is not intended to be administered to patients undiluted.

Refer to the Pharmacy Manual for specific instructions regarding infusion preparation.

### 9.4. Administration and Accountability

The Pharmacy will maintain accurate records of all investigational product supplies. Accurate records will be kept regarding the volume of SAGE-547 Injection or placebo used for each IV preparation, as well as the required infusion rate or rates, and the date and time of preparation. Reasons for departure from the expected dosing regimen must also be recorded. To satisfy regulatory requirements regarding drug accountability, all study medication will be reconciled in full. Refer to the Pharmacy Manual for additional details.

## 10. TREATMENT OF SUBJECTS

### 10.1. Dosing Schedule (Blinded Infusions)

SAGE-547 Injection or placebo will be administered according to the dosing schedules in [Table 5](#). The infusion rates to accomplish these µg/kg/h doses will be calculated according to the weight of the subject obtained within the eight-hour window that follows the declaration of the QW failure at V2 and prior to dosing at V3. The infusion rates will be applied to blinded study drug for the first infusion of study medication.

**Table 5: SAGE-547 or Placebo Dosing Schedule**

Hour	Type and Duration of Study Drug Infusion	Description
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	90 µg/kg/h
H121 – H128	8 hour taper	65 µg/kg/h
H129 – H136	8 hour taper	45 µg/kg/h
H137 – H144	8 hour taper	25 µg/kg/h

## 10.2. Dosing Schedule (Open-Label Infusions)

Those subjects that qualify for the open-label study drug will be administered SAGE-547 Injection will be re-administered according to the dosing schedule in [Table 6](#). The dose will be administered on a µg/kg/h basis, and the subject's weight measured prior to dosing during V10 will be used to calculate the doses. These infusion rates will be applied to SAGE-547 treatment for the open-label second infusions of study medication.

**Table 6: SAGE-547 Open-Label Dosing Schedule**

Hour	Type and Duration of SAGE-547 Infusion	Description
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	150 µg/kg/h
H121 – H126	6 hour taper	125 µg/kg/h
H127 – H132	6 hour taper	95 µg/kg/h
H133 – H138	6 hour taper	65 µg/kg/h
H139 – H144	6 hour taper	35 µg/kg/h

## 10.3. Route of Administration

SAGE-547 Injection is intended for IV administration only. The compatibility of SAGE-547 with other drugs is unknown, and the product should be administered via a dedicated peripheral IV line using any Sage-supplied study-specific IV administration bags and lines. In order to preserve blinding, these instructions also apply to the blinded placebo infusions.

## 10.4. Treatment Period

The treatment period with double-blind SAGE-547 or placebo is six 24-hour periods (144 hours), which may encompass 6-7 calendar days. The open-label study drug treatment period is of identical duration.

## 10.5. Concomitant Medications, Procedures and Treatments

Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. For all randomized and the first 50 qualifying wean success (QWS) subjects, detailed information on all concomitant medications (concomitant AEDs, third-line agents, pressors, and other concomitant medications), procedures, and treatments should

be documented throughout the study from Screening through Visit 12/12R, as described below, and recorded on the eCRF. For subsequent QWS subjects, after the detailed information on all concomitant AEDs, pressors, third-line agents, procedures, and treatments collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant AED or pressor, third-line agent, procedure, and/or treatment, and the start and stop dates and times) from Visit 3 through Visit 12 will be recorded in the eCRF. For subsequent QWS subjects, after the detailed information on all concomitant medications collected during the screening period (Visits 1 and 2) has been recorded, only minimal information, to include the name of the concomitant medications and indication only will be recorded from Visit 3 through Visit 12.

SAGE-547 has demonstrated inhibitory effects on cytochrome P450 isoenzyme 2C9 (CYP2C9). Therefore, AEDs such as phenytoin and phenobarbital that are primarily metabolized by CYP2C9 should be closely monitored during SAGE-547 administration to ensure target exposures are maintained.

#### **10.5.1. Concomitant AEDs**

Subjects may enter the study on AEDs, and be administered AEDs during the study. All of these must be recorded on the eCRF with details including date and time of starting and stopping each AED, the route of administration, changes in doses, and frequency of administration. In addition, details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the eCRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.

#### **10.5.2. Concomitant Third-Line Agents**

All third-line agents (as defined in [Section 8](#)) administered since the diagnosis of SE will be recorded on the eCRF, whatever path the patient took for entry into the study. Details will include the name of the drug, the start and stop dates and times, and, after consent, the doses with start and stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

In addition, those changes in dose that constitute a wean attempt will be marked as such on the eCRF. In this way the start and stop dates and times of all wean attempts (see [Section 11](#) for definitions) will be recorded, as will the type of wean (QW, OW, or TW) and the outcome of the wean attempt (successful, failed and dose of this third-line agent increased or failed and this third-line agent stopped and another third-line agent started). Those wean attempts that occur after the TW up to and including Visit 12/12R will be marked “AW”.

Some third-line agents (such as propofol) are also used to induce sedation to facilitate a subject’s ability to tolerate the ventilator. For subjects requiring such sedation, propofol is the preferred agent unless there are contraindications. The eCRF will make clear from the indication for the third-line agent when it is being used for burst or seizure suppression and when it is being used as ventilator support or for another purpose. The investigator will add a note to the eCRF to justify that the doses used are appropriate for sedation and not for seizure or burst suppression. The doses used for ventilator support and other similar uses are usually much lower than those used for seizure or burst suppression, and use of these third-line agents for these other purposes does not constitute a wean failure under this protocol.

### **10.5.3. Concomitant Pressors**

The start and stop dates and times of all pressors will be recorded as well as the start and stop dates and times of all dose changes.

### **10.5.4. Other Concomitant Medications**

All other concomitant medications must be recorded on the eCRF with details including date and time of starting and stopping, the route of administration, dose, and frequency of administration.

## **11. STUDY ASSESSMENTS**

### **11.1. Efficacy Assessments**

#### **11.1.1. Primary Efficacy**

Success or failure will be determined, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo infusion and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the blinded (first) infusion of SAGE-547 or placebo. In addition, subjects must have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) to be deemed to be successes. All subjects who fail to complete their infusion of randomized treatment or do not have at least one attempt during study treatment to wean off all third-line agents will be considered as “failures” for the primary endpoint.

##### **11.1.1.1. Weaning**

Third-line agents are anesthetic agents that are administered in order to reach a seizure or burst suppression EEG pattern. For the purposes of this study, third-line agents are defined as continuous intravenous infusions of pentobarbital/thiopental, midazolam, propofol, and ketamine at maintenance doses alone or in combination sufficient to produce a burst or seizure suppression pattern on the EEG. The following are considered to be minimum maintenance doses of these agents that may be expected alone or in combination to achieve EEG burst suppression. If subjects are on lower doses than these and are not in EEG burst suppression for the first 12 hours of the blinded study drug infusion, they will be considered to be protocol violators and will exit the study.

- Pentobarbital: 1 mg/kg/hour
- Thiopental: 3mg/kg/hour
- Midazolam: 0.1 mg/kg/hour
- Propofol: 3 mg/kg/hour
- Ketamine 1.2 mg/kg/hour

The timing and nature of the third-line agent weans will be guided by the Clinical Standardization Guidelines for the study, and the clinical judgment of the investigator, and will always be primarily done in the best medical interests of the subject. Advice about weaning may be sought from the Clinical Standardization Team, a group of fellow investigators with experience of performing clinical trials in subjects with SRSE. The Clinical Standardization Team will be able to discuss EEGs in real time related to key study timepoints (terminal wean and the period after the end of the

blinded study drug infusion if the terminal wean was successful) in a timely manner in order to provide advice about compliance with the Clinical Standardization Guidelines.

The following guidance for weaning applies to all weans of third-line agents undertaken during the study. Continued determined efforts to liberate subjects from sedation must be undertaken for the entire duration of the blinded study drug infusion. Each failed wean from third-line agents should be followed by a 6-24 hour period of suppression and then another wean attempt, with further optimization of the AED regimen.

Weans include the qualifying wean (QW); the terminal wean (TW), which is the wean of the third-line agent if the subject is on only one third-line agent or the wean of the last third-line agent if the subject is on more than one third-line agent; the other weans (OW), which are the weans of the third-line agents other than the TW if the subject is on more than one third-line agent. The guidance also applies to additional weans (AW), which are the weans from third-line agents that take place after the TW for the first blinded study drug infusion or the second open-label study drug infusion.

### **QW Guidance**

- Wean to be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace that third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Investigators should allow 24 hours to lapse after the end of a “successful” qualifying wean before finally declaring the QW a success. If a third-line agent needs to be re-instituted within that 24 hours, the QW is a failure, and the subject may then be randomized in the study.

### **OW Guidance**

- First OW should not begin before H49 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- If the subject is on two third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the TW. However the OW may be completed over a shorter or longer time period and may overlap if clinically indicated with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- If the subject is on three third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the wean of the second agent. The second agent should be weaned over 24 hours and that wean completed before starting the TW. However the OWs may be completed over a shorter or longer time period and may overlap if clinically indicated with each other and with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the



dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.

- All OWs should be completed before H96 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **TW Guidance**

- The TW is defined as the wean of the last third-line agent.
- If the subject is on one third-line agent, the TW should not begin before H49 and should begin no later than H97 after starting administration of study drug or starting the open-label infusion of SAGE-547. If the subject has had one or more OWs, the TW should ideally begin as soon as the last OW is complete but in any case not later than H97 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- The TW must be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace this third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Every effort must be made to complete the TW before H120 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547, but the TW must be complete before H144 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **AW Guidance**

- AWs will take place when medically indicated in the opinion of the investigator.
- Ideally the AW should take place over 24 hours, but completion may be over a shorter or longer time period than this. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.

#### **11.1.1.2. EEG**

Electroencephalographs (EEGs) that are representative of the intermittent or continuous EEG being used to support key investigator decisions will be collected at the following time points:

- A 24-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst or seizure suppression for the second path to eligibility, and a variable pattern for the third path to eligibility. This EEG also aims to capture the burst or seizure suppression pattern during the 24 hours that precede the QW. . If the CEEG does not capture the 24 hours that precede the QW, additional EEG data collected as standard of care prior to the CEEG and prior to the

QW may be collected to assess the depth of burst or seizure suppression in the 24 hour period prior to the QW.

- EEG will be performed to cover the qualifying wean (QWEEG). EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for up to 24 hours after the end of the QW. The duration of the QWEEG will be up to 48.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s), the decision to re-institute a third-line agent(s) at doses intended to induce burst or seizure suppression, and the decision that the QW is a success.
- EEG will be performed from three hours prior to the start of the blinded infusion to 12 hours after the start of the blinded infusion. This will be called the BIEEG. The intent of this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG and to assess the depth of burst suppression in the first 12 hours of blinded study drug infusion.
- EEG will be performed to cover the final or terminal wean of third-line agent (TWEEG). The TW is the wean of the final third-line agent during the blinded administration of study drug or the open-label infusion of SAGE-547; if the subject was on one third-line agent, the TW is the wean of that agent. If the subject was on three third-line agents, the TW is the wean of the third and final agent. EEG recording will start 30 minutes prior to the start of the TW, continue for up to 24 hours during the TW, and then continue for the one hour after the end of the TW. The duration of the TWEEG will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the final third-line agent or the decision to re-institute a third-line agent at doses intended to induce burst or seizure suppression because any seizure activity could not be managed using intermittent bolus doses of AEDs.
- EEG will be performed during the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 (TAEED). The TAEED is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the start of the taper (at Hour 119.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours during the taper, and then continue for the one hour after the end of the taper (to Hour 145 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547). The duration of the TAEED will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst or seizure suppression because any seizure activity seen during the taper could not be managed using intermittent bolus doses of AEDs.
- EEG will be obtained to cover the end of the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 and the ensuing 24-hour period, during which the primary endpoint is assessed (PAEED). The PAEED is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the end of taper (at Hour 143.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours after the end of the blinded administration of study treatment or the open-label infusion of SAGE-547, and then continue for the one hour after the end of the 24-hour assessment period (to Hour 169 after starting the blinded administration of study

treatment or after starting the open-label infusion of SAGE-547). The duration of the PAEEG will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst or seizure suppression because any seizure activity seen in the 24 hours following the end of the blinded administration of study treatment or the open-label infusion of SAGE-547 that could not be managed using intermittent bolus doses of AEDs.

In practice, most subjects are on continuous EEG monitoring or long periods of intermittent EEG monitoring. However, this protocol does not mandate continuous EEG monitoring and breaks from EEG monitoring to provide relief to the scalp from the irritating effects of the electrodes are advised, according to local practice. If a break in EEG monitoring is mandated by local practice guidelines at a time when one of the protocolled EEG segments is to be collected, the break in EEG monitoring will take precedence, with the reason for missing the EEG reading noted on the eCRF. The EEGs obtained for the study are therefore part of the existing EEG record rather than being obtained de-novo at each timepoint. For timepoints where there might be some ambiguity, such as the TWEEG, the final EEG record is that of the final attempt to wean the last third-line agent, even if earlier attempts to wean that agent took place. In some cases (the TAEED and PAEEG, for instance), the EEG records will overlap, but different cuts are taken to service the different EEG record requirements.

The electronic EEG file will be de-identified, the date and time of the start and stop of the EEG and the subject number will be attached to the file, and the study time point will be indicated (CEEG, QWEEG, BIEEG, TWEEG, TAEED, and PAEEG). The PI will indicate on the eCRF what the EEG shows, as follows:

- For the CEEG, the PI will describe the EEG pattern that determined which path to eligibility the subject was on.
- For the QWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure or success on the qualifying wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst or seizure suppression during the qualifying wean constitutes a failure); the QWEEG will extend to cover the 24 hours after the end of third line agents in order to confirm that the QW was a success.
- For the BIEEG, the PI will note the date and time of the start of the EEG and the pattern seen on the EEG.
- For the TWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure on the terminal wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst or seizure suppression during the terminal wean).
- For the TAEED, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst or seizure suppression before the end of the SAGE-547 infusion).
- For the PAEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary

endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst or seizure suppression in the 24 hours following the end of the SAGE-547 infusion).

A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm the depth of burst or seizure suppression prior to the QW and during the first 12 hours of the blinded study drug infusion, the PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period (average EEG power at the end of Visit 9 of more than two microvolts):

- All subjects will have the CEEG and QWEEG collected and stored, and the CEEG and QWEEG read;
- Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;
- Those subjects randomized who are not administered the open-label study drug will have the QWEEG, BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the BIEEG, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read;
- Those subjects randomized who later undergo the open-label infusion will have the QWEEG, BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion and the TWEEG, TAEED, and PAEEG related to the open-label study drug infusion collected and stored, and the BIEEG, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read.

All EEG records may be subject to quantitative EEG analysis.

### **11.1.2. Secondary Efficacy**

#### **11.1.2.1. Clinical Global Impression Scale (CGI)**

The clinical global impression scales are often utilized in clinical trials to allow clinicians to integrate several sources of information into a single rating of the subject's condition. Both the CGI-Severity (Question 1, CGI-S) and the CGI-Improvement (Question 2, CGI-I) employ a 7-point Likert scale measuring severity of the disease state in the subject and improvement, respectively. All severity assessments after initiation of SAGE-547 treatment should consider the general state of the subject over the preceding week. The third question on the scale will not be employed in this trial, and where the scale states "mental illness", this means "physical illness" in this trial.

The CGI-S will be evaluated at Visit 1 and at the last visit, Visit 12 or 12R. The CGI-I will be evaluated at Visit 12 or 12R.

#### **11.1.2.2. Epilepsy Status**

At Visit 1, the diagnosis of epilepsy will be documented as a no/yes question. If there was a previous diagnosis of epilepsy, further details will be documented, including:

- Date of diagnosis;
- Details of anti-epileptic drugs currently being taken;

- Type of epilepsy;
- Seizure frequency in the past month.

Information about the current (index) episode of status epilepticus will be obtained at Visit 1:

- Date of onset
- Date of failure to respond to first line agent(s) and the name(s) of the agent(s)
- Date of failure to respond to second line agent(s) and the name(s) of the agent(s)
- Any previous treatment with third line agents and the response to those agents (details of the third line agent drugs and previous wean attempts will be recorded on the Third Line Agent Medication CRF)
- The cause of the index episode of status epilepticus
- If the subject was transferred from another hospital or from within the hospital, the reason for the transfer will be recorded (such as for study enrollment, due to lack of medical options at original hospital or unit, due to lack of beds at the original hospital or unit, family request, other)

Previous (non-index) diagnosis of status epilepticus will be documented as a no/yes question. If SE did occur in the past 12 months, further information will be gathered, including:

- SE, RSE, or SRSE diagnosis, whichever was the most severe diagnosis for each episode;
- Cause;
- Treatment, including experimental treatments and need for intubation/ventilation;
- Dates of onset and duration.

At Visit 12 or Visit 12R, the following information will be gathered:

- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of SE up to and including Visit 12 or Visit 12R;
- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of seizures (convulsive and non-convulsive) up to and including Visit 12 or Visit 12R;
- Number of separate episodes of SE after H144 at the end of Visit 8 or Visit 8R (no/yes); if yes,
  - SE, RSE, or SRSE diagnosis;
  - Cause;
  - Treatment, including experimental treatments and need for intubation/ventilation;
  - Dates of onset and duration.

Note that a separate episode of SE is defined as an episode of SE separated from other periods of status epilepticus by at least 24 hours.

- Diagnosis of epilepsy since Visit 11 or Visit 11R will be documented as a no/yes question. If a diagnosis of epilepsy has been made, further details will be documented, including:

- Status as ongoing or new epilepsy since Visit 11 or Visit 11R after initiation of SAGE-547 treatment;
- Details of anti-epileptic drugs currently being taken;
- Type of epilepsy and seizure frequency in the past week.

## 11.2. Safety Assessments

The safety and tolerability of SAGE-547 will be assessed using adverse events, clinical laboratory measures, vital signs, ECG intervals and morphology, and mortality. All safety assessments should be performed per hospital standard of care and will be collected periodically throughout the study according to [Table 1](#), [Table 2](#), and [Table 3](#) (Schedules of Assessments).

### 11.2.1. Adverse Events

AEs will be collected after informed consent has been signed and prior to study-specific screening procedures not considered standard of care, during subject preparation for SAGE-547 administration and through Visit 12 or Visit 12R. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™) coding system (current version). See [Section 14](#) for additional details.

### 11.2.2. Clinical Laboratory Tests

Blood samples will be taken for hematology, and serum chemistry and GFR will be calculated at:

- Visit 1 and then at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.
- Blood samples will be taken at Visit 11 or Visit 11R for serum chemistry (renal panel only).

Urine samples (20 ml) will be taken for urinalysis and urine NAG analysis at:

- Visit 1 and at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.

These samples will be analyzed at a central laboratory; hour-to-hour medical decisions will be based on sampling for laboratory testing done outside the protocol as part of normal standard of care. GFR will be calculated by the central laboratory.

Any out-of-range values will be flagged by the laboratory; the investigator will add a comment about whether the abnormality is clinically significant. Clinical significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

#### 11.2.2.1. Hematology and Serum Chemistry

Hematology will include complete blood count (CBC) white blood cell count with differential, platelet count and red blood cell (RBC) count, hemoglobin and hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatine kinase,

lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose. In addition triglycerides will be measured in serum chemistry samples (to aid assessment of lipemia in pharmacokinetic samples).

#### **11.2.2.2. Pregnancy Test**

Females of child-bearing potential will be tested for pregnancy by serum pregnancy test at Visit 1. In this study, since an accurate history of menstruation in girls and menopause in older women may not be available at Visit 1, “child-bearing potential” is taken to mean any female aged 18 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy. Female subjects with a positive pregnancy test will be ineligible for study participation.

#### **11.2.2.3. Urinalysis**

Urinalysis will include assessment of protein, blood, leukocytes, glucose, ketones, urobilinogen, pH, and specific gravity.

#### **11.2.3. Vital Signs**

Blood pressure, heart rate, and temperature will be recorded at the following time points relative to the first infusion of study drug, and to the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547:

- Visit 1;
- At 0, +30, +60 minutes (+/-15 minutes) and +2, +4 and +8 hours (+/- 30 minutes) after the start of the infusion;
- At +24, +48, +72, +96, +120, +144, +168, and +192 hours (+/- 2 hours) after the start of the infusion.

#### **11.2.4. Weight and Height**

Weight and height will be measured at Visit 1. Weight will also be obtained at V2, within the eight hour window that follows the declaration of the QW failure and prior to the initiation of the blinded infusion loading dose at H0 of V3, and will be used to calculate the infusion rates throughout the entire blinded treatment course. If a subject qualifies for open-label study drug, the infusion rates for the open-label infusion will be calculated using the subject’s weight measured prior to dosing during V10.

If it is not possible to obtain the actual weight at the above-referenced timepoints, permission from the Clinical Monitor must be obtained to use another method to obtain the subject’s weight (such as information from the LAR or estimating using an established local protocol).

In addition, a daily weight will be obtained and recorded if this is easily obtained, such as the use of a scale bed.

#### **11.2.5. ECG**

For the first 50 subjects randomized in the study, 12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours. If it is not possible to

perform ECG immediately after the collection of PK samples up to 160 hours, ECG must be performed within 15 minutes prior to the collection of PK samples up to 160 hours; at other times the allowed time window for ECGs is +/- 2 hours:

- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +128, +136, +144, +152, +160, and +192 hours after the start of the blinded (first) study drug infusion
- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +126, +132, +138, +144, +152, +160, and +192 hours after the start of the open-label (second) study drug

The heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm.

For the subsequent subjects randomized in the study, the following timepoints for ECG will be used:

- pre-dose and at +1, +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the blinded (first) study drug infusion
- pre-dose and at +1, +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the open-label (second) study drug infusion

It is not necessary to collect these ECGs with the PK samples at these timepoints and, apart from the +1h ECG, there is +/- 2 hour time window for these ECGs.

#### **11.2.6. Mortality**

Mortality will be recorded on the Visit 12 or Visit 12R case report form. If the subject has died, the following information will be collected:

- Date of death;
- Cause of death.

As accurate as possible cause of death will be collected, which will be further categorized as due to one of the following causes:

- SE;
- complications of long term intubation and third-line agent infusions;
- underlying cause of qualifying SE;
- co-morbidity existing at the time of the qualifying SE;
- new co-morbidity or trauma;
- study drug;
- other (specify).

#### **11.2.7. Pharmacogenetic Samples**

If a subject's LAR consents to pharmacogenetic sampling, a blood sample for genetic research will be collected at Visit 1 in order to avoid the possible introduction of bias through the exclusion of patients who may withdraw from study due to an AE (a subject population that may be of specific interest for subsequent genetic analysis). If for any reason a sample cannot be taken prior to treatment, a sample can be drawn at any point prior to completion with the restriction that no more than one genetic sample be taken per subject.



The objective of this research is to collect and store blood samples for possible DNA extraction and exploratory research into how genes or specific genetic variation may influence response (i.e. distribution, safety, tolerability, and efficacy) to SAGE-547. Specific genetic variations of interest include but are not limited to: classes of metabolizing enzymes (e.g. Cytochrome P450 supra-family genes), genes encoding enzymes involved in the production and metabolism of allopregnanolone (e.g. AKR1C4 (3 $\alpha$ -hydroxysteroid dehydrogenase)), genes associated with the GABA receptor (e.g. GABRA1-A6, GABRB1-B3, GABRD, GABRE, GABRG1-3) and genes associated with the production and degradation of GABA.

Future research may suggest other genes or gene categories as candidates for influencing not only response to SAGE-547 but also susceptibility to disorders for which SAGE-547 is being evaluated. Thus, the genetic research may involve study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.

#### **11.2.7.1. Biological Sampling and Coding Procedures (Pharmacogenetics)**

To ensure patient confidentiality, utmost care will be taken in the coding and storage of pharmacogenetic samples.

*Extraction and coding:* DNA will be extracted from the blood sample and the DNA sample will be assigned a unique number replacing information from sampling tube. The assigned DNA number will be used to identify the sample and its corresponding information within Sage Therapeutics or at any designated contract laboratory for the purpose of sequencing of other DNA specific analysis. No personal details sufficient for individual identification will be available to any person (internal or external to Sage Therapeutics) working with the DNA.

*Genotype/Phenotype Analysis:* Samples and data from genetic analysis will be coded. The link between subject enrollment / randomization code and DNA number will be maintained and stored in a secure environment with restricted access. The established link will be used to identify relevant DNA samples for analysis, facilitated correlation of genotype results with clinical data, allow regulatory audit, and to trace samples for destruction in case of withdrawal of consent.

#### **11.2.7.2. Retention of Biological Samples for Pharmacogenetic Analysis**

Extracted DNA is a finite research that is destroyed in the process of being analyzed. Primary blood samples from which DNA can be extracted will be stored and used until no further analyses are possible, a maximum storage period of 25 years from time of last subject last visit has been reached, or an individual or LAR withdraws his/her or their consent.

### **11.2.8. Other Outcomes**

#### **11.2.8.1. Pharmacokinetic Data**

Formal plasma analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS)). In addition, all samples will be analyzed for important SAGE-547 metabolites (if and when these are identified) and Captisol<sup>®</sup> concentrations.

#### Plasma Analysis

Plasma will be collected to assay for SAGE-547 concentrations at the following time points relative to the start of each infusion of study drug:

- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion.
- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open-label SAGE-547 study drug infusion.
- All samples will also be analyzed for plasma concentrations of important metabolites of SAGE-547 if and when these are identified.
- All samples from the first 50 subjects randomized will also be analyzed for plasma concentrations of Captisol®.

The plasma samples will be drawn from the arm contralateral to that used for drug administration. Drawing samples from peripheral arterial or venous lines or from a central line is permissible. PK collection times should be adhered to as strictly as possible. The allowed time window for all samples is: pre-dose in the two hours prior to starting the infusion of study drug; samples up to and including 1h, +/- 5 minutes; subsequent samples, +/- 15 minutes. Subject-specific PK kits for sampling including instructions on collection and processing methods, and storage and shipping conditions, will be provided separately. To maintain the blind, all subjects will have samples taken as outlined above: subjects receiving SAGE-547 will have all samples analyzed for all analytes. Subjects on placebo may have samples analyzed to investigate endogenous allopregnanolone and metabolite concentrations, as well as Captisol® concentrations; experience with the plasma concentration data will determine if and which placebo samples are analyzed.

Each blood sample will be 3 ml in volume for subjects weighing 30 kg or more, and 1 ml in volume for subjects weighing less than 30 kg. Separate aliquots will be obtained from each sample to service the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum blood draw for PK analysis for a subject having two infusions of study drug will be 99 ml (33 ml for subjects weighing less than 30 kg).

Plasma PK parameters for SAGE-547 will be calculated where appropriate (e.g.,  $C_{max}$ ,  $C_{min}$ ,  $t_{max}$ ,  $AUC_{last}$ ,  $AUC_{\infty}$ ,  $CL_s$ ). In addition, similar PK parameters will be calculated for Captisol®. PK parameters for important metabolites of SAGE-547 may be calculated. An evaluation will be made of the feasibility of adopting a population-PK approach to assess drug-drug-interactions with SAGE-547 as victim of AEDs.

In addition, the Visit 9 sample may be analyzed for plasma concentrations of third-line agents.

#### Other Analysis

If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations. The minimum volume of cerebrospinal fluid for analysis is 100 microlitres.

Full details of all pharmacokinetic analyses will be described in the Pharmacokinetic Analysis Plan.

**11.2.8.2. Correlation of QT/QTc Changes and Plasma Concentrations of SAGE-547**

An analysis will be performed to determine whether there is any correlation between changes in QT/QTc interval and plasma concentrations of SAGE-547, in order to investigate any effect that SAGE-547 may have on QT/QTc interval.

**11.2.8.3. Pharmacoeconomic Data**

At Visit 12 or Visit 12R, the following information will be collected: number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital. If the subject dies before Visit 12 or Visit 12R, data will be collected up to the date of death. The definition of “hospital” is the institution that the subject was initially treated in. If the subject is transferred to another hospital, that hospital would be the “discharge destination from the hospital” and the “number of days in hospital” would be the number of days in the initial treating hospital.

For those subjects discharged from hospital before Visit 12/12R, the following questions will be asked:

- On what study day was the subject discharged from hospital?
- What type of facility was the subject discharged to (another hospital, a rehabilitation center, a supported care facility, home, other)?
- How many days did the subject stay in this facility?

The following questions will be answered regarding the stay in the ICU and hospital:

- Was the subject still in the ICU at the end of Visit 10/10R?
- If the FOUR Score was  $\geq 12$  at Visit 10/10R and the subject was in the ICU at Visit 10/10R, what was the reason for the subject not being discharged from the ICU (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, other)?
- Was the subject still an in-patient in the hospital at the end of Visit 12/12R?
- If the FOUR Score was  $\geq 15$  at Visit 12/12R and the subject was in the hospital at Visit 12/12R, what was the reason for the subject not being discharged from the hospital (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, unsuitable home circumstances, other)?

**11.2.8.4. STESS**

The STESS will be assessed during Visit 1 in order to assess the severity of the status epilepticus.

**11.2.8.5. FOUR Score**

The Full Outline of UnResponsiveness or FOUR Score is designed to assess conscious level and unlike other scores, is suitable for subjects who are intubated. It assesses four domains of neurological function (eye responses, motor responses, brainstem reflexes, and breathing pattern).

The FOUR Score will be collected at the following time points relative to each infusion of study drug (the initial blinded infusion and the second open-label infusion if this is administered):

- baseline, +24, +48, +72, +96, +120, +144, +168, and +192 hours (all +/- 2 hours) after the start of the infusion, and at Visit 11/11R and Visit 12/12R.

#### **11.2.8.6. Glasgow Outcome Scale (GOS)**

The GOS is a relatively common assessment scale used to standardize descriptions of the objective degree of recovery from brain injury such as cerebral trauma, or in this case SRSE. It was first used in 1975 ([Jennett and Bond 1975](#)) and allows a prediction of the long-term course of rehabilitation to return to work and everyday life. The scale classifies subjects into 5 groups:

- Death
- Persistent vegetative state
- Severe disability
- Moderate disability
- Good recovery

The GOS will be assessed at Visit 12 or Visit 12R.

#### **11.2.8.7. Supervision Rating Scale (SRS)**

The Supervision Rating (SRS) measures the level of supervision that a patient/subject receives from caregivers. The SRS rates level of supervision on a 13-point ordinal scale that can optionally be grouped into five ranked categories (Independent, Overnight Supervision, Part-Time Supervision, Full-Time Indirect Supervision, and Full-Time Direct Supervision). The SRS was designed to be rated by a clinician based on interviews with the subject and an informant who has observed at first hand the level of supervision received by the subject ([Boake 2000](#)). Scoring is a one-step procedure in which the clinician assigns the rating that is closest to the subject's level. Ratings are based on the level of supervision received, not on how much supervision a subject is judged or predicted to need.

The SRS will be assessed at Visit 1 and Visit 12 or Visit 12R. The Visit 1 assessment will be a retrospective assessment of the supervision required by the subject immediately prior to the admission that included the index episode of status epilepticus.

#### **11.2.8.8. Modified Rankin Scale – 9Q (mRS-9Q)**

The Modified Rankin Scale (mRS) is a commonly used scale to determine disability and functional dependence due to neurological insult such as stroke in adults. The 7-point scale (0 – 6) denotes functional capacity from no symptoms (0) to severe disability (5) and death (6). The Modified Rankin Scale – 9Q is a shortened version consisting of 9 questions that reliably determines the mRS score and was developed to both simplify the assessment and expand the rater base to non- medically trained personnel ([Patel, Rao et al. 2012](#)). The assessment is a web-based tool in the public domain with automatic score calculation and error checking found at [www.modifiedrankin.com](http://www.modifiedrankin.com).

The mRS will be assessed at Visit 1 and at Visit 12 or Visit 12R. The baseline assessment will be a retrospective assessment of the disability and dependence of the subject immediately prior to the admission that included the index episode of status epilepticus.

## 12. STUDY PROCEDURES

The study procedures listed below by study day reflect the required data collection times for this protocol. When a time window is necessary, this is specified below. If no time window is specified, the test may be performed at any time within the specified 24-hour period.

### 12.1. Visit 1 (V2-≤30h)

The baseline period will be up to approximately 84 hours prior to starting blinded study treatment and should include the assessments/procedures listed below and summarized in [Table 1 and Table 2 \(for open-label treatment\)](#), the Schedules of Events.

- Informed consent
- Eligibility checklist
- Verification of inclusion/exclusion criteria.
- Demographic information and medical history obtained by proxy and confirmed by the subject when possible.
- SE and wean history
- Blood will be collected from female subjects 18 years to 55 years for a serum pregnancy test unless they are known to be pre-menstrual or post-menopausal or to have had a hysterectomy.
- Blood and urine samples collected for clinical laboratory testing.
- Pharmacogenetic sample will be collected from consenting/eligible subjects.
- Vital signs
- Height
- Weight
- An ECG reading taken.
- Administration of the STESS.
- Administration of the FOUR Score.
- Administration of SRS.
- Administration of the mRS-9Q assessment.
- Assessment of the CGI scale.
- Evaluation of epilepsy status.
- Administration of continuous IV third-line agents.
- Perform EEG.
- Recording of adverse events.
- Recording of previous and concomitant anti-epileptic drugs.
- Recording of previous and concomitant third-line agents.
- Recording of concomitant pressors.

- Recording of other concomitant medications, procedures, and treatments.

## **12.2. Visit 2 (V3-≤54h)**

- Recording of adverse events.
- Recording of concomitant anti-epileptic drugs.
- Recording of concomitant third-line agents.
- Recording of concomitant pressors.
- Recording of other concomitant medications, procedures, and treatments.
- Wean of continuous third-line agent (QW):
  - If wean is successful, subject is followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (these subjects are Qualifying Wean Success subjects or QWS subjects);
  - If wean is not successful, there is ongoing intravenous administration of at least one continuous IV third-line agent and EEG is performed and the subject is randomized.
- Weight
  - Subject weight will be obtained within the eight-hour period from the declaration of failure of QW and prior to the initiation of the blinded infusion loading dose at H0 of V3. This weight will be the dosing weight used to determine the infusion rate for the entire blinded infusion treatment course.

## **12.3. SAGE-547 Treatment Period**

### **12.3.1. Visit 3/3R (0-24 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs will be recorded at:
  - 0, +30, +60 minutes (+/-15 minutes) and +2, +4, +8 (+/- 30 minutes) and +24 hours (+/- 2 hours) after the start of the infusion
- For the first 50 subjects randomized in the study, ECG readings will be recorded immediately after PK sampling, or within 15 minutes prior to PK sampling, at the following time points:
  - 0 (pre-dose) and at +0.5, +1, +3, +6, +12, and +24 hours after the start of the blinded study drug infusion.
  - Subsequent subjects randomized in the study will have ECG readings recorded at 0 (pre-dose) and +1, +12, and +24 hours after the start of the study drug infusion, it will not be necessary to collect these ECGs with PK samples at these timepoints and, apart from the +1 h ECG, there is +/- 2 hour time window for these ECGs
- A blood sample for PK analysis should be collected at the following time points (all +/- 15 minutes except where otherwise stated):

0 (pre-dose, within two hours of the start of the infusion) and at +0.5, +1 (+/- 5 minutes), +3, +6, +12, and +24 hours after the start of the study drug infusion.

- Completion of the FOUR Score
  - +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the final declaration of QW success)
- Ongoing intravenous administration of a continuous IV third-line agent.
- Study drug administration in loading (Hour 0-1) and maintenance infusions (at completion of Hour 1).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.2. Visit 4/4R (25-48 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +48 hours (+/- 2 hours) after the start of the infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +48 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +48 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +48 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +48 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent.
- Ongoing study drug maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.3. Visit 5/5R (49-72 hours)**

- Weight if easily obtained

- Vital signs should be recorded at:
  - +72 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +72 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +72 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +72 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +72 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.4. Visit 6/6R (73-96 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +96 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +96 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +96 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +96 hours (+/- 15 minutes) after the start of study drug infusion.



- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +96 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Perform EEG.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.5. Visit 7/7R (97-120 hours)**

- Weight if easily obtained
- Vital signs should be recorded at:
  - +120 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +120 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +120 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +120 hours (+/- 15 minutes) after the start of study drug infusion, immediately prior to the end of the maintenance infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +120 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled. Complete wean by 120 hours if at all possible.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## 12.4. SAGE-547 Taper Period

### 12.4.1. Visit 8/8R (121-144 hours)

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +144 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after each PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +128, +136 hours and +144 hours after the start of the blinded study drug infusion
  - +126, +132, +138 hours and +144 hours after the start of the open-label study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +144 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected (+/- 15 minutes unless otherwise stated):
  - +128 (immediately prior to the end of the first taper step), +136 hours (+/- 5 minutes, immediately prior to the end of the second taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of study drug infusion.
  - During the open-label study drug phase of the study PK blood draws at: +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 hours (+/- 5 minutes, immediately prior to the end of the third taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of the study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +144 hours (+/- 2 hours) after the start of the infusion
- Complete wean of third line agents by H144 if not completed by H120.
- Perform EEG.
- Taper of SAGE-547 infusion begins at hour 121.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## **12.5. Follow-up Period**

### **12.5.1. Visit 9/9R (145-168 hours)**

- Vital signs should be recorded at:
  - +168 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +152, +160 hours (+/- 2 hours) after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +152 and +160 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +168 hours (+/- 2 hours) after the start of the infusion
- Perform EEG.
- Assessment of the presence of physiologic brain activity using EEG.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.5.2. Visit 10/10R (169-192 hours)**

- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +192 hours (+/- 2 hours) after the start of the infusion
- At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine eligibility for the open-label treatment with the higher dose of study drug. This determination may occur at any point during Visit 10: the higher dose open-label infusion must begin within the Visit 10 window. All patients receiving the higher dose open-label treatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.
- Weight if the subject qualifies for the open-label study drug (Visit 10 only, not Visit 10R).
- Recording of adverse events (QWS subjects also).

- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.3. Visit 11/11R (Visit 3/3R + 14d (±2))**

- Blood samples collected for clinical laboratory testing (renal panel only).
- Completion of the FOUR Score (QWS subjects also).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.4. Visit 12/12R (Visit 3/3R + 21d (±2))**

All assessments also performed for QWS subjects.

- Completion of the FOUR Score.
- Administration of the GOS.
- Administration of the SRS.
- Administration of the mRS-9Q assessment.
- Evaluation of epilepsy status (see [Section 11.1.2.2](#) for details).
- Assessment of the CGI Scale.
- Recording of adverse events.
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications.
- Collection of pharmacoeconomic data.
- Mortality will be assessed throughout the study period.

## **13. STATISTICS**

### **13.1. Statistical Plan**

Complete details for the analysis and reporting of data from this study will be contained in the Statistical Analysis Plan (SAP).

#### **13.1.1. Interim Analysis**

When approximately 50% of subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### 13.1.2. Study Populations

The **Safety Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to actual treatment. This analysis population will be used for all safety analyses.

The **Intent to Treat Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to randomized treatment. This analysis population will be used for all efficacy analyses.

The **Modified Intent to Treat Population** is defined as all subjects who:

1. complete their initial course of blinded SAGE-547 or placebo treatment unless the non-completion was due a drug-related adverse event; and
2. have at least one attempt to wean from third-line agents prior to the end of blinded study treatment infusion unless the failure to wean was because seizures were not controlled.

Subjects will be classified according to randomized treatment. This analysis population will be used for sensitivity analyses of the primary endpoint and select secondary efficacy endpoints.

Narratives will be prepared for all subjects who do not complete the infusion of blinded study medication or were not subjected to any wean attempts. Narratives will include details of the cause of SE, the comorbid conditions, the adverse event(s), and reasons for non-completion of the infusion or failure to attempt weaning. This blinded narrative will be reviewed by the medical monitors and the patient adjudicated as MITT eligible or ineligible. Acceptable reasons for defining a subject as MITT ineligible include death or withdrawal of consent due to progression of the underlying cause of SE or comorbid conditions, unless the cause of death or progression of disease were thought by the investigator, sponsor, or DSMB to be related to study drug.

The **Per-Protocol (PP) Population** is defined as a subset of the MITT population but will exclude data from all subjects with significant protocol violations or deviations. Subjects will be classified according to actual treatment received. This data set will be used for sensitivity analyses to examine the robustness of results for the primary and key secondary efficacy endpoints.

The **Pharmacokinetics Population** is defined as all subjects who at least had an infusion of blinded SAGE-547 initiated and have at least one pharmacokinetic sample collected.

The **Pharmacogenetic Population** is defined all subjects who consent to being included in the pharmacogenetic assessment and provide a pharmacogenetic sample.

Summary statistics of all data collected will be presented for subjects who were QW successes.

### 13.1.3. General Aspects

Tabular displays of descriptive statistics will be provided for all variables. Summary tables will include n, mean, mean, standard deviation, minimum and maximum for continuous variable and frequency and percentage for categorical variables.

### 13.1.4. Analysis of Primary Endpoint

The analysis of response to treatment (see Section 11.1.1 for definition of primary endpoint) between SAGE-547 treated subjects and placebo treated subjects will be performed on the ITT population using a Cochran-Mantel-Haenszel (CMH) test with variables for treatment, concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior

to randomization (one vs two or more). The CMH general association statistic and its associated p-value will be presented. The comparison of treatment response rates will be conducted at the 5% level of significance. To confirm the CMH results, a permutation test will also be conducted.

An additional analysis of the primary endpoint will also be performed on the MITT population. In addition sensitivity analyses of the primary endpoint will be performed using the ITT population based on:

- the number of third-line agents (one, two, or three) subjects were administered post-randomization; and
- which third line agent was the subject of the first TW.

### **13.1.5. Analysis of Secondary Efficacy Endpoints**

Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section (Section 6). Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. The analysis of the secondary endpoints will also be performed on the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

### **13.1.6. Analysis of Other Endpoints**

Safety and “Other” endpoints will only be summarized by treatment group.

Summaries of safety endpoints will be based on the overall Safety Population.

### **13.1.7. Epilepsy and SRSE Status**

Diagnosis of epilepsy and recurrence of RSE or SRSE will be documented as the percentage of subjects by time point and overall. Kaplan-Meier curves may be plotted if sufficient data are available.

Utilization of AEDs during follow-up and during recurrence will be summarized.

### **13.1.8. Questionnaires**

The data collected from each questionnaire will be interpreted according to the standard methodology for that questionnaire. There will be no adjustment for missing values.

### **13.1.9. Pharmacokinetic Data Analysis**

Details of the pharmacokinetic data analysis will be described in detail in a separate Pharmacokinetic Analysis Plan.

### **13.1.10. Pharmacogenetic Data Analysis**

Any genotype data generated in this study will be stored within a secured database within Sage Therapeutics and / or a third party contracted to work with Sage Therapeutics to analyze the samples. Because the number of subjects agreeing to participate in the genetic research component of the study is unknown, it is not possible to establish, a priori, whether sufficient samples will be obtained to support formal statistical evaluation of data. As a consequence a Pharmacogenetic Analysis Plan will only be prepared where appropriate and the results obtained from any genetic research will be reported in a report separate from the main study CSR.

### **13.1.11. Open-Label Study Drug Subjects**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are treated with SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo.

### **13.1.12. EEG-Responders**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who are classified as EEG-responders/non-responders based on the independent assessment of the PAEEG. Summaries will be derived for the two randomized treatment groups.

### **13.1.13. QT/QTc Assessment**

An analysis of the correlation between changes in QT/QTc intervals and SAGE-547 plasma levels will be performed to investigate if there is a potential effect that SAGE-547 may have on QT/QTc interval. A detailed description of the QT/QTc assessment will be included in the SAP.

### **13.1.14. Quantitative EEG**

The nine EEG records for each subject may be subjected to exploratory quantitative EEG analysis, the details of which will be included in the EEG Analysis Plan. In summary the following comparisons may be made, SAGE-547 versus placebo: the QWEEG versus the TWEEG (main analysis); the CEEG versus PAEEG (subsidiary analysis); and TAEEG versus PAEEG (exploratory analysis).

## **13.2. Determination of Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between treatment groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

### **13.3. Statistical Analysis Plan**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.



## **14. ADVERSE EVENTS**

The safety procedures in this study will be detailed in a Safety Management Plan, which will be agreed and signed before the first subject is randomized in the study. [Section 14.1](#) summarizes Investigator responsibilities regarding the identification and documentation of AEs, the classification of AEs for relationship to study drug and severity, and the reporting of AE information to the Sponsor and the IRB.

[Section 14.2](#) summarizes Sponsor/Medical Monitor Responsibilities regarding monitoring of AE data and reporting relevant safety information to FDA.

[Section 14.3](#) lists important AE definitions.

### **14.1. Investigator Responsibilities**

#### **14.1.1. Identification and Documentation of Adverse Events by Investigator**

Subjects will be evaluated and questioned generally (if possible) to identify AEs during the course of the study. AEs will be collected from the signature of the consent form through Visit 12/12R. Adverse events that occur prior to completion of screening will be captured on the Medical History eCRF. Adverse events that occur after completion of screening will be recorded on the Adverse Event eCRF.

All AEs revealed by observation, other diagnostic procedures, or spontaneously reported by the subject and/or in response to an open question from study personnel will be recorded on the Adverse Event Form. Any clinically significant deterioration in laboratory assessments or other clinical findings are considered an AE and must be recorded on the Adverse Event Form, unless otherwise stated. AE information recorded will be entered into the database on an ongoing basis.

AEs with a relationship considered related to study drug (probable, possible) should be followed until the event is resolved or the Investigator determines the event is stable or no longer clinically significant. AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

For SAEs, an electronic Serious Adverse Event eCRF must be completed with as much information as possible and submitted in the time frame described below in [Section 14.1.3](#). When new significant information is obtained as well as when the outcome of an event is known, the electronic SAE eCRF should be updated within 24 hours. If the subject was an outpatient at the time of the SAE and was re-hospitalized due to the SAE, a copy of relevant hospital records (e.g., admission report, laboratory test results, discharge summary, etc.) may be requested to be included as part of the subject medical file.

All SAEs will be followed until resolved or until a stable status has been achieved.

**14.1.2. Adverse Event Classification****14.1.2.1. Relationship to Investigational Drug**

None:	No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state.
Possible:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject, but this is not known for sure.
Probable:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

**14.1.2.2. Severity**

Mild	Discomfort noticed, but no disruption to daily activity.  For subjects that are unconscious, this may be a slight or minor change in a lab result or clinical sign or symptom that does not require immediate corrective action.
Moderate	Discomfort sufficient to reduce or affect normal daily activity, but is not hazardous to health; prescription drug therapy may be employed to treat the AE.  For subjects that are unconscious, this may be a clinically meaningful change that may require immediate corrective action.
Severe	Inability to work or perform normal daily activity and represented a definite hazard to health; prescription drug therapy and/or hospitalization may be employed to treat the AE.  For unconscious subjects, this may be a significant clinical change that requires immediate corrective action.

**14.1.2.3. Action Taken with Investigational Drug**

None	Study medication was continued without change.
Discontinued	Study medication was terminated.
Dose adjusted	Study medication dose/infusion rate was changed and then continued per protocol.
Interrupted	Study medication was interrupted and then continued per protocol.
Unknown	The action taken with regard to study medication is unknown.
Not applicable	Administration of study medication was not ongoing.

**14.1.2.4. Assessment of Outcome**

Ongoing	At the end of the study, the event has not resolved or stabilized.
Ongoing and stable	The event is ongoing but has stabilized and is unlikely to change
Resolved	The event has resolved or the subject recovered without sequelae.
Resolved with sequelae	The event has at least one secondary outcome that may result in permanent disability and/or functional limitation.
Unknown	The status of the event is unknown.
Death	The subject has expired.

**14.1.3. Investigator Reporting to Sponsor and Sponsor Emergency Contact**

All new SAEs that come to the Investigator and/or Sponsor's notice during the course of the study (up to and including the last study visit) must be reported by the Investigator on the designated electronic report form within 24 hours of the point in time when the Investigator becomes aware of the SAE. As additional information becomes available, the designated electronic report form must be updated within 24 hours.

Investigators must report any SAE, whether or not considered drug related. The report must include an assessment of whether there is a reasonable possibility that the drug caused the event.

In a medical emergency (ie, an event that requires immediate attention regarding the treatment of a subject, operation of the clinical study, and/or the use of investigational drug), study site staff will apply appropriate medical intervention according to current standards of care, and contact the Medical Monitor.

**14.1.4. Medical Monitor and Emergency Contact Information**

[REDACTED], MD  
[REDACTED]

In a study related medical emergency situation, when the assigned Medical Monitor cannot be reached by a caller, an on-call Physician can be reached 24 hours per day, 7 days per week via an [REDACTED] Call-Center:

- Telephone: [REDACTED]  
(this is a chargeable telephone number allowing a global reach from both landlines and mobile phones)

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On this internet page a list of country-specific toll-free telephone numbers is provided. It should be noted that not all countries globally have access to toll-free numbers as indicated on the “24/7 Medical Help desk” index. Countries without toll-free numbers need to dial the chargeable number as indicated above. Furthermore, toll-free numbers are not available from mobile phones.

#### **14.1.5. SAE Reporting Contact Information**

Contact information and reporting instructions are provided in the Safety Management Plan.

#### **14.1.6. Reporting to Institutional Review Boards (IRBs)**

It is the responsibility of the Investigator to promptly notify the institution’s IRB of all serious and unexpected suspected adverse reactions (see [Section 14.3](#) for definitions).

### **14.2. Sponsor/Medical Monitor Responsibilities**

#### **14.2.1. Monitoring of Adverse Event Data**

The Medical Monitor will review any newly reported adverse events in an ongoing basis. If the aggregate assessment indicates that an event is occurring more frequently than would normally be expected in this population, or as previously observed, and the sponsor believes that the events are causally related to the administration of SAGE-547, the Sponsor will then report that information in an IND safety report.

#### **14.2.2. Data Safety Monitoring Board**

An independent DSMB will monitor the clinical, PK and PD data for safety signals throughout the study and will be asked to assess the placebo response rate at the time of the interim analysis to determine final sample size. In order to perform their monitoring function the DSMB will have access to un-blinded safety data as necessary.

The composition and procedures for the board will be described in a separate DSMB Charter.

#### **14.2.3. Reporting to FDA**

The Sponsor must report in an IND safety report any suspected adverse reaction to study treatment that is both serious and unexpected (21 CFR 312.32(c)(1)(i)). Before submitting an IND safety report, the Sponsor will ensure the event meets all three of the definitions: (1) suspected adverse reaction, (2) serious, (3) unexpected. If the AE does not meet all three of the definitions, it should not be submitted as an IND safety report. The Sponsor should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the adverse event and, therefore, that the event meets the definition of a suspected adverse reaction.

If there is a serious and unexpected suspected adverse reaction, the Sponsor will notify the appropriate regulatory agency(ies) and all appropriate parties on an expedited basis. In addition, Sponsors must submit expedited reports of an increased rate of occurrence or severity of serious suspected adverse reactions over that listed in the protocol or Investigational Brochure.

SUSARs will be unblinded prior to reporting to FDA. Unless it is necessary to unblind for the safety of the patient, the investigator will not be informed of the unblinding of the subject.

Under 21 CFR 312.32, Sponsors should identify in the protocol SAEs that it does not plan to report individually in an expedited manner, because they are known consequences of the disease or otherwise common in the study population. Given the grave condition and prognosis of SRSE being studied, individual occurrences of seizures or seizure activity will not be reported expeditiously in this study. Regardless of which events are reported in an expedited manner, all adverse events will be closely monitored throughout the study.

#### **14.2.4. Reporting to European Regulatory Authorities**

The Sponsor or its designee is responsible for SUSAR notification to the relevant regulatory authorities as outlined in the ICH Guidelines. All investigators participating in the study will also be informed as required by regulations.

Any SUSAR is subject to expedited reporting in the EU. The Sponsor or its designee, will report any single SUSAR to the appropriate National CAs and IECs within 7 days if the SUSAR is life-threatening or fatal (with the relevant follow-up information subsequently communicated within an additional eight days), and within 15 days if the SUSAR is neither life-threatening nor fatal. SUSARs reported will be those that have arisen in the present clinical trial and SUSARs that have arisen in other clinical trials conducted by the Sponsor with the same medicinal product.

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to competent authorities of the concerned Member States and to IEC(s)/IRBs as required by national laws.

### **14.3. Adverse Event Definitions**

#### **14.3.1. Adverse Event**

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

#### **14.3.2. Suspected Adverse Reaction**

Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

#### **14.3.3. Life-Threatening**

An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

#### **14.3.4. Serious**

An AE or suspected adverse reaction is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE – see definition above
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disability
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

#### **14.3.5. Unexpected**

An AE or suspected adverse reaction is considered “unexpected”:

- If it is not listed in the Investigational Brochure or is not listed at the specificity or severity that has been observed, or
- If an Investigational Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigational Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigational Brochure listed only cerebral vascular accidents.

“Unexpected,” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigational Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

#### **14.4. Emergency Identification of Study Medication**

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject’s treatment in the study via the IVRS; this normally requires prior approval by the medical monitor. However, if the subject is at immediate risk and the Investigator believes that immediate knowledge of the study treatment will alter medical management, discussion with the medical monitor may take place after unblinding. The Investigator will not unblind the medical monitor during that discussion. The process of unblinding will ensure that only the investigator is unblinded; the medical monitor, study management team, and data management team will not be made aware of the treatment allocation of an individual subject. All

cases of emergency unblinding will be fully documented in a way that does not unblind the medical monitor, study management team, and data management team.

## **15. STUDY ADMINISTRATIVE CONSIDERATIONS**

### **15.1. Quality Control and Quality Assurance**

The Investigators and institutions will permit trial related monitoring, audits, IRB review, and regulatory inspections as requested by FDA, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed informed consent forms, etc.) in addition to case report forms.

Quality assurance and quality control systems with written standard operating procedures (SOPs) will be followed to ensure this trial will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The site's dedicated study monitor will arrange to visit the Investigator at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be identified and resolved. The study monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality assurance officers named by Sage Therapeutics or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements, made by the Sponsor with the Investigator/institution and any other parties involved with the clinical trial, will be in writing in a separate agreement.

### **15.2. Data Handling and Recordkeeping**

#### **15.2.1. Data Handling**

Procedures for data handling (including electronic data) used in this protocol will be documented in a Data Management Plan.

#### **15.2.2. Case Report Form Completion**

eCRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of demographics, study drug administration, study procedures, AEs, questionnaire completion, efficacy assessments and subject status, including survival.

The Investigator will maintain copies of the eCRFs at the study site. For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate eCRF.

### **15.2.3. Retention of Study Records**

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval and until there are no pending or contemplated marketing applications or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to an appropriate person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

## **15.3. Confidentiality**

To maintain subject privacy, all eCRFs, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available trial registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by Sage Therapeutics to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

## **15.4. Publication Policy**

All information concerning SAGE-547 is considered confidential and shall remain the sole property of Sage Therapeutics. The Investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval from Sage Therapeutics. No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between Sage Therapeutics and the Investigator.

## **15.5. Protocol Amendments**

Changes to the conduct of the study should be prepared as a protocol amendment by the Sponsor. Protocol amendments should receive written IRB/IEC approval prior to implementation at the investigative site, except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the trial (eg, change of monitor, telephone numbers). In this case, Sage Therapeutics will amend and implement the protocol change



and subsequently notify the regulatory authorities and the Investigative sites who will notify the respective IRB, as appropriate.

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**APPENDIX 1. APPENDIX 1: FOUR SCORE****FOUR score****Full Outline of UnResponsiveness****Eye response**

- E4: eyelids open or opened, tracking, or blinking to command
- E3: eyelids open but not tracking
- E2: eyelids closed but open to loud voice
- E1: eyelids closed but open to pain
- E0: eyelids remain closed with pain

**Motor response**

- M4: thumbs-up, fist or peace sign
- M3: localizing to pain
- M2: flexion response to pain
- M1: extension response to pain
- M0: no response to pain or generalized myoclonus status

**Brainstem reflexes**

- B4: pupil and corneal reflexes present
- B3: one pupil wide and fixed
- B2: pupil or corneal reflexes absent
- B1: pupil and corneal reflexes absent
- B0: absent pupil, corneal and cough reflex

**Respiration pattern**

- R4: not intubated, regular breathing pattern
- R3: not intubated, Cheyne-Stokes breathing pattern
- R2: not intubated, irregular breathing
- R1: breathes above ventilatory rate
- R0: breathes at ventilator rate or apnea

Reference ([Iyer, Hoel et al. 2009](#)).

**APPENDIX 2. GLASGOW OUTCOME SCALE (GOS)****GLASGOW  
OUTCOME  
SCALE**

Patient Name: \_\_\_\_\_  
 Rater Name: \_\_\_\_\_  
 Date: \_\_\_\_\_

*Note:* The scale presented here is based on the original article by Jennett and Bond. It has become common practice in clinical trial administration, however, to use a modified version that places the scores in reverse order (i.e., "good recovery" = 1, "moderate disability" =2, etc.).

Score	Description
1	DEATH
2	PERSISTENT VEGETATIVE STATE Patient exhibits no <i>obvious cortical</i> function.
3	SEVERE DISABILITY (Conscious but disabled). Patient depends upon others for daily support due to mental or physical disability or both.
4	MODERATE DISABILITY (Disabled but independent). Patient is independent as far as daily life is concerned. The disabilities found include varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes.
5	GOOD RECOVERY Resumption of normal activities even though there may be minor neurological or psychological deficits.

**TOTAL (1-5):** \_\_\_\_\_

Reference ([Jennett and Bond 1975](#)).

## APPENDIX 3. SUPERVISION RATING SCALE (SRS)

### SUPERVISION RATING SCALE (SRS)

**Instructions:** Circle the rating that is closest to the amount of supervision that the patient *actually receives*. "Supervision" means that someone is responsible for being with the patient.

<u>Rating</u>	<u>Description</u>
<u>Level 1: INDEPENDENT</u>	
1	The patient lives alone or independently. Other persons can live with the patient, but they cannot take responsibility for supervision (for example, a child or elderly person).
2	The patient is unsupervised overnight. The patient lives with one or more persons who <i>could</i> be responsible for supervision (for example, a spouse or roommate), but they are <i>all</i> sometimes absent overnight.
<u>Level 2: OVERNIGHT SUPERVISION</u>	
3	The patient is only supervised overnight. One or more supervising persons are always present overnight but they are <i>all</i> sometimes absent for the rest of the day.
<u>Level 3: PART-TIME SUPERVISION</u>	
4	The patient is supervised overnight and part-time during waking hours, but is allowed on independent outings. One or more supervising persons are always present overnight and are also present during part of waking hours every day. However, the patient is sometimes allowed to leave the residence without being accompanied by someone who is responsible for supervision.
5	The patient is supervised overnight and part-time during waking hours, but is unsupervised during working hours. Supervising persons are <i>all</i> sometimes absent for enough time for them to work full-time outside the home.
6	The patient is supervised overnight and during most waking hours. Supervising persons are <i>all</i> sometimes absent for periods longer than one hour, but less than the time needed to hold a full-time job away from home.
7	The patient is supervised overnight and during almost all waking hours. Supervising persons are <i>all</i> sometimes absent for periods shorter than one hour.
<u>Level 4: FULL-TIME INDIRECT SUPERVISION</u>	
8	The patient is under full-time indirect supervision. At least one supervising person is <i>always</i> present, but the supervising person does not check on the patient more than once every 30 minutes.
9	Same as #8 plus requires overnight safety precautions (for example, a deadbolt on outside door).
<u>Level 5: FULL-TIME DIRECT SUPERVISION</u>	
10	The patient is under full-time direct supervision. At least one supervising person is always present and the supervising person checks on the patient more than once every thirty minutes.
11	The patient lives in a setting in which the exits are physically controlled by others (for example, a locked ward).
12	Same as #11 plus a supervising person is designated to provide full-time line-of-sight supervision (for example, an escape watch or suicide watch).
13	The patient is in physical restraints.

3/12/93

Corwin Boake, Ph.D., TIRR, 1333 Moursund, Houston, TX 77030-3405, 713/799-6990

## APPENDIX 4. MODIFIED RANKIN SCALE – LEVEL OF FUNCTION SURVEY (mRS-9Q)

1. Do you have any symptoms that are bothering you? (For example, trouble with reading or writing, trouble speaking, problems with vision, numbness, weakness, balance trouble, or problems with swallowing?)	YES <input type="radio"/>	NO <input type="radio"/>
2. Are you able to do the same work as before?	YES <input type="radio"/>	NO <input type="radio"/>
3. Are you able to keep up with your hobbies?	YES <input type="radio"/>	NO <input type="radio"/>
4. Have you maintained your ties to friends and family?	YES <input type="radio"/>	NO <input type="radio"/>
5. Do you need help making a simple meal, doing household chores, or balancing a checkbook?	YES <input type="radio"/>	NO <input type="radio"/>
6. Do you need help with shopping or traveling close to home?	YES <input type="radio"/>	NO <input type="radio"/>
7. Do you need another person to help you walk?	YES <input type="radio"/>	NO <input type="radio"/>
8. Do you need help with eating, going to the toilet, or bathing?	YES <input type="radio"/>	NO <input type="radio"/>
9. Do you stay in bed most of the day and need constant nursing care?	YES <input type="radio"/>	NO <input type="radio"/>

## APPENDIX 5. CLINICAL GLOBAL IMPRESSION (CGI)

### Clinical Global Impression (CGI)

#### 1. Severity of illness

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- |                             |   |
|-----------------------------|---|
| 0 = Not assessed            | 4 = Moderately ill                        |
| 1 = Normal, not at all ill  | 5 = Markedly ill                          |
| 2 = Borderline mentally ill | 6 = Severely ill                          |
| 3 = Mildly ill              | 7 = Among the most extremely ill patients |

#### 2. Global improvement: Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.

Compared to his condition at admission to the project, how much has he changed?

- |                        |                     |
|------------------------|---------------------|
| 0 = Not assessed       | 4 = No change       |
| 1 = Very much improved | 5 = Minimally worse |
| 2 = Much improved      | 6 = Much worse      |
| 3 = Minimally improved | 7 = Very much worse |

#### 3. Efficacy index: Rate this item on the basis of drug effect only.

Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.

EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect		Side effects			
		None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
<b>Marked</b>	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
<b>Moderate</b>	Decided improvement. Partial remission of symptoms	05	06	07	08
<b>Minimal</b>	Slight improvement which doesn't alter status of care of patient	09	10	11	12
<b>Unchanged or worse</b>		13	14	15	16
Not assessed = 00					

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare



**APPENDIX 6. STATUS EPILEPTICUS SEVERITY SCORE (STESS)**

Outcome Predictor	Feature	Score
Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type (prior to first treatment)	Simple-partial, complex-parial, absence, myoclonic (complicating idiopathic generalized epilepsy)	0
	Generalized-convulsive	1
	Nonconvulsive status epilepticus in coma	2
Age	< 65 years	0
	≥ 65 years	2
History of previous seizures	Yes	0
	No or unknown	1
Summed Total		

**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY  
TO EVALUATE THE EFFICACY AND SAFETY OF SAGE-547 INJECTION  
IN THE TREATMENT OF SUBJECTS WITH SUPER-REFRACTORY  
STATUS EPILEPTICUS**

**PROTOCOL NUMBER: 547-SSE-301**

**IND NUMBER: 117901**

**EudraCT Number: 2015-002142-31**

Product: SAGE-547 Injection (allopregnanolone)

Sponsor Contact: [REDACTED], MD

[REDACTED]  
Sage Therapeutics  
215 First Street  
Cambridge, MA 02142  
[REDACTED]

Medical Monitor: [REDACTED], MD

Date of Protocol: 09 March 2015  
Date of Amendment One 27 May 2015  
Date of Amendment Two 17 November 2015  
Date of Amendment Three 22 April 2016  
Date of Amendment Four 12 August 2016

**Confidentiality Statement**

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

**PROTOCOL NUMBER: 547-SSE-301**

Sponsor [REDACTED]:

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

CRO [REDACTED]:

[REDACTED]

## 1. SIGNATURE PAGE

Title of protocol: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus

Protocol No: 547-SSE-301

### Sponsor Approval

---

[REDACTED], MD  
Sage Therapeutics

---

Date (dd/mmm/yyyy)

---

[REDACTED]  
Sage Therapeutics

---

Date (dd/mmm/yyyy)

---

[REDACTED], MPH  
Sage Therapeutics

---

Date (dd/mmm/yyyy)

---

[REDACTED]  
Sage Therapeutics

---

Date (dd/mmm/yyyy)

**Investigator Agreement**

By signing this page, I attest that I have read and understand the contents of Clinical Protocol 547-SSE-301 and any current amendments. I agree to adhere to the design, conduct, and reporting requirements of the study as stated in the clinical protocol and to my obligations to the Sponsor as described in the protocol and executed contracts between myself, my Institution, and the Sponsor. I also agree to adhere to any subsequent amendments to the clinical protocol.

Investigator's Signature: \_\_\_\_\_

Investigator's Name: \_\_\_\_\_

Institution: \_\_\_\_\_

Date (dd/mmm/yyyy): \_\_\_\_\_

## 2. SYNOPSIS

<b>Name of Sponsor:</b> Sage Therapeutics 215 First Street Cambridge, MA 02142		
<b>Protocol No.</b> 547-SSE-301		<b>Phase:</b> 3
<b>Name of Investigational Product:</b> SAGE-547 Injection		
<b>Name of Active Ingredient:</b> Allopregnanolone		
<b>Title of the Protocol:</b> A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus		
<b>Dosing Regimen: SAGE-547 or Placebo Dosing Schedule</b>		
<b>Hour</b>	<b>Type and Duration of SAGE-547 Infusions</b>	<b>Dose</b>
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	90 µg/kg/h
H121 – H128	8 hour taper	65 µg/kg/h
H129 – H136	8 hour taper	45 µg/kg/h
H137 – H144	8 hour taper	25 µg/kg/h
<b>Dosing Regimen: SAGE-547 Open-Label Dosing Schedule</b>		
<b>Hour</b>	<b>Type and Duration of SAGE-547 Infusion</b>	<b>Dose</b>
H1	One hour loading infusion	300 µg/kg/h
H2 –H120	119 hour maintenance infusion	150 µg/kg/h
H121 – H126	6 hour taper	125 µg/kg/h
H127 – H132	6 hour taper	95 µg/kg/h
H133 – H138	6 hour taper	65 µg/kg/h
H139 – H144	6 hour taper	35 µg/kg/h
<b>Study Sites</b> Up to 180 sites in the USA, Israel, Europe, and Canada.		
<b>Number of Subjects</b>		

The study will randomize 140 subjects at up to 180 sites.

### Study Population

Subjects will be aged two years or more, in SRSE<sup>1</sup> (as defined in the Inclusion Criteria [Section 8.1](#)), and being managed in an intensive care setting.

### Duration of Subject Involvement

Individual subject participation will be up to 30 days.

### Study Design

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

Patients will follow one of three paths to entry to the study. The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst or seizure suppression with a third-line agent. These subjects will be consented for the study after admission to the intensive care unit, before or after any third-line agents are administered for burst or seizure suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their legally authorized representative (LAR). Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours. Once burst or seizure suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The second path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst or seizure suppression pattern on the EEG. These subjects may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst or seizure suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst or seizure suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst or seizure suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

<sup>1</sup> In this study, the term Super-Refractory Status Epilepticus or SRSE is equivalent to “Refractory Status Epilepticus (RSE) that has failed standard treatment” and the two terms are used interchangeably.

The third path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst or seizure suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These subjects may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 treatment or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within eight hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo).

The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that subjects, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as both the ability to wean the subject off all third-line agents before the end of the infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication infusion, and concurrent signs of physiologic brain activity as determined by EEG. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#) and [Table 2](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo will all subsequently be eligible to be administered SAGE-547 at the higher dose.

### Visit Schedule

The visit schedule and an overview of events at each visit is provided in [Table 1](#), [Table 2](#) and [Table 3](#) Schedule of Assessments.



**Study Objectives*****Primary objective:***

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult and pediatric subjects with SRSE, and for the response to endure at least 24 hours after the end of the SAGE-547 or placebo infusion (primary response).

***Secondary objectives:***

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in the Clinical Global Impression scale (CGI) between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

***Safety objectives:***

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

***Other objectives:***

1. To evaluate the impact of treatment with a higher dose SAGE-547 infusion;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;

3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;
6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS) (age  $\geq 17$  years).

## Endpoints

### *Primary endpoint:*

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### *Secondary endpoints:*

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### *Safety endpoints:*

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.

**Other endpoints:**

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who are treated with a higher dose of SAGE-547.
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS) (age  $\geq 17$  years).

**Inclusion Criteria**

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects two (2) years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed zero, one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst or seizure suppression pattern; or who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst or seizure suppression pattern.

**Exclusion Criteria**

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone or any excipients in SAGE-547.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy with highly malignant/malignant EEG features ([Westhall, Rosetti et al. 2016](#)).

4. Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing underlying neurological disorder.
5. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis but for whatever reason, dialysis that would adequately remove Captisol<sup>®</sup> is not planned;
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the opinion of the investigator, of less than 30 days.
6. Subjects who are being administered more than three third-line agents concomitantly or in whom the qualifying wean cannot be completed within 24 hours, or who are being administered a third-line agent for other indications such as management of raised intra-cranial pressure that would preclude weaning according to this protocol.
7. Subjects with a living will that does not allow heroic measures.
8. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
9. Subjects who have been treated or randomized in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not have received study drug/placebo and then re-enroll).

### **Pharmacogenetic Research**

In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **Statistical Analysis**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

### **Interim Analysis**

When approximately 50% of the subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### **Analysis of Primary Endpoint**

The analysis of response to treatment between SAGE-547 treated subjects and placebo treated subjects will be performed using a Cochran-Mantel-Haenszel test with variables for treatment, concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). In this analysis, a treatment responder is a subject who is successfully weaned off all third-line agents and blinded study medication prior to the end of study treatment infusion and remains off third-line agents for at least 24 hours following cessation of the blinded study medication, and who has concurrent signs of physiologic brain activity as determined by EEG. The analysis will be based on the ITT Population. The comparison of treatment response rates will be conducted at the 5% level of significance.

### **Analysis of Secondary Efficacy Endpoints**

The primary analysis will be repeated for the MITT population. Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section. Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. Secondary analyses will be repeated for the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from Baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third-line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

Summaries of safety endpoints will be based on the overall Safety Population which is defined as all subjects who at least initiated the infusion with blinded study treatment.

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who are treated with a higher dose of SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo. Summary statistics will be presented for subjects who were QW successes.

### **Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

**Table 1: Schedule of Assessments for Protocol 547-SSE-301: One Infusion of Study Drug (blinded)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical/SE/Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X	X	X	X	X	X	X	X		X		
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X		X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X		X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X		X	X		X		X		X		
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X			
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>o</sup>											X
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV 3rd-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>p</sup>				
EEG	X	X			X			X	X			
Randomization		X										
Study Drug Administration <sup>q</sup>			X	X	X	X	X	X				
TW Outcome & Open-label Treatment Decision										X <sup>r</sup>		
Physiologic Brain Activity									X			
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

**Table 2: Schedule of Assessments for Protocol 547-SSE-301: Two Infusions of Study Drug (one blinded, one open-label)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V3R
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	0-24h
Eligibility Checklist	X										S
Informed Consent <sup>a</sup>	X										E
Inclusion/Exclusion Criteria	X										E
Demography <sup>b</sup>	X										
Medical and SE and Wean History <sup>c</sup>	X										T
Height	X										A
Weight <sup>d</sup>	X	X	X	X	X	X	X	X		X	B
Serum Pregnancy Test <sup>e</sup>	X										L
Hematology <sup>f</sup>	X		X	X		X		X		X	E
Serum Chemistry and GFR <sup>g</sup>	X		X	X		X		X		X	
Urinalysis <sup>h</sup>	X		X	X		X		X		X	E
Pharmacogenetic sample	X										X
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X	T
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X	E
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X		N
STESS	X										I
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	O
Glasgow Outcome Score (GOS)											N
Supervision Rating Scale (SRS)	X <sup>o</sup>										
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>										
Epilepsy Status	X										N
Clinical Global Impression (CGI)	X										E
Continuous IV Third-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>p</sup>			X
EEG	X	X				X		X	X		T
Randomization		X									
Study Drug Administration <sup>q</sup>			X	X	X	X	X	X			
TW Outcome and Open-label Treatment Decision										X <sup>r</sup>	P
Physiologic Brain Activity									X		
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	A
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	G
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	E
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X	
Pharmacoeconomic Data											
Mortality											

**Table 2 continued**

	V3R	V4R	V5R	V6R	V7R	V8R	V9R	V10R	V11R	V12R
	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3R+14d (±2d)	V3R+21d (±2d)
Weight <sup>d</sup>	X	X	X	X	X	X				
Serum Pregnancy Test <sup>e</sup>										
Hematology <sup>f</sup>	X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X	X		X		X		X		
Vital Signs <sup>i</sup>	X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>	X	X	X	X	X	X	X			
STESS										
FOUR Score <sup>m</sup>	X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)										X
Supervision Rating Scale (SRS)										X
Modified Rankin Score (mRS) <sup>n</sup>										X
Epilepsy Status										X
Clinical Global Impression Scale (CGI)										X
Continuous IV Third-Line Agent(s)	X	X	Wean	Wean	Wean	Wean <sup>p</sup>				
EEG			X			X	X			
Randomization										
Study Drug Administration <sup>q</sup>	X	X	X	X	X	X				
TW Success and Physiologic Brain Activity							X			
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data										X
Mortality										X



**Table 3: Schedule of Assessments for Protocol 547-SSE-301: Qualifying Wean Successes**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical and SE and Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X											
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X											
Serum Chemistry and GFR <sup>f</sup>	X											
Urinalysis <sup>h</sup>	X											
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X											
ECG <sup>j</sup>	X											
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>o</sup>											X
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV Third-Line Agent(s)	X	Wean										
EEG	X	X										
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors <sup>v</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

<sup>a</sup> Written informed consent by proxy (LAR) will be obtained prior to starting any study-related procedures not considered standard of care.

<sup>b</sup> Demographic information will be obtained by proxy and confirmed by the subject when possible.

<sup>c</sup> Medical history will be obtained by proxy and confirmed by the subject when possible. All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Dosing changes with the third-line agent(s) that constitute a wean attempt will be marked as such on the CRF, and the start/stop dates and times of all wean attempts prior to V3 will be recorded, as well as the outcome of the wean attempt.

<sup>d</sup> Weight will be collected at Screening (V1) and prior to administration of the blinded study drug infusion at V2 and the open-label study drug infusion at V10. The weights at V2 and V10 will be used to determine the appropriate infusion rate of the blinded and open-label infusions respectively. If easily obtained (such as via a scale-bed), weight will also be recorded once during each subsequent 24 hour period of the initial study drug infusion period (V3-V8) and second infusion period (V3R-V8R, if applicable).

<sup>e</sup> Serum pregnancy test for females aged 10 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy.

<sup>f</sup> Blood samples will be taken for hematology and serum chemistry and GFR calculation at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will document whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

<sup>g</sup> Blood samples will be taken at V11 or V11R for serum chemistry (renal panel only).

<sup>h</sup> Urine samples will be taken for urinalysis and NAG at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will add a comment about whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

<sup>i</sup> Vital signs will be recorded at the following time points relative to the start of each infusion of study drug: Screening (V1), at 0, 30, 60 minutes ( $\pm 15$  minutes), at 2, 4, and 8 hours ( $\pm 30$  minutes), and at 24, 48, 72, 96, 120, 144, 168, and 192 hours ( $\pm 2$  hours).

<sup>j</sup> For the first 50 subjects randomized in the study, ECG (12-lead) should be performed at Screening (V1) and at the following times relative to the start of study drug infusion. For the blinded (first) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 128, 136, 144, 152, 160, and 192 hours ( $\pm 2$  hours). For the open-label SAGE-547 (second) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 126, 132, 138, 144, 152, 160, and 192 hours ( $\pm 2$  hours). Heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours. If it is not possible to perform ECG immediately after PK sampling up to 160 hours, ECG must be performed within 15 minutes prior to PK sampling up to 160 hours. Following randomization of the first 50 subjects, subsequent subjects randomized in the study will have ECG collected at the following timepoints: Pre-dose and at 1, 12, 24, 48, 72, 96, 120, 144, and 192 hours after the start of the blinded (first) study drug infusion; and, Pre-dose and at 1, 12, 24, 48, 72, 96, 120, 144, and 192 hours after the start of the open-label (second) study drug infusion. It is not necessary for to collect these ECGs with the PK samples at these timepoints and, apart from the 1 h ECG, there is  $\pm 2$  hour time window for these ECGs.

<sup>k</sup> Plasma will be collected to assay for study drug concentrations at the following time points relative to the start of each infusion of study drug: For the blinded (first) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion. For the open-label SAGE-547 (second) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open-label SAGE-547 study drug infusion. Pre-dose samples may be taken within two hours before starting the infusion of study drug; timepoints up to and including 1h will have a time window of  $\pm 5$  minutes; all other timepoints will have a window of  $\pm 15$  minutes.

<sup>m</sup> FOUR Score assessments will be performed at Screening (V1), 24, 48, 72, 96, 120, 144, 168, and 192 hours (all  $\pm 2$  hours) relative to the start of each infusion of study drug, and at V11 or V11R, and at V12 or V12R.

<sup>n</sup> Modified Rankin Score (mRS) applicable for subjects  $\geq 17$  years old only.

<sup>o</sup> SRS at V1 will be a retrospective assessment of the supervision required by the subject immediately prior to admission that includes the index episode of the SE, and mRS at V1 will be a retrospective assessment of the disability and dependence of the subject immediately prior to admission that includes the index episode of the SE.

<sup>p</sup> Target for complete wean of all continuous IV third-line agents by 144 hours at V8/V8R if not completed by 120 hours at V7/V7R.

<sup>q</sup> Study drug infusion is intended for IV administration only with a dedicated peripheral IV line using Sage-approved IV administration bags and lines.

<sup>r</sup> At V10 only a decision to re-treat at a higher dose of SAGE-547 will be made by the Investigator if the continuous IV third-line agent wean has failed or the third-line agent requires re-introduction during V9. Subjects who become eligible for open-label study drug at a higher dose of SAGE-547 will discontinue the planned visit schedule at V10, then repeat V3 (V3R) and all applicable subsequent visits.

<sup>s</sup> AEs will be collected from the time Informed Consent is obtained and prior to the start of study-specific screening procedures not considered standard of care. Collection of AEs will continue throughout the study from V1 through V12 or V12R.

<sup>t</sup> Subjects may enter the study on AEDs and Pressors and be administered AEDs and Pressors during the study. For all randomized and the first 50 QWS subjects, all Concomitant AEDs and Pressors must be recorded on the CRF with details including date and time of starting/stopping each AED and Pressor, the route of administration, changes in doses, and frequency of administration. Details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the CRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”. For subsequent QWS subjects, after the detailed information on all concomitant AEDs and Pressors collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant AED and Pressor and the start and stop dates and times) from Visit 3 to Visit 12 will be recorded in the eCRF.

<sup>u</sup> All third-line agents administered since the diagnosis of SE will be recorded on the CRF. For all randomized and the first 50 QWS subjects, details will include the name of the drug, the start/stop dates and times, and, after consent, the doses with start/stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R. For subsequent QWS subjects, after the detailed information on all concomitant third-line agents collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant third-line agent and the start and stop dates and times) from Visit 3 to Visit 12 will be recorded in the eCRF.

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**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
AE	adverse event
AED	anti-epileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the time-concentration curve
AW	additional weans
BDZ	benzodiazepine
BIEEG	blinded infusion electroencephalogram
BUN	blood urea nitrogen
CBC	complete blood count
CEEG	consent electroencephalogram
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
C <sub>max</sub>	maximum plasma concentration
C <sub>min</sub>	minimum plasma concentration
CNS	central nervous system
CRF	case report form
CSR	clinical study report
CYP2C9	cytochrome P450 enzyme involved in drug metabolism
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EEG	electroencephalogram
EIND	Emergency Use Investigational New Drug Application
EP	European Pharmacopeia
ESETT	Established Status Epilepticus Treatment Trial
FDA	Food and Drug Administration
FOUR	Full Outline of UnResponsiveness
GABA	$\gamma$ -aminobutyric acid
GABA <sub>A</sub>	$\gamma$ -aminobutyric acid-gated chloride channel
GCP	Good Clinical Practice

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
GFR	glomerular filtration rate
GOS	Glasgow Outcome Scale
H	hour
HPLC	high performance liquid chromatography
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent to Treat
IV	intravenous
IVRS	Interactive Voice Randomization System
LAR	legally authorized representative
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent to Treat
mRS-9Q	Modified Rankin Score - 9Q
MS/MS	tandem mass spectrometry
nM	nanomolar
NMDA	n-methyl-D-aspartic acid
OW	other weans
PAEEG	primary endpoint electroencephalogram
PD	pharmacodynamics
PK	pharmacokinetic
QOL	quality of life
QW	qualifying wean
QWEEG	qualifying wean electroencephalogram
RBC	red blood cell
RSE	refractory status epilepticus

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
SAE	serious adverse event
SAP	Statistical Analysis Plan
SE	status epilepticus
SOP	standard operating procedure
SRS	Severity Rating Scale
SRSE	Super-refractory status epilepticus
SSRI	Selective serotonin re-uptake inhibitors
STESS	Status Epilepticus Severity Score
SUSAR	Suspected Unexpected Serious Adverse Reactions
SWFI	Sterile Water for Injection
TAEEG	taper electroencephalogram
T <sub>max</sub>	time at maximum plasma concentration
TW	terminal wean
TWEEG	terminal wean electroencephalogram
US	United States
USP	United States Pharmacopeia

### 3. INTRODUCTION AND RATIONALE

#### 3.1. Status Epilepticus

Status epilepticus (SE) is a life-threatening seizure condition in which the brain is in a state of persistent seizure triggered by neuronal hyperexcitability. The Neurocritical Care Society defines SE as one continuous unremitting seizure lasting longer than five minutes or recurrent seizures without regaining consciousness between seizures for greater than five minutes (Brophy, Bell et al. 2012). Common causes of SE include preexisting epilepsy, cerebrovascular disease (in adults), electrolyte and metabolic disturbances, anoxia, encephalopathies, head trauma, high fever (in children, especially in the first year of life) and drug or substance intoxication. SE is associated with substantial morbidity and mortality.

##### 3.1.1. Epidemiology of SE

Geography, sex, age, and race influence the epidemiology of SE, whose incidence has a bimodal distribution, peaking in infants/young children and the elderly (Hauser 1990; DeLorenzo, Pellock et al. 1995; Wu, Shek et al. 2002). The incidence of SE in the elderly population is at least twice that in the general population. Concurrent medical conditions often exist in the elderly population, which can complicate therapy and worsen the prognosis of SE (Chapman, Smith et al. 2001).

The annual incidence of SE in the US is generally quoted to be within the range of 18/100,000 to 61/100,000, based on a 19-year retrospective study in Rochester, Minnesota (Hesdorffer, Logroscino et al. 1998) and a 2-year prospective study in Richmond, Virginia (DeLorenzo, Pellock et al. 1995), respectively. Two studies from Europe give annual incidences of a similar magnitude, ranging between 9.9/100,000 and 15.8/100,000 (Coeytaux, Jallon et al. 2000; Knake, Rosenow et al. 2001). It is thus estimated that in the United States each year there are as many as 150,000 cases of SE (DeLorenzo, Pellock et al. 1995).

#### 3.2. Refractory SE

When a patient begins to seize, the emergency medical technician will administer a first-line intravenous (IV) benzodiazepine (BDZ), such as diazepam, lorazepam or midazolam (Silbergleit, Durkalski et al. 2012), which is done either at the scene of the seizure or in the ambulance. If this is unsuccessful at abating the seizure, additional doses of the first-line therapy will be administered in the emergency room. Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line therapy, which is an IV anti-epileptic drug (AED) such as phenytoin or valproic acid (Novy, Logroscino et al. 2010; Shorvon 2011; Hocker, Britton et al. 2013).

Approximately 20-30% of patients refractory to first-line treatment will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to approximately 70-80% of patients who receive second-line therapy refractory to that therapy.

If a patient's SE continues after administration of BDZs and AEDs, the subject is diagnosed as having refractory status epilepticus (RSE), which must be treated quickly to terminate the seizure activity, maintain the patient's airway, and prevent cerebral damage. RSE

patients are immediately admitted to the Intensive Care Unit (ICU) and placed in a medically-induced coma to stop all seizure-related activity. The drugs used to induce coma are continuously-infused IV agents, commonly propofol, midazolam, or pentobarbital, referred to as third-line agents (Brophy, Bell et al. 2012).

The RSE patient is continually monitored using electroencephalography (EEG) to ensure that seizure and/or burst suppression is achieved. Burst suppression is a pattern of brain waves seen on an EEG, characterized by periods of activity alternating with periods of little or no activity in the brain, informing medical personnel of the effectiveness of the medically-induced coma. The goal of burst suppression is to allow the brain and corresponding neuronal tissue to restore function and reset to normal pre-seizure levels.

### **3.2.1. Epidemiology of RSE**

Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line AED therapy. In turn, approximately 20 – 30% of these patients treated with AEDs will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to 28% of the total estimated SE patient population refractory to second-line therapy. Based on the previously-cited estimated incidence in the US, this means that there are up to 42,000 incident cases of RSE in the USA, annually (DeLorenzo, Pellock et al. 1995).

## **3.3. Super-refractory SE**

After 24 hours of burst or seizure suppression, the patient is weaned off of the third-line therapy. If the weaning is unsuccessful (neuronal activity has not returned to normal), the third-line agent is re-administered or a different third-line agent is started, and the patient is considered to be in super-refractory status epilepticus (SRSE) (Chapman, Smith et al. 2001; Shorvon 2011; Brophy, Bell et al. 2012). SAGE-547 is being developed as an adjunct to third-line therapy in patients in RSE who have failed standard treatment. In this protocol, the term “RSE that has failed standard treatment” is deemed to be equivalent to the term “SRSE” and the two may be used interchangeably.

### **3.3.1. Epidemiology of SRSE**

The incidence of SRSE is very poorly understood, mainly because the diagnostic codes used for SE do not generally differentiate its nature as responding or refractory to treatment. Based on the variable reporting of outcomes data, the incident cases of SRSE could represent between one and two-thirds of the RSE patients (Novy, Logroscino et al. 2010; Ferlisi and Shorvon 2012; Hocker, Britton et al. 2013; Sutter, Marsch et al. 2013). More detailed epidemiology studies are needed to better elucidate the proportion of RSE patients whose condition becomes super-refractory. A recent review of ICU discharge data in the USA suggests an annual incidence of approximately 35,000, based on patients who required at least three days in the ICU for SE [Sage data on file].

### **3.3.2. Outcomes of SRSE**

SE has varying degrees of mortality depending on the underlying etiologies. Table 4 outlines the acute mortality in patients with SE by etiology (Neligan and Shorvon 2010). The mortality rate of SRSE is estimated to be 30% to 50% using current standard of care.

The causes of death from SE (and therefore SRSE) are heterogeneous, resulting from neuronal cell death, complications of underlying medical conditions, or adverse effects of the current standard treatments. Prognosis worsens and mortality increases with longer duration of SE, i.e. with SE that develops into RSE or SRSE (Neligan and Shorvon 2010), and with longer duration of medically-induced coma (Ferlisi and Shorvon 2012). There is an obvious unmet medical need to improve upon the current standard of care treatment regimens.

Morbidity is high and survivors have outcomes ranging from poor function to vegetative state (Shorvon 2011). Approximately one third of patients with RSE and SRSE will recover, but with chronic neurologic or other deficits (Neligan and Shorvon 2010; Hocker, Britton et al. 2013). In all, it is estimated that less than 25-30% of all SRSE patients have a favorable functional outcome.

**Table 4: Approximate Mortality of Status Epilepticus in Different Etiologies**

Underlying Etiology	Associated Acute Mortality in Patients with SE (%)
Drug reduction/withdrawal, poor AED compliance, or low AED levels	0-10
Cerebrovascular Disease	20-60
Metabolic Disorders	10-35
Acute CNS Infection	0-30
Anoxia	60-100
Alcohol Abuse	0-10
Head Trauma	0-25
Drug Overdose/Toxicity	10-25
Brain Tumors	0-20
Cryptogenic/Idiopathic	5-20

### 3.3.3. Unmet Medical Need in Super-refractory Status Epilepticus

Treatment approaches for SRSE consist of diagnosis and treatment of underlying medical conditions, adding and changing anti-seizure drugs, and repeated attempts at weaning from IV anesthetic agents. Treatment of SRSE has three aims:

- to prevent excitotoxicity, which begins within 24 hours of SE onset;
- to prevent cerebral damage by initiating neuroprotective burst or seizure suppression;
- to prevent the complications of extended periods of anesthesia or unconsciousness (Shorvon 2011).

Currently, there are no therapies that have been specifically approved for RSE or SRSE. The primary drugs used to induce coma are continuously infused IV anesthetics such as propofol, midazolam, or pentobarbital/thiopental, known as third-line agents. Use of these drugs to control SRSE has only been studied in small retrospective reviews or small prospective studies without



controls (Hocker, Britton et al. 2013) therefore there is no agreement on which drug is optimal nor on an optimal dosing regimen for the treatments that are used.

The most common adverse effect of the third-line agents is hemodynamic instability; in addition, they are not universally effective, with breakthrough seizures and withdrawal seizures requiring dose adjustments and changes in third-line agent(s). The drug thought to be most effective in SRSE, pentobarbital, is also associated with the most toxic adverse effect profile, comprising decreased blood pressure and cardiorespiratory collapse (Claassen, Hirsch et al. 2002). The ability to wean patients successfully off the third-line agents as quickly as possible is therefore paramount, and an adjunct to SRSE treatment that enhances the success of the third-line agents and supports their successful weaning in a short timeframe would be an important addition to the therapeutic armamentarium. Preliminary clinical data show that SAGE-547 has been a successful adjunct to third-line therapy in this regard.

### 3.4. SAGE-547 Injection

Allopregnanolone is an endogenous, naturally occurring neuroactive steroid formed in the corpus luteum of the ovary, adrenal cortex and central nervous system (CNS) (Holzbauer, Birmingham et al. 1985; Paul and Purdy 1992; Ottander, Poromaa et al. 2005). It is a metabolite of progesterone created by the actions of 5- $\alpha$  reductase and 3- $\alpha$  hydroxy-steroid dehydrogenase. Allopregnanolone is a potent positive allosteric modulator of both synaptic and extra-synaptic GABA<sub>A</sub> receptors.

SAGE-547 Injection (allopregnanolone aqueous formulation in Captisol<sup>®</sup>) is being developed for the treatment of patients in RSE who have not responded to standard treatment. SAGE-547 Injection is a solution of 5 mg/mL allopregnanolone in Sterile Water for Injection (SWFI), USP and 250 mg/mL betadex sulfobutyl-ether sodium, NF. It is further diluted with Sterile Water for Injection, USP (SWFI) in IV bags to achieve an allopregnanolone concentration of approximately 1.67 mg/mL in an approximately isotonic solution and will be administered intravenously.

#### 3.4.1. Scientific Rationale for SAGE-547 in SRSE

Ineffective recruitment of inhibitory neurotransmission, together with excessive neuronal excitation, likely plays a role in the initiation and propagation of the electrical disturbance occurring in SE. GABA ( $\gamma$ -aminobutyric acid), the major inhibitory neurotransmitter in the central nervous system (CNS), is released from GABAergic neurons and binds to several types of GABA receptors (GABA<sub>A</sub>, GABA<sub>B</sub>, and GABA<sub>C</sub>) on target neurons. GABA<sub>A</sub> receptors are macromolecular proteins that form a chloride ion channel complex and contain specific binding sites for GABA and a number of allosteric regulators, including barbiturates, benzodiazepines, and some anesthetic agents. GABA receptor-mediated inhibition contributes significantly to the normal termination of a seizure (Kapur and Macdonald 1997). SAGE-547 is a positive allosteric modulator of the GABA<sub>A</sub> receptor.

The importance of terminating seizure activity as soon as possible is underpinned by a growing body of evidence from research and clinical observation that SE becomes more difficult to control as its duration increases. It has been postulated that this occurs due to a mechanistic shift from inadequate GABAergic inhibitory receptor-mediated transmission to excessive N-methyl-D-aspartic acid (NMDA) excitatory receptor-mediated transmission (Kapur and Macdonald 1997). As prolonged epileptiform bursting results in a reduction of GABA<sub>A</sub>-mediated synaptic

inhibition, antiepileptic treatments which rely on enhancing intrasynaptic GABA<sub>A</sub> neurotransmission become less effective the longer SE continues.

Furthermore, the constitutive process of synaptic GABA<sub>A</sub> receptor internalization is accelerated by the increased neuronal activity associated with seizures. These findings suggest that the rate of GABA<sub>A</sub> receptor internalization is regulated by neuronal activity, and its acceleration contributes to the reduction of inhibitory transmission observed during prolonged seizures (Kapur and Macdonald 1997). Of note is that SAGE-547 binds to extrasynaptic as well as intrasynaptic GABA<sub>A</sub> receptors; extrasynaptic receptors remain active with ongoing seizure activity, resulting in a putative mode of action for SAGE-547 in SRSE.

Status epilepticus induces cerebral damage that includes neuronal cell necrosis, gliosis, and network reorganization. The major cause of cell death in cerebral damage is excitotoxicity, which is initiated by glutaminergic receptor over-activation, causing calcium to flood the cell, thereby leading to apoptosis and necrosis. This process is initiated within a few hours of the start of seizure activity, and provides the medical imperative to terminate SE as quickly as possible. To prevent the consequences of the excitotoxicity cascade, it is recommended that anesthesia be initiated within 1-2 hours of onset of seizures at doses designed to induce EEG suppression patterns (Shorvon and Ferlisi 2011).

### **3.4.2. SAGE-547 Clinical Program in the Treatment of SRSE**

The current SAGE-547 development program includes:

- a completed Phase 2 open-label trial, Study 547-SSE-201;
- this proposed Phase 3 randomized, double-blind, placebo-controlled trial, Study 547-SSE-301;
- an ongoing open-label, expanded access protocol, Study 547-SSE-302;
- a number of EINDs for SAGE-547 in patients with SRSE.

The designs of these studies are all similar, with a five to six day infusion of SAGE-547 (or placebo), during which time attempts are made to wean the subject off all third-line agents. In the Phase 3 studies, those subjects who cannot be weaned off third-line agents while being administered SAGE-547 (or placebo) may be eligible for a second open-label infusion of SAGE-547 at a higher dose. Follow up of subjects is for 21 – 30 days after the first infusion of study medication.

### **3.4.3. Data from the SAGE-547 Development Program**

The data from 30 subjects included in the on-going clinical evaluation of SAGE-547 for the treatment of adults and children with SRSE clearly offers preliminary evidence that SAGE-547 could provide substantial and clinically significant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate. These subjects comprise 20 from the ongoing Phase 2 trial (71% success rate in 12/17 evaluable subjects) and 10 subjects who received EIND treatments (78% success rate in 7/9 evaluable subjects).

Successful therapy of SRSE has been defined as “the SE is completely controlled by the therapy, without breakthrough of withdrawal seizures, or discontinuation due to side effects or death during therapy,” (Ferlisi and Shorvon 2012). By this definition, which is in accord with the

efficacy assessments used in the overall clinical evaluation of SAGE-547, 19 of the 26 (73%) subjects with SRSE who completed the SAGE-547 infusion were treatment successes. As data collection is ongoing, this information is preliminary and subject to change upon further monitoring.

Published reports on RSE and SRSE have stated mortality rate ranges from 35% to 65%. The underlying etiologies of SE in the 547-SAGE-201 study and EINDs are heterogeneous, and each one conveys a different risk of mortality and longer term morbidity. However, the death rate in subjects who have received SAGE-547, 6 out of 30 (20%) subjects, appears to be lower than the published rates. None of the deaths were considered related to SAGE-547: brain tumor, organophosphate toxicity, respiratory failure, respiratory arrest due to ventilator support withdrawal, and breast cancer.

In the Phase 2 study, 20 SAEs (15 non-fatal) have been reported in 13 (65%) subjects, and of these 3 events in 2 subjects (10%) were considered by the investigator to be related to SAGE-547: pulmonary emboli and tracheostomy dehiscence/infection. The Sponsor did not consider these events to be related to SAGE-547, rather to the underlying disease states. Four of the 20 subjects (20%) experienced AEs considered possibly related to SAGE-547 by the investigator, namely moderate myopathy and severe pulmonary emboli in 1 subject, moderate tracheostomy dehiscence and tracheostomy infection in 1 subject, moderate thrombocytosis in 1 subject and moderate BUN, ALT and AST elevation in 1 subject.

Review of the most current safety data from 547-SAGE-201 reveals that there were changes in serum chemistry, hematology, and urinalysis during the study, but that none of those changes were assessed as related to SAGE-547. There were also no SAGE-547-related changes to vital signs.

Despite the heterogeneity in the underlying causes of SE, the ages of the subject, comorbidities, which normally complicate the treatment of SE, and the fact that all subjects had failed current standard of care treatment, a large majority of subjects had a successful therapy outcome, with discontinuation of all third-line agents and resolution of SE.

Refer to the Investigational Brochure for further information on the pre-clinical and clinical data supporting the use of SAGE-547 in SRSE.

### **3.5. Study Rationale - SAGE-547 in SRSE**

#### **3.5.1. Justification for the Control Group**

Although SAGE-547 has demonstrated extremely promising activity in subjects with SRSE, both in the Phase 2 study and during the EINDs, these have been open-label investigations with no control data for comparison. Generally in the literature there are few data describing the success rates of wean attempts of third-line agents, and few comparative data on the effectiveness of the three main third-line agents, propofol, pentobarbital/thiopental, and midazolam.

Several options for a control group in Study 547-SSE-301 were considered:

- No control group was thought to be unacceptable since there are no reliable published data on success rates in this population that could be used for broad comparisons;
- An active control was considered but found to be impractical since none of the third-line agents are approved for their use in SRSE, no standardized dosing regimens or

treatment guidelines have been adopted for the management of SRSE, and clinicians were unlikely to agree which of the available third-line agents would be reserved for the active control arm;

- Historical controls were considered but abandoned because of the practical difficulties of obtaining high quality data, the lack of ability to prospectively match cases, and a suspicion that clinical practice in the standard of care of SRSE is evolving, mandating the use of prospective, concurrent control data;
- Comparison to standard of care alone was considered as a feasible design. However, in a field where no widely adopted treatment guidelines exist, there was a concern that knowledge of the treatment group (SAGE-547 plus standard of care versus standard of care alone) would alter the behavior of the investigators such that they could be more aggressive with weaning in the SAGE-547 group;
- Placebo control is not without its challenges since the preliminary efficacy data for SAGE-547 show that the compound exerts central pharmacological effects and is associated with positive outcomes in around 70% of patients. There is therefore a potential ethical concern about administering placebo to desperately ill patients who have often exhausted all treatment options for SRSE. This concern has been addressed in two ways: firstly all patients receive current standard of care; secondly, all subjects who fail to be weaned from their third-line agents at the end of the blinded infusion of study drug will be administered open-label SAGE-547 without un-blinding their initial treatment allocation, so treatment with the investigational product is not denied, but delayed about a week in the setting of ongoing receipt of full current standard of care.

It was therefore decided that a blinded, placebo-controlled design was appropriate for Study 547-SSE-301.

### **3.5.2. Justification for the Dose Regimen**

The standard dose regimen has been studied in 19 subjects in the 547-SSE-201 Phase 2 trial; the average peak plasma concentration of SAGE-547 at the end of the loading dose was approximately 144 ng/ml. The average plasma concentration during the maintenance infusion was approximately 70 ng/ml. At these concentrations, there were no clear safety signals although two-thirds of subjects experienced an SAE and there were four deaths, all related to the underlying comorbid conditions. The standard dosing regimen was associated with an approximate 70% successful treatment outcome. For these reasons, the standard dosing regimen has been adopted for the initial SAGE-547 infusion to be compared in a blinded fashion to placebo.

In the 547-SSE-201 trial, three subjects have thus far received the higher dose regimen. This dose regimen has also been well tolerated. The average peak plasma concentrations at the end of the loading dose for both dosing regimens will be in the same range, as the loading dose is the same for both regimens. The average plasma concentrations observed during the higher maintenance dose are 102 ng/ml (n=2). The rationale for adopting the higher dose regimen as the open-label infusion of SAGE-547 for subjects who are retreated in this 547-SSE-301 trial is that those who fail on the standard SAGE-547 dose regimen are afforded the opportunity to have access to a higher dose. The justification to also administer the higher dose regimen to failures on placebo is that the regimen has thus far been well tolerated, and this methodology preserves the blind for the initial infusion.

A five-day dosing regimen with SAGE-547 was investigated in the Phase 2 study, 547-SSE-201. There were some cases when weaning off all third-line agents was not possible within 48 hours, but weaning was completed after the end of the infusion of SAGE-547. For this reason, the duration of dosing with SAGE-547 has been increased from 120 hours (five days) in Phase 2 to 144 hours (six days) in this Phase 3 study.

### **3.5.3. Rationale for Genetic Testing Sub-study**

Sage Therapeutics intends to perform genetic research in the SAGE-547 development program in order to explore how genetic variations may affect the metabolism and activity of SAGE-547. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials, and, possibly, to genetically-guided treatment strategies for optimizing decision making with respect to individual benefit:risk. Participation of subjects in genetic research as part of the overall clinical study is optional.

## **3.6. Benefit-Risk Evaluation of the Present Study**

Previous reports of human administration of exogenous allopregnanolone indicate that for exposures in men and women up to 150 nM, the most commonly reported AEs were sedation (recorded as sleepiness or tiredness), feelings of intoxication (like alcohol), flushing, and mild headache (Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007). No SAEs were reported (Navarro, Kaddouz et al. 2003; Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007; Kask, Backstrom et al. 2008; Kask, Backstrom et al. 2009; Timby, Hedstrom et al. 2011a). In view of the reduced consciousness and sedation of study subjects at entry into this protocol, none of these previously-reported events are likely to impact subjects in this study.

To date, in the SAGE-547 Phase 2 study and the EIND subjects, a majority of subjects demonstrated a successful therapy outcome (>70%). The majority in the clinical trial (65%) have also experienced SAEs, but none has been considered related to SAGE-547 by the Sponsor (SAEs in 2 subjects (10%) were considered possibly related by Investigator). Five deaths have been reported in 30 subjects (20%), all related to the underlying cause of SRSE and not related to SAGE-547 – this is in the context of published mortality rates between 35% and 65%. These preliminary data suggest that SAGE-547 has the potential to provide clinically relevant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate.

The underlying etiologies of SE are heterogeneous, and each one conveys a different risk of mortality. Subjects who survive SRSE still have a high risk of severe morbidity (Neligan and Shorvon 2010). The subjects treated with SAGE-547 in Study 547-SSE-201, are heterogeneous in factors such as age and etiology of SE, factors that usually complicate treatment and can increase morbidity and mortality. Even with this heterogeneity, the preliminary efficacy and safety data for SAGE-547 are very encouraging, and the mortality rate suggests that the risk to benefit assessment of this treatment rests on the side of benefit.

## **4. ETHICS**

### **4.1. Institutional Review Board or Independent Ethics Committee**

This protocol will be reviewed and approved by the Institutional Review Board (IRB) where the study is conducted. The IRB will meet all FDA requirements governing IRBs (CFR, Title 21, Part 56).

### **4.2. Ethical Conduct of the Study**

The Sponsor, the Medical Monitor, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable ICH and GCP guidelines, and must also conduct the study in accordance with local regulations.

### **4.3. Subject Information and Informed Consent**

Subjects prospectively enrolled in this study will be unable to give consent. Therefore, consent will be given by proxy by a legally authorized representative (LAR). Written informed consent is required for each subject prior to any testing under this protocol not considered standard of care, including screening tests and evaluations. Should a subject gain the ability to sufficiently comprehend the situation and consent during the course of the study, written informed consent or verbal assent will be documented as required or recommended by the institution's IRB.

The form of consent to be obtained will depend on the condition of the subject as determined by the Principal Investigator. The informed consent form (ICF), as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50.

It is the responsibility of the Investigator to obtain consent and to provide the subject's LAR with a copy of the signed and dated informed consent form. The informed consent form for subject participation must also be available as part of the subject file for review by the site's dedicated study monitor or any authorized auditor of the Sponsor or regulatory authorities.

All ICFs used in this study must be approved by the appropriate IRB and by the Sponsor. The ICF must not be altered without the prior agreement of the relevant IRB and the Sponsor.

### **4.4. Ethical and Regulatory Considerations for Pharmacogenetic Sub-study**

#### **4.4.1. Informed Consent for Pharmacogenetics**

The genetic component of this study is optional and subjects may participate in other components of the main study without having to agree to participate in the genetic component. If subject chooses to participate in the genetic component of the study, the subject or LAR must sign and date a specific consent form for the genetic component of the study in addition to the main study consent form. The principal investigator(s) is responsible for ensuring that consent is freely given and that the subject understands that they may discontinue from the genetic aspect of the study independent of their decision to remain within or withdrawal from the main study.

#### **4.4.2. Subject Data Protection Relative to Pharmacogenomics**

Sage Therapeutics will not provide individual genotype results to subjects, their family members, their general physician, their employer or any insurance company unless required to do so by law. While extra precautions will be taken to preserve confidentiality and to prevent genetic data from being linked to an individual's identity outside of a restricted access site, in certain exceptional situations (e.g. in case of a medical emergency or as a consequence of a specific regulatory need), certain individuals may see both genetic data and the personal identifiers of a subject; however in all cases a subject's medical information and genetic files will remain physically separated.

## **5. STUDY OBJECTIVES**

### **5.1. Primary Objective**

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult and pediatric subjects with SRSE, and for the response to endure at least 24 hours after cessation of the SAGE-547 or placebo infusion (primary response).

### **5.2. Secondary Objectives**

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in Clinical Global Impression Scale between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### **5.3. Safety Objectives**

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

## **5.4. Other Objectives**

1. To evaluate the impact of treatment with a higher dose SAGE-547 infusion;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;
6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS) (age  $\geq 17$  years).

## **6. ENDPOINTS**

### **6.1. Primary Endpoint**

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### **6.2. Secondary Endpoints**

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) and to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;



6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### **6.3. Safety Endpoints**

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.

### **6.4. Other Endpoints**

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who are treated with a higher dose of SAGE-547;
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS) (age  $\geq 17$  years).

## **7. INVESTIGATIONAL PLAN**

### **7.1. Overview of Study Design**

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE. [Figure 1](#) provides an overview of the study design and [Figure 2](#) gives the details of treatment and follow-up on the active treatment arm. Patients will follow one of three paths to entry to the study. The first path is for patients who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst or seizure suppression with a third-line agent. These patients will be consented for the study after admission to the intensive care unit, before or after any third-line agents are administered for burst or seizure suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their

LAR. Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours. Once burst or seizure suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned during the QW will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst or seizure suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The second path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst or seizure suppression pattern on the EEG. These patients may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst or seizure suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst or seizure suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst or seizure suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst or seizure suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The third path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst or seizure suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These patients may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst or seizure suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst or seizure suppression and will be randomized to concomitant SAGE-547 or placebo. Burst or seizure suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within eight hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. Randomization will be

stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third line agent wean attempts prior to randomization (one vs two or more).

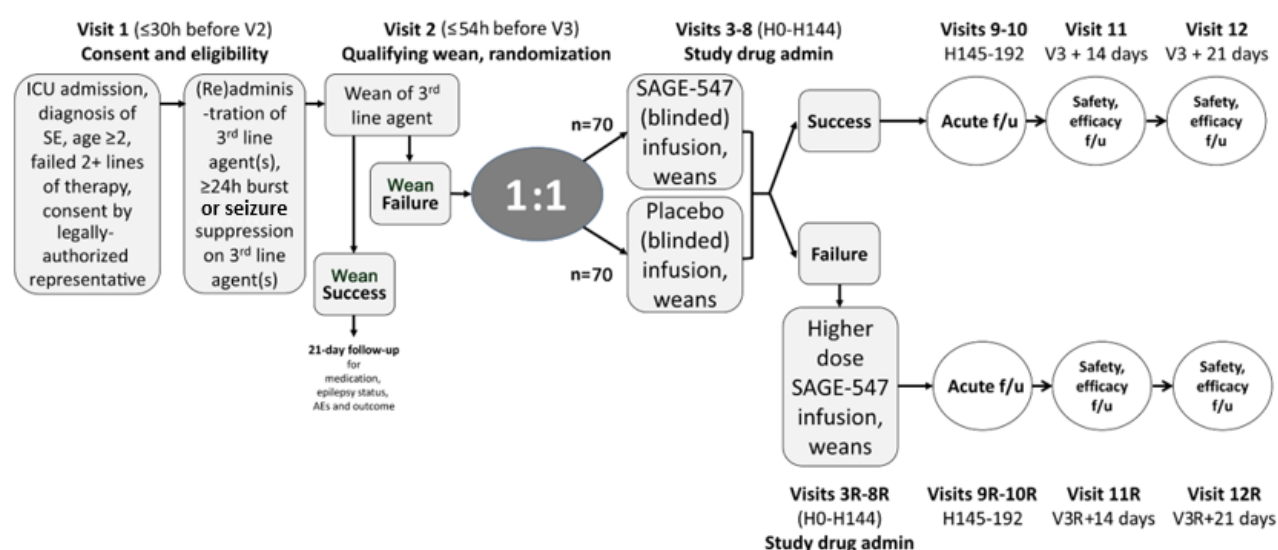
The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as the ability to wean the subject off all third-line agents before the end of the first infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication. Subjects must also have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) at the end of the primary endpoint assessment period as determined by EEG in order to be deemed a success. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#), [Table 2](#) and [Table 3](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion may be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. Eligibility for the open-label treatment must be confirmed in writing by the medical monitor prior to the open-label infusion starting. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo may all subsequently be eligible to be administered SAGE-547 at the higher dose.

**Figure 1: Study Design**



## **7.2. Trial Conduct**

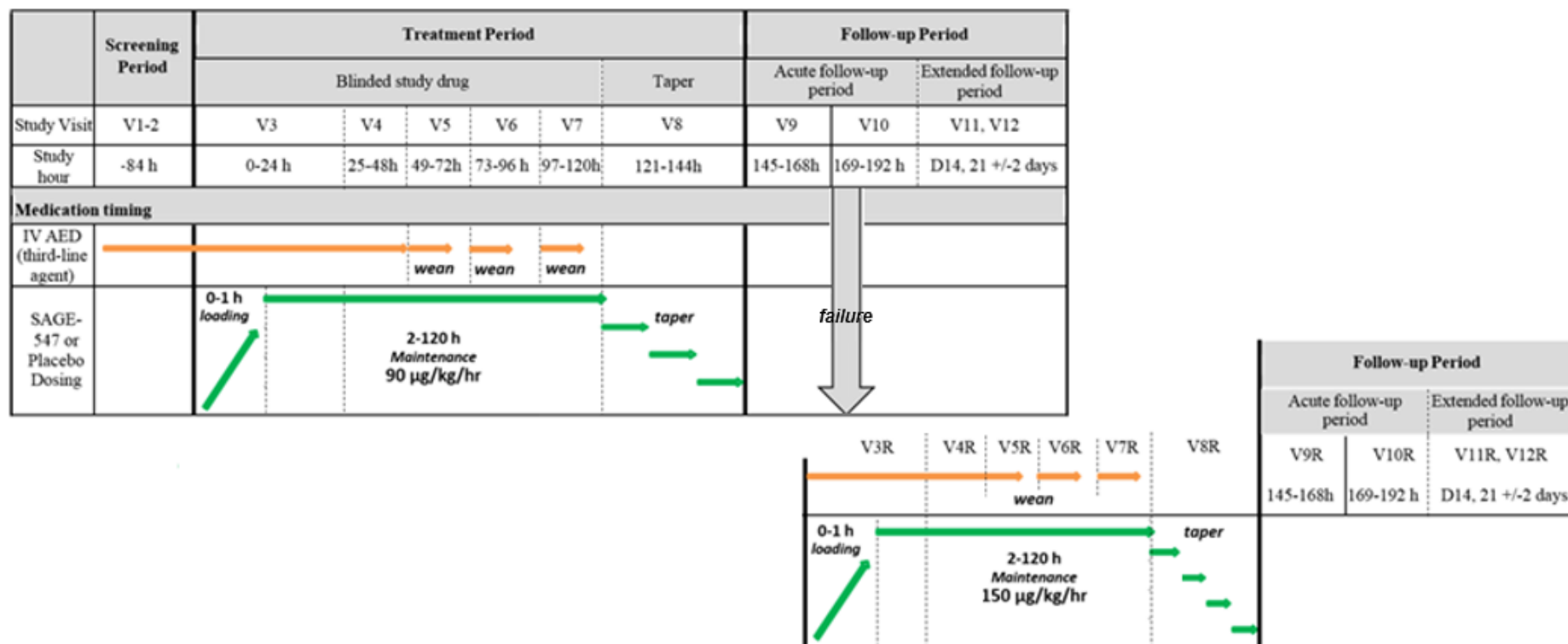
This study will be conducted according to the principles of the World Medical Association Declaration of Helsinki and most recent amendment, and in compliance with the protocol approved by the IRBs/Independent Ethics Committees (IECs), and in accordance with ICH Guidelines on GCP standards.

## **7.3. Blinding and Randomization**

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo). Details of the dynamic randomization process will be included in the SAP.

The randomized portion of the study will be blinded, with the two treatment products (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

The second infusion of SAGE-547 will be administered on an open-label basis to subjects who meet the criteria for open-label treatment.

**Figure 2: Details of Treatment Administration and Follow-up**

## 8. SELECTION AND WITHDRAWAL OF SUBJECTS

The study will randomize 140 patients at up to 180 sites. All subjects deemed eligible to enroll must have written Medical Monitor approval on a case-by-case basis prior to undertaking the qualifying wean.

### 8.1. Inclusion Criteria

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects two (2) years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; *or* who have previously failed zero, one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst or seizure suppression pattern; *or* who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst or seizure suppression pattern.

### 8.2. Exclusion Criteria

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy with highly malignant/malignant EEG features ([Westhall, Rosetti et al. 2016](#)).
4. Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing underlying neurological disorder.
5. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis but for whatever reason, dialysis that would adequately remove Captisol® is not planned;
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;

- d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the experience of the investigator, is less than 30 days.
6. Subjects who are being administered more than three third-line agents concomitantly or for whom the qualifying wean cannot be completed within 24 hours or who are being administered a third-line agent for indications such as raised intra-cranial pressure that would preclude weaning according to this protocol.
7. Subjects with a living will that does not allow heroic measure.
8. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
9. Subjects who have been treated or randomized in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not have received study drug/placebo and then re-enroll).

### **8.3. Selection and Consent of Subjects for Pharmacogenetic Substudy**

All subjects will be asked to participate in pharmacogenetic research; however, participation in research is voluntary and a subject can decide to decline his/her participation without penalty or loss of benefit. Participation or lack thereof will not be a cause for exclusion from any aspect of the main study. In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **8.4. Subject Withdrawal / Study Termination**

#### **8.4.1. Withdrawal/Discontinuation of Individual Subjects**

The reasons for study drug discontinuation and/or subject withdrawal from the study must be recorded in the subject's electronic case report form (eCRF). The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject has been discontinued/withdrawn due to an AE.

##### **8.4.1.1. Withdrawal from the Study**

Subjects or their LAR may withdraw subjects from the study at any time for any reason without compromising the subject's medical care. The Investigator will also withdraw subjects upon the request of Sage Therapeutics or upon termination of the study.

Subjects who withdraw from the study prior to Visit 10 (or 10R) should complete the procedures scheduled for the day of study drug taper (Hour 121-144; Visit 8/8R) on the day of their withdrawal, including the SAGE-547 taper schedule, with the addition of the mortality assessment from Visit 12/12R. Subjects who withdraw from the study after Visit 10/10R should undergo study procedures as outlined for Visit 12/12R on the day of their withdrawal. In all cases, the reason for subject withdrawal will be recorded in the eCRF.

Withdrawal of subjects for any reason should be discussed with the Medical Monitor.

#### **8.4.1.2. Discontinuation of Study Drug**

If it is necessary to discontinue the study drug earlier than planned, subjects should continue to be followed per protocol to capture safety and efficacy assessments for the duration of the study period.

The investigator may withdraw the subject from the study drug for the following reasons:

- Upon subject's or LAR's request
- The subject or LAR is unwilling or unable to adhere to the protocol-specified visits
- The subject experiences an intolerable adverse event
- During the course of the study, the subject develops symptoms or conditions listed in the exclusion criteria.
- Other medical reason, at the discretion of the Investigator and/or the Medical Monitor

Subjects who discontinue the study due to an AE considered related to study drug should be followed until the event is resolved, considered stable, or the Investigator determines the event is no longer clinically significant. Study drug discontinuation due to AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

#### **8.4.2. Study Termination**

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of AEs or other findings suggesting unacceptable risk to subjects, administrative or operational reasons. In the event of study termination, Sage Therapeutics will provide written notification to the Investigator. Investigational sites must promptly notify their IRB and initiate withdrawal procedures for participating subjects.

## **9. INVESTIGATIONAL PRODUCT**

### **9.1. Identity of Investigational Product**

SAGE-547 Injection (allopregnanolone)

### **9.2. Clinical Supplies**

#### **9.2.1. SAGE-547**

Adequate supplies of SAGE-547 Injection and materials for intravenous administration will be provided to each site.

SAGE-547 Injection is a clear, colorless sterile solution of allopregnanolone intended for intravenous injection. SAGE-547 Injection is an aqueous solution of 5 mg/mL allopregnanolone in 250 mg/mL Captisol® (betadex sulfobutyl-ether sodium, NF). It is presented either un-buffered or buffered with 10 mM citrate at a pH of 6.0 in either 20 mL or 50 mL vials. SAGE-547 is further diluted according to the Pharmacy Manual to achieve an approximately isotonic solution and will be administered intravenously.

No preservatives are included in the drug product, which is intended to be used as a single-use vial. All inactive components (excipients) used in the formulation are compendial grade and conform to



current USP/EP, and include sodium citrate, citric acid and betadex sulfobutyl-ether sodium (Captisol®).

### **9.2.2. Placebo**

Placebo will be identical to SAGE-547 and presented in identical vials. Placebo will be manufactured in a similar way to SAGE-547 and comprises all excipients but no SAGE-547.

### **9.2.3. Blinding**

The vials of SAGE-547 and placebo will be identical in every way so that they are indistinguishable by the pharmacist, investigator, anyone treating or managing the patient, the monitors, and the sponsor. In this way the first infusion of study drug administered to each patient will be double-blind.

For the blinded study drug infusions, subject-specific dosing kits will be provided. These dosing kits will be pre-labelled with kit number for the first blinded infusion. For the second-infusion, open-label kits will be provided, which will require subject assignment by the pharmacy for reconciliation purposes. The study kits must be stored under refrigerated conditions (2-8 °C). IV administration bags and lines may be provided for the blinded and open-label infusions. Refer to the Pharmacy Manual for additional details.

The label for the SAGE-547 Injection vials will include standard product identification information according to the Code of Federal Regulations, 21CFR 312.6. All study labels will also contain the following statement:

Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use.

## **9.3. Preparation of SAGE-547 or Placebo Injection for Dosing**

The Pharmacy will be responsible for preparing the blinded and open-label study drug for subject dosing. The prepared admixture will be assigned a room temperature (20-25 °C) storage shelf life of 30 hours from time of compounding.

SAGE-547, which is hypertonic, will require dilution with SWFI to achieve an approximately isotonic solution according to the instructions provided in the Pharmacy Manual. Exactly the same procedures will be used to prepare the placebo admixture, so that all site staff remain blinded as to treatment allocation for the first infusion of study drug. SAGE-547 Injection is not intended to be administered to patients undiluted.

Refer to the Pharmacy Manual for specific instructions regarding infusion preparation.

## **9.4. Administration and Accountability**

The Pharmacy will maintain accurate records of all investigational product supplies. Accurate records will be kept regarding the volume of SAGE-547 Injection or placebo used for each IV preparation, as well as the required infusion rate or rates, and the date and time of preparation. Reasons for departure from the expected dosing regimen must also be recorded. To satisfy regulatory requirements regarding drug accountability, all study medication will be reconciled in full. Refer to the Pharmacy Manual for additional details.

## 10. TREATMENT OF SUBJECTS

### 10.1. Dosing Schedule (Blinded Infusions)

SAGE-547 Injection or placebo will be administered according to the dosing schedules in [Table 5](#). The infusion rates to accomplish these  $\mu\text{g/kg/h}$  doses will be calculated according to the weight of the subject obtained within the eight-hour window that follows the declaration of the QW failure at V2 and prior to dosing at V3. The infusion rates will be applied to blinded study drug for the first infusion of study medication.

**Table 5: SAGE-547 or Placebo Dosing Schedule**

Hour	Type and Duration of Study Drug Infusion	Description
H1	One hour loading Infusion	300 $\mu\text{g/kg/h}$
H2 – H120	119 hour maintenance infusion	90 $\mu\text{g/kg/h}$
H121 – H128	8 hour taper	65 $\mu\text{g/kg/h}$
H129 – H136	8 hour taper	45 $\mu\text{g/kg/h}$
H137 – H144	8 hour taper	25 $\mu\text{g/kg/h}$

### 10.2. Dosing Schedule (Open-Label Infusions)

Those subjects that qualify for the open-label study drug will be administered SAGE-547 Injection according to the dosing schedule in [Table 6](#). The dose will be administered on a  $\mu\text{g/kg/h}$  basis, and the subject's weight measured prior to dosing during V10 will be used to calculate the doses. These infusion rates will be applied to SAGE-547 treatment for the open-label second infusions of study medication.

**Table 6: SAGE-547 Open-Label Dosing Schedule**

Hour	Type and Duration of SAGE-547 Infusion	Description
H1	One hour loading Infusion	300 $\mu\text{g/kg/h}$
H2 –H120	119 hour maintenance infusion	150 $\mu\text{g/kg/h}$
H121 – H126	6 hour taper	125 $\mu\text{g/kg/h}$
H127 – H132	6 hour taper	95 $\mu\text{g/kg/h}$
H133 – H138	6 hour taper	65 $\mu\text{g/kg/h}$
H139 – H144	6 hour taper	35 $\mu\text{g/kg/h}$

### 10.3. Route of Administration

SAGE-547 Injection is intended for IV administration only. The compatibility of SAGE-547 with other drugs is unknown, and the product should be administered via a dedicated peripheral IV line using any Sage-supplied study-specific IV administration bags and lines. In order to preserve blinding, these instructions also apply to the blinded placebo infusions.

## **10.4. Treatment Period**

The treatment period with double-blind SAGE-547 or placebo is six 24-hour periods (144 hours), which may encompass 6-7 calendar days. The open-label study drug treatment period is of identical duration.

## **10.5. Concomitant Medications, Procedures and Treatments**

Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. For all randomized and the first 50 qualifying wean success (QWS) subjects, detailed information on all concomitant medications (concomitant AEDs, third-line agents, pressors, and other concomitant medications), procedures, and treatments should be documented throughout the study from Screening through Visit 12/12R, as described below, and recorded on the eCRF. For subsequent QWS subjects, after the detailed information on all concomitant AEDs, pressors, third-line agents, procedures, and treatments collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant AED or pressor, third-line agent, procedure, and/or treatment, and the start and stop dates and times) from Visit 3 through Visit 12 will be recorded in the eCRF. For subsequent QWS subjects, after the detailed information on all concomitant medications collected during the screening period (Visits 1 and 2) has been recorded, only minimal information, to include the name of the concomitant medications and indication only will be recorded from Visit 3 through Visit 12.

SAGE-547 has demonstrated inhibitory effects on cytochrome P450 isoenzyme 2C9 (CYP2C9). Therefore, AEDs such as phenytoin and phenobarbital that are primarily metabolized by CYP2C9 should be closely monitored during SAGE-547 administration to ensure target exposures are maintained.

### **10.5.1. Concomitant AEDs**

Subjects may enter the study on AEDs, and be administered AEDs during the study. All of these must be recorded on the eCRF with details including date and time of starting and stopping each AED, the route of administration, changes in doses, and frequency of administration. In addition, details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the eCRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.

### **10.5.2. Concomitant Third-Line Agents**

All third-line agents (as defined in [Section 8](#)) administered since the diagnosis of SE will be recorded on the eCRF, whatever path the patient took for entry into the study. Details will include the name of the drug, the start and stop dates and times, and, after consent, the doses with start and stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

In addition, those changes in dose that constitute a wean attempt will be marked as such on the eCRF. In this way the start and stop dates and times of all wean attempts (see [Section 11](#) for definitions) will be recorded, as will the type of wean (QW, OW, or TW) and the outcome of the wean attempt (successful, failed and dose of this third-line agent increased or failed and this third-

line agent stopped and another third-line agent started). Those wean attempts that occur after the TW up to and including Visit 12/12R will be marked “AW”.

Some third-line agents (such as propofol) are also used to induce sedation to facilitate a subject’s ability to tolerate the ventilator. For subjects requiring such sedation, propofol is the preferred agent unless there are contraindications. The eCRF will make clear from the indication for the third-line agent when it is being used for burst or seizure suppression and when it is being used as ventilator support or for another purpose. The investigator will add a note to the eCRF to justify that the doses used are appropriate for sedation and not for seizure or burst suppression. The doses used for ventilator support and other similar uses are usually much lower than those used for seizure or burst suppression, and use of these third-line agents for these other purposes does not constitute a wean failure under this protocol.

### **10.5.3. Concomitant Pressors**

The start and stop dates and times of all pressors will be recorded as well as the start and stop dates and times of all dose changes.

### **10.5.4. Other Concomitant Medications**

All other concomitant medications must be recorded on the eCRF with details including date and time of starting and stopping, the route of administration, dose, and frequency of administration.

## **11. STUDY ASSESSMENTS**

### **11.1. Efficacy Assessments**

#### **11.1.1. Primary Efficacy**

Success or failure will be determined, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo infusion and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the blinded (first) infusion of SAGE-547 or placebo. In addition, subjects must have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) to be deemed to be successes. All subjects who fail to complete their infusion of randomized treatment or do not have at least one attempt during study treatment to wean off all third-line agents will be considered as “failures” for the primary endpoint.

#### **11.1.1.1. Weaning**

Third-line agents are anesthetic agents that are administered in order to reach a seizure or burst suppression EEG pattern. For the purposes of this study, third-line agents are defined as continuous intravenous infusions of pentobarbital/thiopental, midazolam, propofol, and ketamine at maintenance doses alone or in combination sufficient to produce a burst or seizure suppression pattern on the EEG. The following are considered to be minimum maintenance doses of these agents that may be expected alone or in combination to achieve EEG burst suppression. If subjects are on lower doses than these and are not in EEG burst suppression for the first 12 hours of the blinded study drug infusion, they will be considered to be protocol violators and will exit the study.

- Pentobarbital: 1 mg/kg/hour
- Thiopental: 3 mg/kg/hour
- Midazolam: 0.1 mg/kg/hour
- Propofol: 3 mg/kg/hour
- Ketamine 1.2 mg/kg/hour

The timing and nature of the third-line agent weans will be guided by the Clinical Standardization Guidelines for the study, and the clinical judgment of the investigator, and will always be primarily done in the best medical interests of the subject. Advice about weaning may be sought from the Clinical Standardization Team, a group of fellow investigators with experience of performing clinical trials in subjects with SRSE. The Clinical Standardization Team will be able to discuss EEGs related to key study timepoints (terminal wean and the period after the end of the blinded study drug infusion if the terminal wean was successful) in a timely manner in order to provide advice about compliance with the Clinical Standardization Guidelines.

The following guidance for weaning applies to all weans of third-line agents undertaken during the study. Continued determined efforts to liberate subjects from sedation must be undertaken for the entire duration of the blinded study drug infusion. Each failed wean from third-line agents should be followed by a 6-24 hour period of suppression and then another wean attempt, with further optimization of the AED regimen.

Weans include the qualifying wean (QW); the terminal wean (TW), which is the wean of the third-line agent if the subject is on only one third-line agent or the wean of the last third-line agent if the subject is on more than one third-line agent; the other weans (OW), which are the weans of the third-line agents other than the TW if the subject is on more than one third-line agent. The guidance also applies to additional weans (AW), which are the weans from third-line agents that take place after the TW for the first blinded study drug infusion or the second open-label study drug infusion.

### **QW Guidance**

- Wean to be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace that third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Investigators should allow 24 hours to lapse after the end of a “successful” qualifying wean before finally declaring the QW a success. If a third-line agent needs to be re-instituted within that 24 hours, the QW is a failure, and the subject may then be randomized in the study.

### **OW Guidance**

- First OW should not begin before H49 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

- If the subject is on two third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the TW. However the OW may be completed over a shorter or longer time period and may overlap if clinically indicated with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- If the subject is on three third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the wean of the second agent. The second agent should be weaned over 24 hours and that wean completed before starting the TW. However the OWs may be completed over a shorter or longer time period and may overlap if clinically indicated with each other and with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- All OWs should be completed before H96 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **TW Guidance**

- The TW is defined as the wean of the last third-line agent.
- If the subject is on one third-line agent, the TW should not begin before H49 and should begin no later than H97 after starting administration of study drug or starting the open-label infusion of SAGE-547. If the subject has had one or more OWs, the TW should ideally begin as soon as the last OW is complete but in any case not later than H97 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- The TW must be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace this third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Every effort must be made to complete the TW before H120 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547, but the TW must be complete before H144 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **AW Guidance**

- AWs will take place when medically indicated in the opinion of the investigator.

- Ideally the AW should take place over 24 hours, but completion may be over a shorter or longer time period than this. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.

#### 11.1.1.2. EEG

Electroencephalographs (EEGs) that are representative of the intermittent or continuous EEG being used to support key investigator decisions will be collected at the following time points:

- A 24-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst or seizure suppression for the second path to eligibility, and a variable pattern for the third path to eligibility. This EEG also aims to capture the burst or seizure suppression pattern during the 24 hours that precede the QW. If the CEEG does not capture the 24 hours that precede the QW, additional EEG data collected as standard of care prior to the CEEG and prior to the QW may be collected to assess the depth of burst or seizure suppression in the 24 hour period prior to the QW.
- EEG will be performed to cover the qualifying wean (QWEEG). EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for up to 24 hours after the end of the QW. The duration of the QWEEG will be up to 48.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s), the decision to re-institute a third-line agent(s) at doses intended to induce burst or seizure suppression, and the decision that the QW is a success.
- EEG will be performed from three hours prior to the start of the blinded infusion to 12 hours after the start of the blinded infusion. This will be called the BIEEG. The intent of this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG and to assess the depth of burst suppression in the first 12 hours of blinded study drug infusion.
- EEG will be performed to cover the final or terminal wean of third-line agent (TWEEG). The TW is the wean of the final third-line agent during the blinded administration of study drug or the open-label infusion of SAGE-547; if the subject was on one third-line agent, the TW is the wean of that agent. If the subject was on three third-line agents, the TW is the wean of the third and final agent. EEG recording will start 30 minutes prior to the start of the TW, continue for up to 24 hours during the TW, and then continue for the one hour after the end of the TW. The duration of the TWEEG will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the final third-line agent or the decision to re-institute a third-line agent at doses intended to induce burst or seizure suppression because any seizure activity could not be managed using intermittent bolus doses of AEDs.

- EEG will be performed during the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 (TAEED). The TAEED is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the start of the taper (at Hour 119.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours during the taper, and then continue for the one hour after the end of the taper (to Hour 145 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547). The duration of the TAEED will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst or seizure suppression because any seizure activity seen during the taper could not be managed using intermittent bolus doses of AEDs.
- EEG will be obtained to cover the end of the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 and the ensuing 24-hour period, during which the primary endpoint is assessed (PAEED). The PAEED is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the end of taper (at Hour 143.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours after the end of the blinded administration of study treatment or the open-label infusion of SAGE-547, and then continue for the one hour after the end of the 24-hour assessment period (to Hour 169 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547). The duration of the PAEED will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst or seizure suppression because any seizure activity seen in the 24 hours following the end of the blinded administration of study treatment or the open-label infusion of SAGE-547 that could not be managed using intermittent bolus doses of AEDs.

In practice, most subjects are on continuous EEG monitoring or long periods of intermittent EEG monitoring. However, this protocol does not mandate continuous EEG monitoring and breaks from EEG monitoring to provide relief to the scalp from the irritating effects of the electrodes are advised, particularly in children, according to local practice. If a break in EEG monitoring is mandated by local practice guidelines at a time when one of the protocolled EEG segments is to be collected, the break in EEG monitoring will take precedence, with the reason for missing the EEG reading noted on the eCRF. The EEGs obtained for the study are therefore part of the existing EEG record rather than being obtained de-novo at each timepoint. For timepoints where there might be some ambiguity, such as the TWEED, the final EEG record is that of the final attempt to wean the last third-line agent, even if earlier attempts to wean that agent took place. In some cases (the TAEED and PAEED, for instance), the EEG records will overlap, but different cuts are taken to service the different EEG record requirements.

The electronic EEG file will be de-identified, the date and time of the start and stop of the EEG and the subject number will be attached to the file, and the study time point will be indicated (CEEG, QWEED, BIEED, TWEED, TAEED, and PAEED). The PI will indicate on the eCRF what the EEG shows, as follows:



- For the CEEG, the PI will describe the EEG pattern that determined which path to eligibility the subject was on.
- For the QWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure or success on the qualifying wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst or seizure suppression during the qualifying wean constitutes a failure); the QWEEG will extend to cover the 24 hours after the end of third line agents in order to confirm that the QW was a success.
- For the BIEEG, the PI will note the date and time of the start of the EEG and the pattern seen on the EEG.
- For the TWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure on the terminal wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst or seizure suppression during the terminal wean).
- For the TAEED, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst or seizure suppression before the end of the SAGE-547 infusion).
- For the PAEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst or seizure suppression in the 24 hours following the end of the SAGE-547 infusion).

A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm the depth of burst or seizure suppression prior to the QW and during the first 12 hours of the blinded study drug infusion, the PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period (average EEG power at the end of Visit 9 of more than two microvolts):

- All subjects will have the CEEG and QWEEG collected and stored, and the CEEG and QWEEG read;
- Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;
- Those subjects randomized who are not administered the open-label study drug will have the QWEEG, BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the BIEEG, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read;
- Those subjects randomized who later undergo the open-label infusion will have the QWEEG, BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion and the TWEEG, TAEED, and PAEEG related to the open-label study drug

infusion collected and stored, and the BIEEG, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read.

All EEG records may be subject to quantitative EEG analysis.

### **11.1.2. Secondary Efficacy**

#### **11.1.2.1. Clinical Global Impression Scale (CGI)**

The clinical global impression scales are often utilized in clinical trials to allow clinicians to integrate several sources of information into a single rating of the subject's condition. Both the CGI-Severity (Question 1, CGI-S) and the CGI-Improvement (Question 2, CGI-I) employ a 7-point Likert scale measuring severity of the disease state in the subject and improvement, respectively. All severity assessments after initiation of SAGE-547 treatment should consider the general state of the subject over the preceding week. The third question on the scale will not be employed in this trial, and where the scale states "mental illness", this means "physical illness" in this trial.

The CGI-S will be evaluated at Visit 1 and at the last visit, Visit 12 or 12R. The CGI-I will be evaluated at Visit 12 or 12R.

#### **11.1.2.2. Epilepsy Status**

At Visit 1, the diagnosis of epilepsy will be documented as a no/yes question. If there was a previous diagnosis of epilepsy, further details will be documented, including:

- Date of diagnosis;
- Details of anti-epileptic drugs currently being taken;
- Type of epilepsy;
- Seizure frequency in the past month.

Information about the current (index) episode of status epilepticus will be obtained at Visit 1:

- Date of onset
- Date of failure to respond to first line agent(s) and the name(s) of the agent(s)
- Date of failure to respond to second line agent(s) and the name(s) of the agent(s)
- Any previous treatment with third line agents and the response to those agents (details of the third line agent drugs and previous wean attempts will be recorded on the Third Line Agent Medication CRF)
- The cause of the index episode of status epilepticus
- If the subject was transferred from another hospital or from within the hospital, the reason for the transfer will be recorded (such as for study enrollment, due to lack of medical options at original hospital or unit, due to lack of beds at the original hospital or unit, family request, other)

Previous (non-index) diagnosis of status epilepticus will be documented as a no/yes question. If SE did occur in the past 12 months, further information will be gathered, including:

- SE, RSE, or SRSE diagnosis, whichever was the most severe diagnosis for each episode;
- Cause;
- Treatment, including experimental treatments and need for intubation/ventilation;
- Dates of onset and duration.

At Visit 12 or Visit 12R, the following information will be gathered:

- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of SE up to and including Visit 12 or Visit 12R;
- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of seizures (convulsive and non-convulsive) up to and including Visit 12 or Visit 12R;
- Number of separate episodes of SE after H144 at the end of Visit 8 or Visit 8R (no/yes); if yes,
  - SE, RSE, or SRSE diagnosis;
  - Cause;
  - Treatment, including experimental treatments and need for intubation/ventilation;
  - Dates of onset and duration.

Note that a separate episode of SE is defined as an episode of SE separated from other periods of status epilepticus by at least 24 hours.

- Diagnosis of epilepsy since Visit 11 or Visit 11R will be documented as a no/yes question. If a diagnosis of epilepsy has been made, further details will be documented, including:
  - Status as ongoing or new epilepsy since Visit 11 or Visit 11R after initiation of SAGE-547 treatment;
  - Details of anti-epileptic drugs currently being taken;
  - Type of epilepsy and seizure frequency in the past week.

## **11.2. Safety Assessments**

The safety and tolerability of SAGE-547 will be assessed using adverse events, clinical laboratory measures, vital signs, ECG intervals and morphology, and mortality. All safety assessments should be performed per hospital standard of care and will be collected periodically throughout the study according to [Table 1](#), [Table 2](#), and [Table 3](#) (Schedules of Assessments).

### **11.2.1. Adverse Events**

AEs will be collected after informed consent has been signed and prior to study-specific screening procedures not considered standard of care, during subject preparation for SAGE-547 administration and through Visit 12 or Visit 12R. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™) coding system (current version). See [Section 14](#) for additional details.

### 11.2.2. Clinical Laboratory Tests

Blood samples will be taken for hematology, and serum chemistry and GFR will be calculated at:

- Visit 1 and then at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.
- Blood samples will be taken at Visit 11 or Visit 11R for serum chemistry (renal panel only).

Urine samples (20 ml) will be taken for urinalysis and urine NAG analysis at:

- Visit 1 and at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.

For adults and children  $\geq 30$  kg, these samples will be analyzed at a central laboratory; hour-to-hour medical decisions will be based on sampling for laboratory testing done outside the protocol as part of normal standard of care. GFR will be calculated by the central laboratory. For children under 30 kg, results of local laboratory testing undertaken at the protocolled timepoints may be sent to the central laboratory for inclusion in the central study laboratory database; this obviates the need for additional blood sampling for central laboratory testing.

Any out-of-range values will be flagged by the laboratory; the investigator will add a comment about whether the abnormality is clinically significant. Clinical significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

#### 11.2.2.1. Hematology and Serum Chemistry

Hematology will include complete blood count (CBC) white blood cell count with differential, platelet count and red blood cell (RBC) count, hemoglobin and hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose. In addition triglycerides will be measured in serum chemistry samples (to aid assessment of lipemia in pharmacokinetic samples).

#### 11.2.2.2. Pregnancy Test

Females of child-bearing potential will be tested for pregnancy by serum pregnancy test at Visit 1. In this study, since an accurate history of menstruation in girls and menopause in older women may not be available at Visit 1, "child-bearing potential" is taken to mean any female aged 10 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy. Female subjects with a positive pregnancy test will be ineligible for study participation.

#### 11.2.2.3. Urinalysis

Urinalysis will include assessment of protein, blood, leukocytes, glucose, ketones, urobilinogen, pH, and specific gravity.

### 11.2.3. Vital Signs

Blood pressure, heart rate, and temperature will be recorded at the following time points relative to the first infusion of study drug, and to the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547:

- Visit 1;
- At 0, +30, +60 minutes (+/-15 minutes) and +2, +4 and +8 hours (+/- 30 minutes) after the start of the infusion;
- At +24, +48, +72, +96, +120, +144, +168, and +192 hours (+/- 2 hours) after the start of the infusion.

### 11.2.4. Weight and Height

Weight and height will be measured at Visit 1. Weight will also be obtained at V2, within the eight hour window that follows the declaration of the QW failure and prior to the initiation of the blinded infusion loading dose at H0 of V3, and will be used to calculate the infusion rates throughout the entire blinded treatment course. If a subject qualifies for open-label study drug, the infusion rates for the open-label infusion will be calculated using the subject's weight measured prior to dosing during V10.

If it is not possible to obtain an actual weight at the above-referenced time points, permission from the Clinical Monitor must be obtained to use another method to obtain the subject's weight (such as information from the LAR or estimating using an established local protocol).

In addition, a daily weight will be obtained and recorded if this is easily obtained, such as the use of a scale bed.

### 11.2.5. ECG

For the first 50 subjects randomized in the study, 12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours. If it is not possible to perform ECG immediately after the collection of PK samples up to 160 hours, ECG must be performed within 15 minutes prior to the collection of PK samples up to 160 hours; at other times the allowed time window for ECGs is +/- 2 hours:

- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +128, +136, +144, +152, +160, and +192 hours after the start of the blinded (first) study drug infusion
- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +126, +132, +138, +144, +152, +160, and +192 hours after the start of the open-label (second) study drug

The heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm.

For the subsequent subjects randomized in the study, the following timepoints for ECG will be used:

- pre-dose and at +1, +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the blinded (first) study drug infusion

- pre-dose and at +1, +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the open-label (second) study drug infusion

It is not necessary to collect these ECGs with the PK samples at these timepoints and, apart from the +1h ECG, there is +/- 2 hour time window for these ECGs.

#### **11.2.6. Mortality**

Mortality will be recorded on the Visit 12 or Visit 12R case report form. If the subject has died, the following information will be collected:

- Date of death;
- Cause of death.

As accurate as possible cause of death will be collected, which will be further categorized as due to one of the following causes:

- SE;
- complications of long term intubation and third-line agent infusions;
- underlying cause of qualifying SE;
- co-morbidity existing at the time of the qualifying SE;
- new co-morbidity or trauma;
- study drug;
- other (specify).

#### **11.2.7. Pharmacogenetic Samples**

If a subject's LAR consents to pharmacogenetic sampling, a blood sample for genetic research will be collected at Visit 1 in order to avoid the possible introduction of bias through the exclusion of patients who may withdraw from study due to an AE (a subject population that may be of specific interest for subsequent genetic analysis). If for any reason a sample cannot be taken prior to treatment, a sample can be drawn at any point prior to completion with the restriction that no more than one genetic sample be taken per subject.

The objective of this research is to collect and store blood samples for possible DNA extraction and exploratory research into how genes or specific genetic variation may influence response (i.e. distribution, safety, tolerability, and efficacy) to SAGE-547. Specific genetic variations of interest include but are not limited to: classes of metabolizing enzymes (e.g. Cytochrome P450 supra-family genes), genes encoding enzymes involved in the production and metabolism of allopregnanolone (e.g. AKR1C4 (3 $\alpha$ -hydroxysteroid dehydrogenase)), genes associated with the GABA receptor (e.g. GABRA1-A6, GABRB1-B3, GABRD, GABRE, GABRG1-3) and genes associated with the production and degradation of GABA.

Future research may suggest other genes or gene categories as candidates for influencing not only response to SAGE-547 but also susceptibility to disorders for which SAGE-547 is being evaluated. Thus, the genetic research may involve study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.

### 11.2.7.1. Biological Sampling and Coding Procedures (Pharmacogenetics)

To ensure patient confidentiality, utmost care will be taken in the coding and storage of pharmacogenetic samples.

*Extraction and coding:* DNA will be extracted from the blood sample and the DNA sample will be assigned a unique number replacing information from sampling tube. The assigned DNA number will be used to identify the sample and its corresponding information within Sage Therapeutics or at any designated contract laboratory for the purpose of sequencing of other DNA specific analysis. No personal details sufficient for individual identification will be available to any person (internal or external to Sage Therapeutics) working with the DNA.

*Genotype/Phenotype Analysis:* Samples and data from genetic analysis will be coded. The link between subject enrollment / randomization code and DNA number will be maintained and stored in a secure environment with restricted access. The established link will be used to identify relevant DNA samples for analysis, facilitated correlation of genotype results with clinical data, allow regulatory audit, and to trace samples for destruction in case of withdrawal of consent.

### 11.2.7.2. Retention of Biological Samples for Pharmacogenetic Analysis

Extracted DNA is a finite research that is destroyed in the process of being analyzed. Primary blood samples from which DNA can be extracted will be stored and used until no further analyses are possible, a maximum storage period of 25 years from time of last subject last visit has been reached, or an individual or LAR withdraws his/her or their consent.

### 11.2.8. Other Outcomes

#### 11.2.8.1. Pharmacokinetic Data

Formal plasma analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS)). In addition, all samples will be analyzed for important SAGE-547 metabolites (if and when these are identified) and Captisol<sup>®</sup> concentrations.

#### Plasma Analysis

Plasma will be collected to assay for SAGE-547 concentrations at the following time points relative to the start of each infusion of study drug:

- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion.
- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open-label SAGE-547 study drug infusion.

- All samples will also be analyzed for plasma concentrations of important metabolites of SAGE-547 if and when these are identified.
- All samples from the first 50 subjects randomized will also be analyzed for plasma concentrations of Captisol®.

The plasma samples will be drawn from the arm contralateral to that used for drug administration. Drawing samples from peripheral arterial or venous lines or from a central line is permissible. PK collection times should be adhered to as strictly as possible. The allowed time window for all samples is: pre-dose in the two hours prior to starting the infusion of study drug; samples up to and including 1h, +/- 5 minutes; subsequent samples, +/- 15 minutes. Subject-specific PK kits for sampling including instructions on collection and processing methods, and storage and shipping conditions, will be provided separately. To maintain the blind, all subjects will have samples taken as outlined above: subjects receiving SAGE-547 will have all samples analyzed for all analytes. Subjects on placebo may have samples analyzed to investigate endogenous allopregnanolone and metabolite concentrations, as well as Captisol® concentrations; experience with the plasma concentration data will determine if and which placebo samples are analyzed.

Each blood sample will be 3 ml in volume for adults and children weighing 30 kg or more, and 1 ml in volume for children weighing less than 30 kg. Separate aliquots will be obtained from each sample to service the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum blood draw for PK analysis for a subject having two infusions of study drug will be 99 ml (33 ml for children weighing less than 30 kg).

Plasma PK parameters for SAGE-547 will be calculated where appropriate (e.g.,  $C_{max}$ ,  $C_{min}$ ,  $t_{max}$ ,  $AUC_{last}$ ,  $AUC_{\infty}$ ,  $CL_s$ ). In addition, similar PK parameters will be calculated for Captisol®. PK parameters for important metabolites of SAGE-547 may be calculated. An evaluation will be made of the feasibility of adopting a population-PK approach to assess drug-drug-interactions with SAGE-547 as victim of AEDs.

In addition, the Visit 9 sample may be analyzed for plasma concentrations of third-line agents.

#### Other Analysis

If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations. The minimum volume of cerebrospinal fluid for analysis is 100 microlitres.

Full details of all pharmacokinetic analyses will be described in the Pharmacokinetic Analysis Plan.

#### **11.2.8.2. Correlation of QT/QTc Changes and Plasma Concentrations of SAGE-547**

An analysis will be performed to determine whether there is any correlation between changes in QT/QTc interval and plasma concentrations of SAGE-547, in order to investigate any effect that SAGE-547 may have on QT/QTc interval.

#### **11.2.8.3. Pharmacoeconomic Data**

At Visit 12 or Visit 12R, the following information will be collected: number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital. If the subject dies before Visit 12 or Visit 12R, data will be collected up to the date of



death. The definition of “hospital” is the institution that the subject was initially treated in. If the subject is transferred to another hospital, that hospital would be the “discharge destination from the hospital” and the “number of days in hospital” would be the number of days in the initial treating hospital.

For those subjects discharged from hospital before Visit 12/12R, the following questions will be asked:

- On what study day was the subject discharged from hospital?
- What type of facility was the subject discharged to (another hospital, a rehabilitation center, a supported care facility, home, other)?
- How many days did the subject stay in this facility?

The following questions will be answered regarding the stay in the ICU and hospital:

- Was the subject still in the ICU at the end of Visit 10/10R?
- If the FOUR Score was  $\geq 12$  at Visit 10/10R and the subject was in the ICU at Visit 10/10R, what was the reason for the subject not being discharged from the ICU (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, other)?
- Was the subject still an in-patient in the hospital at the end of Visit 12/12R?
- If the FOUR Score was  $\geq 15$  at Visit 12/12R and the subject was in the hospital at Visit 12/12R, what was the reason for the subject not being discharged from the hospital (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, unsuitable home circumstances, other)?

#### **11.2.8.4. STESS**

The STESS will be assessed during Visit 1 in order to assess the severity of the status epilepticus.

#### **11.2.8.5. FOUR Score**

The Full Outline of UnResponsiveness or FOUR Score is designed to assess conscious level and unlike other scores, is suitable for subjects who are intubated. It assesses four domains of neurological function (eye responses, motor responses, brainstem reflexes, and breathing pattern).

The FOUR Score will be collected at the following time points relative to each infusion of study drug (the initial blinded infusion and the second open-label infusion if this is administered):

- baseline, +24, +48, +72, +96, +120, +144, +168, and +192 hours (all +/- 2 hours) after the start of the infusion, and at Visit 11/11R and Visit 12/12R.

#### **11.2.8.6. Glasgow Outcome Scale (GOS)**

The GOS is a relatively common assessment scale used to standardize descriptions of the objective degree of recovery from brain injury such as cerebral trauma, or in this case SRSE. It was first used in 1975 ([Jennett and Bond 1975](#)) and allows a prediction of the long-term course of rehabilitation to return to work and everyday life. The scale classifies subjects into 5 groups:

- Death

- Persistent vegetative state
- Severe disability
- Moderate disability
- Good recovery

The GOS will be assessed at Visit 12 or Visit 12R.

#### **11.2.8.7. Supervision Rating Scale (SRS)**

The Supervision Rating (SRS) measures the level of supervision that a patient/subject receives from caregivers. The SRS rates level of supervision on a 13-point ordinal scale that can optionally be grouped into five ranked categories (Independent, Overnight Supervision, Part-Time Supervision, Full-Time Indirect Supervision, and Full-Time Direct Supervision). The SRS was designed to be rated by a clinician based on interviews with the subject and an informant who has observed at first hand the level of supervision received by the subject (Boake 2000). Scoring is a one-step procedure in which the clinician assigns the rating that is closest to the subject's level. Ratings are based on the level of supervision received, not on how much supervision a subject is judged or predicted to need.

The SRS will be assessed at Visit 1 and Visit 12 or Visit 12R. The Visit 1 assessment will be a retrospective assessment of the supervision required by the subject immediately prior to the admission that included the index episode of status epilepticus.

#### **11.2.8.8. Modified Rankin Scale – 9Q (mRS-9Q)**

The Modified Rankin Scale (mRS) is a commonly used scale to determine disability and functional dependence due to neurological insult such as stroke in adults. The 7-point scale (0 – 6) denotes functional capacity from no symptoms (0) to severe disability (5) and death (6). The Modified Rankin Scale – 9Q is a shortened version consisting of 9 questions that reliably determines the mRS score and was developed to both simplify the assessment and expand the rater base to non- medically trained personnel (Patel, Rao et al. 2012). The assessment is a web-based tool in the public domain with automatic score calculation and error checking found at [www.modifiedrankin.com](http://www.modifiedrankin.com).

The mRS will be assessed at Visit 1 and at Visit 12 or Visit 12R in subjects  $\geq 17$  years of age. The baseline assessment will be a retrospective assessment of the disability and dependence of the subject immediately prior to the admission that included the index episode of status epilepticus.

## **12. STUDY PROCEDURES**

The study procedures listed below by study day reflect the required data collection times for this protocol. When a time window is necessary, this is specified below. If no time window is specified, the test may be performed at any time within the specified 24-hour period.

### **12.1. Visit 1 (V2- $\leq 30$ h)**

The baseline period will be up to approximately 84 hours prior to starting blinded study treatment and should include the assessments/procedures listed below and summarized in [Table 1](#) and [Table 2](#) (for open-label treatment), the Schedules of Events.

- Informed consent
- Eligibility checklist
- Verification of inclusion/exclusion criteria.
- Demographic information and medical history obtained by proxy and confirmed by the subject when possible.
- SE and wean history
- Blood will be collected from female subjects 10 years to 55 years for a serum pregnancy test unless they are known to be pre-menstrual or post-menopausal or to have had a hysterectomy.
- Blood and urine samples collected for clinical laboratory testing.
- Pharmacogenetic sample will be collected from consenting/eligible subjects.
- Vital signs
- Height
- Weight
- An ECG reading taken.
- Administration of the STESS.
- Administration of the FOUR Score.
- Administration of SRS.
- Administration of the mRS-9Q assessment.
- Assessment of the CGI scale.
- Evaluation of epilepsy status.
- Administration of continuous IV third-line agents.
- Perform EEG.
- Recording of adverse events.
- Recording of previous and concomitant anti-epileptic drugs.
- Recording of previous and concomitant third-line agents.
- Recording of concomitant pressors.
- Recording of other concomitant medications, procedures, and treatments.

## **12.2. Visit 2 (V3-≤54h)**

- Recording of adverse events.
- Recording of concomitant anti-epileptic drugs.
- Recording of concomitant third-line agents.
- Recording of concomitant pressors.

- Recording of other concomitant medications, procedures, and treatments.
- Wean of continuous third-line agent (QW):
  - If wean is successful, subject is followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (these subjects are Qualifying Wean Success subjects or QWS subjects);
  - If wean is not successful, there is ongoing intravenous administration of at least one continuous IV third-line agent and EEG is performed and the subject is randomized.
- Weight
  - Subject weight will be obtained within the eight-hour period from the declaration of failure of QW and prior to the initiation of the blinded infusion loading dose at H0 of V3. This weight will be the dosing weight used to determine the infusion rate for the entire blinded infusion treatment course.

### **12.3. SAGE-547 Treatment Period**

#### **12.3.1. Visit 3/3R (0-24 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs will be recorded at:
  - 0, +30, +60 minutes (+/-15 minutes) and +2, +4, +8 (+/- 30 minutes) and +24 hours (+/- 2 hours) after the start of the infusion
- For the first 50 subjects randomized in the study, ECG readings will be recorded immediately after PK sampling, or within 15 minutes prior to PK sampling, at the following time points:
  - 0 (pre-dose) and at +0.5, +1, +3, +6, +12, and +24 hours after the start of the study drug infusion.
  - Subsequent subjects randomized in the study will have ECG readings recorded at 0 (pre-dose) and +1, +12, and +24 hours after the start of the study drug infusion, it will not be necessary to collect these ECGs with PK samples at these timepoints and, apart from the +1 h ECG, there is +/- 2 hour time window for these ECGs.
- A blood sample for PK analysis should be collected at the following time points (all +/- 15 minutes except where otherwise stated):
  - 0 (pre-dose, within two hours of the start of the infusion) and at +0.5, +1 (+/- 5 minutes), +3, +6, +12, and +24 hours after the start of the study drug infusion.
- Completion of the FOUR Score
  - +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the final declaration of QW success)
- Ongoing intravenous administration of a continuous IV third-line agent.

- Study drug administration in loading (Hour 0-1) and maintenance infusions (at completion of Hour 1).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.3.2. Visit 4/4R (25-48 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +48 hours (+/- 2 hours) after the start of the infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +48 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +48 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +48 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +48 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent.
- Ongoing study drug maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.3.3. Visit 5/5R (49-72 hours)**

- Weight if easily obtained
- Vital signs should be recorded at:
  - +72 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +72 hours after the start of the study drug infusion

- Subsequent subjects randomized in the study will have an ECG reading recorded at +72 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +72 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +72 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.4. Visit 6/6R (73-96 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +96 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +96 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +96 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +96 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +96 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.

- Perform EEG.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.3.5. Visit 7/7R (97-120 hours)**

- Weight if easily obtained
- Vital signs should be recorded at:
  - +120 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +120 hours after the start of the study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +120 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected:
  - +120 hours (+/- 15 minutes) after the start of study drug infusion, immediately prior to the end of the maintenance infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +120 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled. Complete wean by 120 hours if at all possible.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## **12.4. SAGE-547 Taper Period**

### **12.4.1. Visit 8/8R (121-144 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:

- +144 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after each PK sampling, or within 15 minutes prior to PK sampling at the following time points:
  - +128, +136 hours and +144 hours after the start of the blinded study drug infusion
  - +126, +132, +138 hours and +144 hours after the start of the open-label study drug infusion
  - Subsequent subjects randomized in the study will have an ECG reading recorded at +144 hours after the start of the study drug infusion, it will not be necessary to collect the ECG with PK samples at this timepoint, and there is +/- 2 hour time window for this ECG collection.
- A blood sample for PK analysis should be collected (+/- 15 minutes unless otherwise stated):
  - +128 (immediately prior to the end of the first taper step), +136 hours (+/- 5 minutes, immediately prior to the end of the second taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of study drug infusion.
  - During the open-label study drug phase of the study PK blood draws at: +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 hours (+/- 5 minutes, immediately prior to the end of the third taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of the study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +144 hours (+/- 2 hours) after the start of the infusion
- Complete wean of third line agents by H144 if not completed by H120.
- Perform EEG.
- Taper of SAGE-547 infusion begins at hour 121.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## **12.5. Follow-up Period**

### **12.5.1. Visit 9/9R (145-168 hours)**

- Vital signs should be recorded at:
  - +168 hours (+/- 2 hours) after the start of the study drug infusion
- For the first 50 subjects randomized in the study, an ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at + 152 hours:
  - +152, +160 hours (+/- 2 hours) after the start of the study drug infusion



- A blood sample for PK analysis should be collected:
  - +152 and +160 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +168 hours (+/- 2 hours) after the start of the infusion
- Perform EEG.
- Assessment of the presence of physiologic brain activity using EEG.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.2. Visit 10/10R (169-192 hours)**

- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +192 hours (+/- 2 hours) after the start of the infusion
- At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine eligibility for the open-label treatment with the higher dose of study drug. This determination may occur at any point during Visit 10: the higher dose open-label infusion must begin within the Visit 10 window. All patients receiving the higher dose open-label treatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.
- Weight if the subject qualifies for the open-label study drug (Visit 10 only, not Visit 10R).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.3. Visit 11/11R (Visit 3/3R + 14d (±2))**

- Blood samples collected for clinical laboratory testing (renal panel only).
- Completion of the FOUR Score (QWS subjects also).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### 12.5.4. Visit 12/12R (Visit 3/3R + 21d ( $\pm 2$ ))

All assessments also performed for QWS subjects.

- Completion of the FOUR Score.
- Administration of the GOS.
- Administration of the SRS.
- Administration of the mRS-9Q assessment.
- Evaluation of epilepsy status (see [Section 11.1.2.2](#) for details).
- Assessment of the CGI Scale.
- Recording of adverse events.
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications.
- Collection of pharmacoeconomic data.
- Mortality will be assessed throughout the study period.

### 13. STATISTICS

#### 13.1. Statistical Plan

Complete details for the analysis and reporting of data from this study will be contained in the Statistical Analysis Plan (SAP).

##### 13.1.1. Interim Analysis

When approximately 50% of subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

##### 13.1.2. Study Populations

The **Safety Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to actual treatment. This analysis population will be used for all safety analyses.

The **Intent to Treat Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to randomized treatment. This analysis population will be used for all efficacy analyses.

The **Modified Intent to Treat Population** is defined as all subjects who:

1. complete their initial course of blinded SAGE-547 or placebo treatment unless the non-completion was due a drug-related adverse event; and

2. have at least one attempt to wean from third-line agents prior to the end of blinded study treatment infusion unless the failure to wean was because seizures were not controlled.

Subjects will be classified according to randomized treatment. This analysis population will be used for sensitivity analyses of the primary endpoint and select secondary efficacy endpoints.

Narratives will be prepared for all subjects who do not complete the infusion of blinded study medication or were not subjected to any wean attempts. Narratives will include details of the cause of SE, the comorbid conditions, the adverse event(s), and reasons for non-completion of the infusion or failure to attempt weaning. This blinded narrative will be reviewed by the medical monitors and the patient adjudicated as MITT eligible or ineligible. Acceptable reasons for defining a subject as MITT ineligible include death or withdrawal of consent due to progression of the underlying cause of SE or comorbid conditions, unless the cause of death or progression of disease were thought by the investigator, sponsor, or DSMB to be related to study drug.

The **Per-Protocol (PP) Population** is defined as a subset of the MITT population but will exclude data from all subjects with significant protocol violations or deviations. Subjects will be classified according to actual treatment received. This data set will be used for sensitivity analyses to examine the robustness of results for the primary and key secondary efficacy endpoints.

The **Pharmacokinetics Population** is defined as all subjects who at least had an infusion of blinded SAGE-547 initiated and have at least one pharmacokinetic sample collected.

The **Pharmacogenetic Population** is defined all subjects who consent to being included in the pharmacogenetic assessment and provide a pharmacogenetic sample.

Summary statistics of all data collected will be presented for subjects who were QW successes.

### 13.1.3. General Aspects

Tabular displays of descriptive statistics will be provided for all variables. Summary tables will include n, mean, mean, standard deviation, minimum and maximum for continuous variable and frequency and percentage for categorical variables.

### 13.1.4. Analysis of Primary Endpoint

The analysis of response to treatment (see Section 11.1.1 for definition of primary endpoint) between SAGE-547 treated subjects and placebo treated subjects will be performed on the ITT population using a Cochran-Mantel-Haenszel (CMH) test with variables for treatment, concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). The CMH general association statistic and its associated p-value will be presented. The comparison of treatment response rates will be conducted at the 5% level of significance. To confirm the CMH results, a permutation test will also be conducted.

An additional analysis of the primary endpoint will also be performed on the MITT population. In addition sensitivity analyses of the primary endpoint will be performed using the ITT population based on:

- the number of third-line agents (one, two, or three) subjects were administered post-randomization; and
- which third line agent was the subject of the first TW.

### **13.1.5. Analysis of Secondary Efficacy Endpoints**

Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section (Section 6). Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. The analysis of the secondary endpoints will also be performed on the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

### **13.1.6. Analysis of Other Endpoints**

Safety and “Other” endpoints will only be summarized by treatment group. Summaries of safety endpoints will be based on the overall Safety Population.

### **13.1.7. Epilepsy and SRSE Status**

Diagnosis of epilepsy and recurrence of RSE or SRSE will be documented as the percentage of subjects by time point and overall. Kaplan-Meier curves may be plotted if sufficient data are available.

Utilization of AEDs during follow-up and during recurrence will be summarized.

### **13.1.8. Questionnaires**

The data collected from each questionnaire will be interpreted according to the standard methodology for that questionnaire. There will be no adjustment for missing values.

### **13.1.9. Pharmacokinetic Data Analysis**

Details of the pharmacokinetic data analysis will be described in detail in a separate Pharmacokinetic Analysis Plan.

### **13.1.10. Pharmacogenetic Data Analysis**

Any genotype data generated in this study will be stored within a secured database within Sage Therapeutics and / or a third party contracted to work with Sage Therapeutics to analyze the samples. Because the number of subjects agreeing to participate in the genetic research component of the study is unknown, it is not possible to establish, a priori, whether sufficient samples will be obtained to support formal statistical evaluation of data. As a consequence a Pharmacogenetic Analysis Plan will only be prepared where appropriate and the results obtained from any genetic research will be reported in a report separate from the main study CSR.

**13.1.11. Open-Label Study Drug Subjects**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are treated with SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo.

**13.1.12. EEG-Responders**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who are classified as EEG-responders/non-responders based on the independent assessment of the PAEEG. Summaries will be derived for the two randomized treatment groups.

**13.1.13. QT/QTc Assessment**

An analysis of the correlation between changes in QT/QTc intervals and SAGE-547 plasma levels will be performed to investigate if there is a potential effect that SAGE-547 may have on QT/QTc interval. A detailed description of the QT/QTc assessment will be included in the SAP.

**13.1.14. Quantitative EEG**

The nine EEG records for each subject may be subjected to exploratory quantitative EEG analysis, the details of which will be included in the EEG Analysis Plan. In summary the following comparisons may be made, SAGE-547 versus placebo: the QWEEG versus the TWEEG (main analysis); the CEEG versus PAEEG (subsidiary analysis); and TAEED versus PAEEG (exploratory analysis).

**13.2. Determination of Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between treatment groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

**13.3. Statistical Analysis Plan**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

**14. ADVERSE EVENTS**

The safety procedures in this study will be detailed in a Safety Management Plan, which will be agreed and signed before the first subject is randomized in the study. [Section 14.1](#) summarizes Investigator responsibilities regarding the identification and documentation of AEs, the classification of AEs for relationship to study drug and severity, and the reporting of AE information to the Sponsor and the IRB.

[Section 14.2](#) summarizes Sponsor/Medical Monitor Responsibilities regarding monitoring of AE data and reporting relevant safety information to FDA.

[Section 14.3](#) lists important AE definitions.

## 14.1. Investigator Responsibilities

### 14.1.1. Identification and Documentation of Adverse Events by Investigator

Subjects will be evaluated and questioned generally (if possible) to identify AEs during the course of the study. AEs will be collected from the signature of the consent form through Visit 12/12R. Adverse events that occur prior to completion of screening will be captured on the Medical History eCRF. Adverse events that occur after completion of screening will be recorded on the Adverse Event eCRF.

All AEs revealed by observation, other diagnostic procedures, or spontaneously reported by the subject and/or in response to an open question from study personnel will be recorded on the Adverse Event Form. Any clinically significant deterioration in laboratory assessments or other clinical findings are considered an AE and must be recorded on the Adverse Event Form, unless otherwise stated. AE information recorded will be entered into the database on an ongoing basis.

AEs with a relationship considered related to study drug (probable, possible) should be followed until the event is resolved or the Investigator determines the event is stable or no longer clinically significant. AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

For SAEs, an electronic Serious Adverse Event eCRF must be completed with as much information as possible and submitted in the time frame described below in [Section 14.1.3](#). When new significant information is obtained as well as when the outcome of an event is known, the electronic SAE eCRF should be updated within 24 hours. If the subject was an outpatient at the time of the SAE and was re-hospitalized due to the SAE, a copy of relevant hospital records (e.g., admission report, laboratory test results, discharge summary, etc.) may be requested to be included as part of the subject medical file.

All SAEs will be followed until resolved or until a stable status has been achieved.

### 14.1.2. Adverse Event Classification

#### 14.1.2.1. Relationship to Investigational Drug

None:	No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state.
Possible:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject, but this is not known for sure.
Probable:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

**14.1.2.2. Severity**

Mild	Discomfort noticed, but no disruption to daily activity.  For subjects that are unconscious, this may be a slight or minor change in a lab result or clinical sign or symptom that does not require immediate corrective action.
Moderate	Discomfort sufficient to reduce or affect normal daily activity, but is not hazardous to health; prescription drug therapy may be employed to treat the AE.  For subjects that are unconscious, this may be a clinically meaningful change that may require immediate corrective action.
Severe	Inability to work or perform normal daily activity and represented a definite hazard to health; prescription drug therapy and/or hospitalization may be employed to treat the AE.  For unconscious subjects, this may be a significant clinical change that requires immediate corrective action.

**14.1.2.3. Action Taken with Investigational Drug**

None	Study medication was continued without change.
Discontinued	Study medication was terminated.
Dose adjusted	Study medication dose/infusion rate was changed and then continued per protocol.
Interrupted	Study medication was interrupted and then continued per protocol.
Unknown	The action taken with regard to study medication is unknown.
Not applicable	Administration of study medication was not ongoing.

**14.1.2.4. Assessment of Outcome**

Ongoing	At the end of the study, the event has not resolved or stabilized.
Ongoing and stable	The event is ongoing but has stabilized and is unlikely to change
Resolved	The event has resolved or the subject recovered without sequelae.
Resolved with sequelae	The event has at least one secondary outcome that may result in permanent disability and/or functional limitation.
Unknown	The status of the event is unknown.
Death	The subject has expired.

**14.1.3. Investigator Reporting to Sponsor and Sponsor Emergency Contact**

All new SAEs that come to the Investigator and/or Sponsor's notice during the course of the study (up to and including the last study visit) must be reported by the Investigator on the designated electronic report form within 24 hours of the point in time when the Investigator becomes aware of the SAE. As additional information becomes available, the designated electronic report form must be updated within 24 hours.

Investigators must report any SAE, whether or not considered drug related. The report must include an assessment of whether there is a reasonable possibility that the drug caused the event.

In a medical emergency (i.e., an event that requires immediate attention regarding the treatment of a subject, operation of the clinical study, and/or the use of investigational drug), study site staff will apply appropriate medical intervention according to current standards of care, and contact the Medical Monitor.

**14.1.4. Medical Monitor and Emergency Contact Information**

[REDACTED], MD  
[REDACTED]

In a study related medical emergency situation, when the assigned Medical Monitor cannot be reached by a caller, an on-call Physician can be reached 24 hours per day, 7 days per week via an [REDACTED] Call-Center:

- Telephone: [REDACTED]  
(this is a chargeable telephone number allowing a global reach from both landlines and mobile phones)
- [REDACTED]

On this internet page a list of country-specific toll-free telephone numbers is provided. It should be noted that not all countries globally have access to toll-free numbers as indicated on the "24/7 Medical Help desk" index. Countries without toll-free numbers need to dial the chargeable number as indicated above. Furthermore, toll-free numbers are not available from mobile phones.

**14.1.5. SAE Reporting Contact Information**

Contact information and reporting instructions are provided in the Safety Management Plan.

**14.1.6. Reporting to Institutional Review Boards (IRBs)**

It is the responsibility of the Investigator to promptly notify the institution's IRB of all serious and unexpected suspected adverse reactions (see [Section 14.3](#) for definitions).



## **14.2. Sponsor/Medical Monitor Responsibilities**

### **14.2.1. Monitoring of Adverse Event Data**

The Medical Monitor will review any newly reported adverse events in an ongoing basis. If the aggregate assessment indicates that an event is occurring more frequently than would normally be expected in this population, or as previously observed, and the sponsor believes that the events are causally related to the administration of SAGE-547, the Sponsor will then report that information in an IND safety report.

### **14.2.2. Data Safety Monitoring Board**

An independent DSMB will monitor the clinical, PK and PD data for safety signals throughout the study and will be asked to assess the placebo response rate at the time of the interim analysis to determine final sample size. In order to perform their monitoring function the DSMB will have access to un-blinded safety data as necessary.

The composition and procedures for the board will be described in a separate DSMB Charter.

### **14.2.3. Reporting to FDA**

The Sponsor must report in an IND safety report any suspected adverse reaction to study treatment that is both serious and unexpected (21 CFR 312.32(c)(1)(i)). Before submitting an IND safety report, the Sponsor will ensure the event meets all three of the definitions: (1) suspected adverse reaction, (2) serious, (3) unexpected. If the AE does not meet all three of the definitions, it should not be submitted as an IND safety report. The Sponsor should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the adverse event and, therefore, that the event meets the definition of a suspected adverse reaction.

If there is a serious and unexpected suspected adverse reaction, the Sponsor will notify the appropriate regulatory agency(ies) and all appropriate parties on an expedited basis. In addition, Sponsors must submit expedited reports of an increased rate of occurrence or severity of serious suspected adverse reactions over that listed in the protocol or Investigational Brochure.

SUSARs will be unblinded prior to reporting to FDA. Unless it is necessary to unblind for the safety of the patient, the investigator will not be informed of the unblinding of the subject.

Under 21 CFR 312.32, Sponsors should identify in the protocol SAEs that it does not plan to report individually in an expedited manner, because they are known consequences of the disease or otherwise common in the study population. Given the grave condition and prognosis of SRSE being studied, individual occurrences of seizures or seizure activity will not be reported expeditiously in this study. Regardless of which events are reported in an expedited manner, all adverse events will be closely monitored throughout the study.

### **14.2.4. Reporting to European Regulatory Authorities**

The Sponsor or its designee is responsible for SUSAR notification to the relevant regulatory authorities as outlined in the ICH Guidelines. All investigators participating in the study will also be informed as required by regulations.

Any SUSAR is subject to expedited reporting in the EU. The Sponsor or its designee, will report any single SUSAR to the appropriate National CAs and IECs within 7 days if the SUSAR is life-threatening or fatal (with the relevant follow-up information subsequently communicated within an

additional eight days), and within 15 days if the SUSAR is neither life-threatening nor fatal. SUSARs reported will be those that have arisen in the present clinical trial and SUSARs that have arisen in other clinical trials conducted by the Sponsor with the same medicinal product.

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to competent authorities of the concerned Member States and to IEC(s)/IRBs as required by national laws.

### **14.3. Adverse Event Definitions**

#### **14.3.1. Adverse Event**

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

#### **14.3.2. Suspected Adverse Reaction**

Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

#### **14.3.3. Life-Threatening**

An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

#### **14.3.4. Serious**

An AE or suspected adverse reaction is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE – see definition above
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disability
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

#### **14.3.5. Unexpected**

An AE or suspected adverse reaction is considered “unexpected”:

- If it is not listed in the Investigational Brochure or is not listed at the specificity or severity that has been observed, or
- If an Investigational Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigational Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigational Brochure listed only cerebral vascular accidents.

“Unexpected,” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigational Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

#### **14.4. Emergency Identification of Study Medication**

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject’s treatment in the study via the IVRS; this normally requires prior approval by the medical monitor. However, if the subject is at immediate risk and the Investigator believes that immediate knowledge of the study treatment will alter medical management, discussion with the medical monitor may take place after unblinding. The Investigator will not unblind the medical monitor during that discussion. The process of unblinding will ensure that only the investigator is unblinded; the medical monitor, study management team, and data management team will not be made aware of the treatment allocation of an individual subject. All cases of emergency unblinding will be fully documented in a way that does not unblind the medical monitor, study management team, and data management team.

### **15. STUDY ADMINISTRATIVE CONSIDERATIONS**

#### **15.1. Quality Control and Quality Assurance**

The Investigators and institutions will permit trial related monitoring, audits, IRB review, and regulatory inspections as requested by FDA, the Sponsor, or the Sponsor’s designee, including direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed informed consent forms, etc.) in addition to case report forms.

Quality assurance and quality control systems with written standard operating procedures (SOPs) will be followed to ensure this trial will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The site’s dedicated study monitor will arrange to visit the Investigator at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be identified and resolved. The study monitor will be given access

to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality assurance officers named by Sage Therapeutics or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements, made by the Sponsor with the Investigator/institution and any other parties involved with the clinical trial, will be in writing in a separate agreement.

## **15.2. Data Handling and Recordkeeping**

### **15.2.1. Data Handling**

Procedures for data handling (including electronic data) used in this protocol will be documented in a Data Management Plan.

### **15.2.2. Case Report Form Completion**

eCRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of demographics, study drug administration, study procedures, AEs, questionnaire completion, efficacy assessments and subject status, including survival.

The Investigator will maintain copies of the eCRFs at the study site. For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate eCRF.

### **15.2.3. Retention of Study Records**

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval and until there are no pending or contemplated marketing applications or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to an appropriate person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

## **15.3. Confidentiality**

To maintain subject privacy, all eCRFs, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available trial registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by Sage Therapeutics to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

#### **15.4. Publication Policy**

All information concerning SAGE-547 is considered confidential and shall remain the sole property of Sage Therapeutics. The Investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval from Sage Therapeutics. No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between Sage Therapeutics and the Investigator.

#### **15.5. Protocol Amendments**

Changes to the conduct of the study should be prepared as a protocol amendment by the Sponsor. Protocol amendments should receive written IRB/IEC approval prior to implementation at the investigative site, except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the trial (e.g., change of monitor, telephone numbers). In this case, Sage Therapeutics will amend and implement the protocol change and subsequently notify the regulatory authorities and the Investigative sites who will notify the respective IRB, as appropriate.

## 16. REFERENCES

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**APPENDIX 1. APPENDIX 1: FOUR SCORE****FOUR score****Full Outline of UnResponsiveness****Eye response**

- E4: eyelids open or opened, tracking, or blinking to command
- E3: eyelids open but not tracking
- E2: eyelids closed but open to loud voice
- E1: eyelids closed but open to pain
- E0: eyelids remain closed with pain

**Motor response**

- M4: thumbs-up, fist or peace sign
- M3: localizing to pain
- M2: flexion response to pain
- M1: extension response to pain
- M0: no response to pain or generalized myoclonus status

**Brainstem reflexes**

- B4: pupil and corneal reflexes present
- B3: one pupil wide and fixed
- B2: pupil or corneal reflexes absent
- B1: pupil and corneal reflexes absent
- B0: absent pupil, corneal and cough reflex

**Respiration pattern**

- R4: not intubated, regular breathing pattern
- R3: not intubated, Cheyne-Stokes breathing pattern
- R2: not intubated, irregular breathing
- R1: breathes above ventilatory rate
- R0: breathes at ventilator rate or apnea

Reference ([Iyer, Hoel et al. 2009](#)).



**APPENDIX 2. GLASGOW OUTCOME SCALE (GOS)****GLASGOW  
OUTCOME  
SCALE**

Patient Name: \_\_\_\_\_  
 Rater Name: \_\_\_\_\_  
 Date: \_\_\_\_\_

*Note:* The scale presented here is based on the original article by Jennett and Bond. It has become common practice in clinical trial administration, however, to use a modified version that places the scores in reverse order (i.e., "good recovery" = 1, "moderate disability" =2, etc.).

Score	Description
1	DEATH
2	PERSISTENT VEGETATIVE STATE Patient exhibits no <i>obvious cortical</i> function.
3	SEVERE DISABILITY (Conscious but disabled). Patient depends upon others for daily support due to mental or physical disability or both.
4	MODERATE DISABILITY (Disabled but independent). Patient is independent as far as daily life is concerned. The disabilities found include varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes.
5	GOOD RECOVERY Resumption of normal activities even though there may be minor neurological or psychological deficits.

**TOTAL (1-5):** \_\_\_\_\_

Reference ([Jennett and Bond 1975](#)).

## APPENDIX 3. SUPERVISION RATING SCALE (SRS)

### SUPERVISION RATING SCALE (SRS)

**Instructions:** Circle the rating that is closest to the amount of supervision that the patient *actually receives*. "Supervision" means that someone is responsible for being with the patient.

<u>Rating</u>	<u>Description</u>
<b>Level 1: INDEPENDENT</b>	
1	The patient lives alone or independently. Other persons can live with the patient, but they cannot take responsibility for supervision (for example, a child or elderly person).
2	The patient is unsupervised overnight. The patient lives with one or more persons who <i>could</i> be responsible for supervision (for example, a spouse or roommate), but they are <i>all</i> sometimes absent overnight.
<b>Level 2: OVERNIGHT SUPERVISION</b>	
3	The patient is only supervised overnight. One or more supervising persons are always present overnight but they are <i>all</i> sometimes absent for the rest of the day.
<b>Level 3: PART-TIME SUPERVISION</b>	
4	The patient is supervised overnight and part-time during waking hours, but is allowed on independent outings. One or more supervising persons are always present overnight and are also present during part of waking hours every day. However, the patient is sometimes allowed to leave the residence without being accompanied by someone who is responsible for supervision.
5	The patient is supervised overnight and part-time during waking hours, but is unsupervised during working hours. Supervising persons are <i>all</i> sometimes absent for enough time for them to work full-time outside the home.
6	The patient is supervised overnight and during most waking hours. Supervising persons are <i>all</i> sometimes absent for periods longer than one hour, but less than the time needed to hold a full-time job away from home.
7	The patient is supervised overnight and during almost all waking hours. Supervising persons are <i>all</i> sometimes absent for periods shorter than one hour.
<b>Level 4: FULL-TIME INDIRECT SUPERVISION</b>	
8	The patient is under full-time indirect supervision. At least one supervising person is <i>always</i> present, but the supervising person does not check on the patient more than once every 30 minutes.
9	Same as #8 plus requires overnight safety precautions (for example, a deadbolt on outside door).
<b>Level 5: FULL-TIME DIRECT SUPERVISION</b>	
10	The patient is under full-time direct supervision. At least one supervising person is always present and the supervising person checks on the patient more than once every thirty minutes.
11	The patient lives in a setting in which the exits are physically controlled by others (for example, a locked ward).
12	Same as #11 plus a supervising person is designated to provide full-time line-of-sight supervision (for example, an escape watch or suicide watch).
13	The patient is in physical restraints.

3/12/93

Corwin Boake, Ph.D., TIRR, 1333 Moursund, Houston, TX 77030-3405, 713/799-6990

## APPENDIX 4. MODIFIED RANKIN SCALE – LEVEL OF FUNCTION SURVEY (mRS-9Q)

1. Do you have any symptoms that are bothering you? (For example, trouble with reading or writing, trouble speaking, problems with vision, numbness, weakness, balance trouble, or problems with swallowing?)	YES <input type="radio"/>	NO <input type="radio"/>
2. Are you able to do the same work as before?	YES <input type="radio"/>	NO <input type="radio"/>
3. Are you able to keep up with your hobbies?	YES <input type="radio"/>	NO <input type="radio"/>
4. Have you maintained your ties to friends and family?	YES <input type="radio"/>	NO <input type="radio"/>
5. Do you need help making a simple meal, doing household chores, or balancing a checkbook?	YES <input type="radio"/>	NO <input type="radio"/>
6. Do you need help with shopping or traveling close to home?	YES <input type="radio"/>	NO <input type="radio"/>
7. Do you need another person to help you walk?	YES <input type="radio"/>	NO <input type="radio"/>
8. Do you need help with eating, going to the toilet, or bathing?	YES <input type="radio"/>	NO <input type="radio"/>
9. Do you stay in bed most of the day and need constant nursing care?	YES <input type="radio"/>	NO <input type="radio"/>

## APPENDIX 5. CLINICAL GLOBAL IMPRESSION (CGI)

### Clinical Global Impression (CGI)

#### 1. Severity of illness

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- |                             |   |
|-----------------------------|---|
| 0 = Not assessed            | 4 = Moderately ill                        |
| 1 = Normal, not at all ill  | 5 = Markedly ill                          |
| 2 = Borderline mentally ill | 6 = Severely ill                          |
| 3 = Mildly ill              | 7 = Among the most extremely ill patients |

#### 2. Global improvement: Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.

Compared to his condition at admission to the project, how much has he changed?

- |                        |                     |
|------------------------|---------------------|
| 0 = Not assessed       | 4 = No change       |
| 1 = Very much improved | 5 = Minimally worse |
| 2 = Much improved      | 6 = Much worse      |
| 3 = Minimally improved | 7 = Very much worse |

#### 3. Efficacy index: Rate this item on the basis of drug effect only.

Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.

EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

#### Therapeutic effect

#### Side effects

		None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
<b>Marked</b>	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
<b>Moderate</b>	Decided improvement. Partial remission of symptoms	05	06	07	08
<b>Minimal</b>	Slight improvement which doesn't alter status of care of patient	09	10	11	12
<b>Unchanged or worse</b>		13	14	15	16

Not assessed = 00

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

**APPENDIX 6. STATUS EPILEPTICUS SEVERITY SCORE (STESS)**

Outcome Predictor	Feature	Score
Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type (prior to first treatment)	Simple-partial, complex-parial, absence, myoclonic (complicating idiopathic generalized epilepsy)	0
	Generalized-convulsive	1
	Nonconvulsive status epilepticus in coma	2
Age	< 65 years	0
	≥ 65 years	2
History of previous seizures	Yes	0
	No or unknown	1
Summed Total		

**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED  
STUDY TO EVALUATE THE EFFICACY AND SAFETY OF  
SAGE-547 INJECTION IN THE TREATMENT OF SUBJECTS  
WITH SUPER-REFRACTORY STATUS EPILEPTICUS**

**PROTOCOL NUMBER: 547-SSE-301**

**IND NUMBER: 117901**

**EudraCT Number: 2015-002142-31**

Product: SAGE-547 Injection (allopregnanolone)

Sponsor Contact: [REDACTED], MD

[REDACTED]  
Sage Therapeutics  
215 First Street  
Cambridge, MA 02142

Medical Monitor: [REDACTED], MD

Date of Protocol: 09 March 2015  
Date of Amendment One 27 May 2015  
Date of Amendment Two 17 November 2015  
Date of Amendment Three 22 April 2016

**Confidentiality Statement**

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

**PROTOCOL NUMBER: 547-SSE-301**

Sponsor [REDACTED]:

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]:

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]:

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

CRO [REDACTED]:

[REDACTED]

## 1. SIGNATURE PAGE

Title of Protocol:

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus

Protocol No: 547-SSE-301

### Sponsor Approval

[Redacted Signature]

25 April 2016

[Redacted Name], MD  
[Redacted Title]

Date (dd/mm/yyyy)

Sage Therapeutics

### Investigator Agreement

By signing this page I attest that I have read and understand the contents of Clinical Protocol 547-SSE-301 and any current amendments. I agree to adhere to the design, conduct, and reporting requirements of the study as stated in the clinical protocol and to my obligations to the Sponsor as described in the protocol and executed contracts between myself, my Institution, and the Sponsor. I also agree to adhere to any subsequent amendments to the clinical protocol.

Investigator's Signature: \_\_\_\_\_

Investigator's Name: \_\_\_\_\_

Institution: \_\_\_\_\_

Date: \_\_\_\_\_



## 2. SYNOPSIS

<b>Name of Sponsor:</b> Sage Therapeutics 215 First Street Cambridge, MA 02142																							
<b>Protocol No.</b> 547-SSE-301		<b>Phase:</b> 3																					
<b>Name of Investigational Product:</b> SAGE-547 Injection																							
<b>Name of Active Ingredient:</b> Allopregnanolone																							
<b>Title of the Protocol:</b> A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus																							
<b>Dosing Regimen: SAGE-547 or Placebo Dosing Schedule</b> <table border="1"> <thead> <tr> <th>Hour</th> <th>Type and Duration of SAGE-547 Infusions</th> <th>Dose</th> </tr> </thead> <tbody> <tr> <td>H1</td> <td>One hour loading Infusion</td> <td>300 µg/kg/h</td> </tr> <tr> <td>H2 – H120</td> <td>119 hour maintenance infusion</td> <td>90 µg/kg/h</td> </tr> <tr> <td>H121 – H128</td> <td>8 hour taper</td> <td>65 µg/kg/h</td> </tr> <tr> <td>H129 – H136</td> <td>8 hour taper</td> <td>45 µg/kg/h</td> </tr> <tr> <td>H137 – H144</td> <td>8 hour taper</td> <td>25 µg/kg/h</td> </tr> </tbody> </table>			Hour	Type and Duration of SAGE-547 Infusions	Dose	H1	One hour loading Infusion	300 µg/kg/h	H2 – H120	119 hour maintenance infusion	90 µg/kg/h	H121 – H128	8 hour taper	65 µg/kg/h	H129 – H136	8 hour taper	45 µg/kg/h	H137 – H144	8 hour taper	25 µg/kg/h			
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H139 – H144	6 hour taper	35 µg/kg/h																					
<b>Study Sites</b> Up to 180 sites in the USA, Israel, Europe, and Canada.																							
<b>Number of Subjects</b> The study will randomize 140 subjects at up to 180 sites.																							

**Study Population**

Subjects will be aged two years or more, in SRSE<sup>1</sup> (as defined in the Inclusion Criteria [Section 8.1](#)), and being managed in an intensive care setting.

**Duration of Subject Involvement**

Individual subject participation will be up to 30 days.

**Study Design**

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

Patients will follow one of three paths to entry to the study. The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst suppression with a third-line agent. These subjects will be consented for the study after admission to the intensive care unit, but before any third-line agents are administered for burst suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their legally authorized representative (LAR).

Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours. Once burst suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The second path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst suppression pattern on the EEG. These subjects may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The third path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These subjects may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to

<sup>1</sup> In this study, the term Super-Refractory Status Epilepticus or SRSE is equivalent to "Refractory Status Epilepticus (RSE) that has failed standard treatment" and the two terms are used interchangeably.

concomitant SAGE-547 treatment or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within six hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo).

The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that subjects, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as both the ability to wean the subject off all third-line agents before the end of the infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication infusion, and concurrent signs of physiologic brain activity as determined by EEG. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#) and [Table 2](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo will all subsequently be eligible to be administered SAGE-547 at the higher dose.

### Visit Schedule

The visit schedule and an overview of events at each visit is provided in [Table 1](#), [Table 2](#) and [Table 3](#) Schedule of Assessments.

### Study Objectives

#### *Primary objective:*

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult and pediatric subjects with SRSE, and for the response to endure at least 24 hours after the end of the SAGE-547 or placebo infusion (primary response).

#### *Secondary objectives:*

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in the Clinical Global Impression scale (CGI) between SAGE-547 and placebo up to Visit 12;

5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

***Safety objectives:***

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

***Other objectives:***

1. To evaluate the impact of treatment with a higher dose SAGE-547 infusion;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;
6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS) (age  $\geq 17$  years).

**Endpoints**

***Primary endpoint:***

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

***Secondary endpoints:***

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;

2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

***Safety endpoints:***

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.

***Other endpoints:***

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who are treated with a higher dose of SAGE-547.
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS) (age ≥17 years).

**Inclusion Criteria**

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects two (2) years of age and older.
2. Subjects who have:

- Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
- Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
- Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst suppression pattern; or who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst suppression pattern.

### **Exclusion Criteria**

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone or any excipients in SAGE-547.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy.
4. Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing underlying neurological disorder.
5. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis but for whatever reason, dialysis that would adequately remove Captisol® is not planned;
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the opinion of the investigator, of less than 30 days;
  - e. a do not resuscitate (DNR) order.
6. Subjects who are being administered more than three third-line agents concomitantly or in whom the qualifying wean cannot be completed within 24 hours, or who are being administered a third-line agent for other indications such as management of raised intra-cranial pressure that would preclude weaning according to this protocol.
7. Subjects with a living will that does not allow heroic measures.
8. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.

9. Subjects who have been treated or randomized in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not have received study drug/placebo and then re-enroll).

### **Pharmacogenetic Research**

In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **Statistical Analysis**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

#### **Interim Analysis**

When approximately 50% of the subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### **Analysis of Primary Endpoint**

The analysis of response to treatment between SAGE-547 treated subjects and placebo treated subjects will be performed using a Cochran-Mantel-Haenszel test with variables for treatment, concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). In this analysis, a treatment responder is a subject who is successfully weaned off all third-line agents and blinded study medication prior to the end of study treatment infusion and remains off third-line agents for at least 24 hours following cessation of the blinded study medication, and who has concurrent signs of physiologic brain activity as determined by EEG. The analysis will be based on the ITT Population. The comparison of treatment response rates will be conducted at the 5% level of significance.

### **Analysis of Secondary Efficacy Endpoints**

The primary analysis will be repeated for the MITT population. Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section. Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. Secondary analyses will be repeated for the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from Baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third-line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

Summaries of safety endpoints will be based on the overall Safety Population which is defined as all subjects who at least initiated the infusion with blinded study treatment.

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who are treated with a higher dose of SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo. Summary statistics will be presented for subjects who were QW successes.

**Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).



**Table 1: Schedule of Assessments for Protocol 547-SSE-301: One Infusion of Study Drug (blinded)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical/SE/Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X	X	X	X	X	X	X	X		X		
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X		X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X		X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X		X	X		X		X		X		
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X			
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>o</sup>											X
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV 3rd-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>p</sup>				
EEG	X	X			X			X	X			
Randomization		X										
Study Drug Administration <sup>q</sup>			X	X	X	X	X	X				
TW Outcome & Open-label Treatment Decision										X <sup>r</sup>		
Physiologic Brain Activity									X			
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

**Table 2: Schedule of Assessments for Protocol 547-SSE-301: Two Infusions of Study Drug (one blinded, one open-label)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V3R
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	0-24h
Eligibility Checklist	X										S
Informed Consent <sup>a</sup>	X										E
Inclusion/Exclusion Criteria	X										E
Demography <sup>b</sup>	X										
Medical and SE and Wean History <sup>c</sup>	X										T
Height	X										A
Weight <sup>d</sup>	X	X	X	X	X	X	X	X		X	B
Serum Pregnancy Test <sup>e</sup>	X										L
Hematology <sup>f</sup>	X		X	X		X		X		X	E
Serum Chemistry and GFR <sup>g</sup>	X		X	X		X		X		X	
Urinalysis <sup>h</sup>	X		X	X		X		X		X	E
Pharmacogenetic sample	X										X
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X	T
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X	E
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X		N
STESS	X										I
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	O
Glasgow Outcome Score (GOS)											N
Supervision Rating Scale (SRS)	X <sup>o</sup>										
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>										
Epilepsy Status	X										N
Clinical Global Impression (CGI)	X										E
Continuous IV Third-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>p</sup>			X
EEG	X	X				X		X	X		T
Randomization		X									
Study Drug Administration <sup>q</sup>			X	X	X	X	X	X			
TW Outcome and Open-label Treatment Decision										X <sup>r</sup>	P
Physiologic Brain Activity									X		
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	A
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	G
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	E
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X	
Pharmacoeconomic Data											
Mortality											

**Table 2 continued**

	V3R	V4R	V5R	V6R	V7R	V8R	V9R	V10R	V11R	V12R
	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3R+14d (±2d)	V3R+21d (±2d)
Weight <sup>d</sup>	X	X	X	X	X	X				
Serum Pregnancy Test <sup>e</sup>										
Hematology <sup>f</sup>	X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X	X		X		X		X		
Vital Signs <sup>i</sup>	X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>	X	X	X	X	X	X	X			
STESS										
FOUR Score <sup>m</sup>	X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)										X
Supervision Rating Scale (SRS)										X
Modified Rankin Score (mRS) <sup>n</sup>										X
Epilepsy Status										X
Clinical Global Impression Scale (CGI)										X
Continuous IV Third-Line Agent(s)	X	X	Wean	Wean	Wean	Wean <sup>p</sup>				
EEG			X			X	X			
Randomization										
Study Drug Administration <sup>q</sup>	X	X	X	X	X	X				
TW Success and Physiologic Brain Activity							X			
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data										X
Mortality										X

**Table 3: Schedule of Assessments for Protocol 547-SSE-301: Qualifying Wean Successes**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical and SE and Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X											
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X											
Serum Chemistry and GFR <sup>f</sup>	X											
Urinalysis <sup>h</sup>	X											
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X											
ECG <sup>j</sup>	X											
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>o</sup>											X
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV Third-Line Agent(s)	X	Wean										
EEG	X	X										
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

<sup>a</sup> Written informed consent by proxy (LAR) will be obtained prior to starting any study-related procedures not considered standard of care.

<sup>b</sup> Demographic information will be obtained by proxy and confirmed by the subject when possible.

<sup>c</sup> Medical history will be obtained by proxy and confirmed by the subject when possible. All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Dosing changes with the third-line agent(s) that constitute a wean attempt will be marked as such on the CRF, and the start/stop dates and times of all wean attempts prior to V3 will be recorded, as well as the outcome of the wean attempt.

<sup>d</sup> Weight will be collected at Screening (V1) and prior to administration of the blinded study drug infusion at V2 and the open-label study drug infusion at V10. The weights at V2 and V10 will be used to determine the appropriate infusion rate of the blinded and open-label infusions respectively. If easily obtained (such as via a scale-bed), weight will also be recorded once during each subsequent 24 hour period of the initial study drug infusion period (V3-V8) and second infusion period (V3R-V8R, if applicable).

<sup>e</sup> Serum pregnancy test for females aged 10 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy.

<sup>f</sup> Blood samples will be taken for hematology and serum chemistry and GFR calculation at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will document whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

<sup>g</sup> Blood samples will be taken at V11 or V11R for serum chemistry (renal panel only).

<sup>h</sup> Urine samples will be taken for urinalysis and NAG at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will add a comment about whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

<sup>i</sup> Vital signs will be recorded at the following time points relative to the start of each infusion of study drug: Screening (V1), at 0, 30, 60 minutes ( $\pm 15$  minutes), at 2, 4, and 8 hours ( $\pm 30$  minutes), and at 24, 48, 72, 96, 120, 144, 168, and 192 hours ( $\pm 2$  hours).

<sup>j</sup> ECG (12-lead) should be performed at Screening (V1) and at the following times relative to the start of study drug infusion. For the blinded (first) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 128, 136, 144, 152, 160, and 192 hours ( $\pm 2$  hours). For the open-label SAGE-547 (second) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 126, 132, 138, 144, 152, 160, and 192 hours ( $\pm 2$  hours). Heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours. If it is not possible to perform ECG immediately after PK sampling up to 160 hours, ECG must be performed within 15 minutes prior to PK sampling up to 160 hours.

<sup>k</sup> Plasma will be collected to assay for study drug concentrations at the following time points relative to the start of each infusion of study drug: For the blinded (first) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion. For the open-label SAGE-547 (second) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open-label SAGE-547 study drug infusion. Pre-dose samples may be taken within two hours before starting the infusion of study drug; timepoints up to and including 1h will have a time window of  $\pm 5$  minutes; all other timepoints will have a window of  $\pm 15$  minutes.

<sup>m</sup> FOUR Score assessments will be performed at Screening (V1), 24, 48, 72, 96, 120, 144, 168, and 192 hours (all  $\pm 2$  hours) relative to the start of each infusion of study drug, and at V11 or V11R, and at V12 or V12R.

<sup>n</sup> Modified Rankin Score (mRS) applicable for subjects  $\geq 17$  years old only.

<sup>o</sup> SRS at V1 will be a retrospective assessment of the supervision required by the subject immediately prior to admission that includes the index episode of the SE, and mRS at V1 will be a retrospective assessment of the disability and dependence of the subject immediately prior to admission that includes the index episode of the SE.

<sup>p</sup> Target for complete wean of all continuous IV third-line agents by 144 hours at V8/V8R if not completed by 120 hours at V7/V7R.

<sup>q</sup> Study drug infusion is intended for IV administration only with a dedicated peripheral IV line using Sage-approved IV administration bags and lines.

<sup>r</sup> At V10 only a decision to re-treat at a higher dose of SAGE-547 will be made by the Investigator if the continuous IV third-line agent wean has failed or the third-line agent requires re-introduction during V9. Subjects who become eligible for open-label study drug at a higher dose of SAGE-547 will discontinue the planned visit schedule at V10, then repeat V3 (V3R) and all applicable subsequent visits.

<sup>s</sup> AEs will be collected from the time Informed Consent is obtained and prior to the start of study-specific screening procedures not considered standard of care. Collection of AEs will continue throughout the study from V1 through V12 or V12R.

<sup>t</sup> Subjects may enter the study on AEDs and be administered AEDs during the study. All Concomitant AEDs must be recorded on the CRF with details including date and time of starting/stopping each AED, the route of administration, changes in doses, and frequency of administration. Details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the CRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.

<sup>u</sup> All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Details will include the name of the drug, the start/stop dates and times, and, after consent, the doses with start/stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

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**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
AE	adverse event
AED	anti-epileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the time-concentration curve
AW	additional weans
BDZ	benzodiazepine
BIEEG	blinded infusion electroencephalogram
BUN	blood urea nitrogen
CBC	complete blood count
CEEG	consent electroencephalogram
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
C <sub>max</sub>	maximum plasma concentration
C <sub>min</sub>	minimum plasma concentration
CNS	central nervous system
CRF	case report form
CSR	clinical study report
CYP2C9	cytochrome P450 enzyme involved in drug metabolism
DNR	do not resuscitate
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EEG	electroencephalogram
EIND	Emergency Use Investigational New Drug Application
EP	European Pharmacopeia
ESETT	Established Status Epilepticus Treatment Trial
FDA	Food and Drug Administration
FOUR	Full Outline of UnResponsiveness
GABA	γ-aminobutyric acid
GABA <sub>A</sub>	γ-aminobutyric acid-gated chloride channel

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GOS	Glasgow Outcome Scale
H	hour
HPLC	high performance liquid chromatography
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent to Treat
IV	intravenous
IVRS	Interactive Voice Randomization System
LAR	legally authorized representative
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent to Treat
mRS-9Q	Modified Rankin Score - 9Q
MS/MS	tandem mass spectrometry
nM	nanomolar
NMDA	n-methyl-D-aspartic acid
OW	other weans
PAEEG	primary endpoint electroencephalogram
PD	pharmacodynamics
PK	pharmacokinetic
QOL	quality of life
QW	qualifying wean
QWEEG	qualifying wean electroencephalogram
RBC	red blood cell

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
RSE	refractory status epilepticus
SAE	serious adverse event
SAP	Statistical Analysis Plan
SE	status epilepticus
SOP	standard operating procedure
SRS	Severity Rating Scale
SRSE	Super-refractory status epilepticus
SSRI	Selective serotonin re-uptake inhibitors
STESS	Status Epilepticus Severity Score
SUSAR	Suspected Unexpected Serious Adverse Reactions
SWFI	Sterile Water for Injection
TAEEG	taper electroencephalogram
T <sub>max</sub>	time at maximum plasma concentration
TW	terminal wean
TWEEG	terminal wean electroencephalogram
US	United States
USP	United States Pharmacopeia



### 3. INTRODUCTION AND RATIONALE

#### 3.1. Status Epilepticus

Status epilepticus (SE) is a life-threatening seizure condition in which the brain is in a state of persistent seizure triggered by neuronal hyperexcitability. The Neurocritical Care Society defines SE as one continuous unremitting seizure lasting longer than five minutes or recurrent seizures without regaining consciousness between seizures for greater than five minutes (Brophy, Bell et al. 2012). Common causes of SE include preexisting epilepsy, cerebrovascular disease (in adults), electrolyte and metabolic disturbances, anoxia, encephalopathies, head trauma, high fever (in children, especially in the first year of life) and drug or substance intoxication. SE is associated with substantial morbidity and mortality.

##### 3.1.1. Epidemiology of SE

Geography, sex, age, and race influence the epidemiology of SE, whose incidence has a bimodal distribution, peaking in infants/young children and the elderly (Hauser 1990; DeLorenzo, Pellock et al. 1995; Wu, Shek et al. 2002). The incidence of SE in the elderly population is at least twice that in the general population. Concurrent medical conditions often exist in the elderly population, which can complicate therapy and worsen the prognosis of SE (Chapman, Smith et al. 2001).

The annual incidence of SE in the US is generally quoted to be within the range of 18/100,000 to 61/100,000, based on a 19-year retrospective study in Rochester, Minnesota (Hesdorffer, Logroscino et al. 1998) and a 2-year prospective study in Richmond, Virginia (DeLorenzo, Pellock et al. 1995), respectively. Two studies from Europe give annual incidences of a similar magnitude, ranging between 9.9/100,000 and 15.8/100,000 (Coeytaux, Jallon et al. 2000; Knake, Rosenow et al. 2001). It is thus estimated that in the United States each year there are as many as 150,000 cases of SE (DeLorenzo, Pellock et al. 1995).

#### 3.2. Refractory SE

When a patient begins to seize, the emergency medical technician will administer a first-line intravenous (IV) benzodiazepine (BDZ), such as diazepam, lorazepam or midazolam (Silbergleit, Durkalski et al. 2012), which is done either at the scene of the seizure or in the ambulance. If this is unsuccessful at abating the seizure, additional doses of the first-line therapy will be administered in the emergency room. Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line therapy, which is an IV anti-epileptic drug (AED) such as phenytoin or valproic acid (Novy, Logroscino et al. 2010; Shorvon 2011; Hocker, Britton et al. 2013).

Approximately 20-30% of patients refractory to first-line treatment will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to approximately 70-80% of patients who receive second-line therapy refractory to that therapy.

If a patient's SE continues after administration of BDZs and AEDs, the subject is diagnosed as having refractory status epilepticus (RSE), which must be treated quickly to terminate the seizure activity, maintain the patient's airway, and prevent cerebral damage. RSE

patients are immediately admitted to the Intensive Care Unit (ICU) and placed in a medically-induced coma to stop all seizure-related activity. The drugs used to induce coma are continuously-infused IV agents, commonly propofol, midazolam, or pentobarbital, referred to as third-line agents (Brophy, Bell et al. 2012).

The RSE patient is continually monitored using electroencephalography (EEG) to ensure burst suppression is achieved. Burst suppression is a pattern of brain waves seen on an EEG, characterized by periods of activity alternating with periods of little or no activity in the brain, informing medical personnel of the effectiveness of the medically-induced coma. The goal of burst suppression is to allow the brain and corresponding neuronal tissue to restore function and reset to normal pre-seizure levels.

### **3.2.1. Epidemiology of RSE**

Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line AED therapy. In turn, approximately 20 – 30% of these patients treated with AEDs will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to 28% of the total estimated SE patient population refractory to second-line therapy. Based on the previously-cited estimated incidence in the US, this means that there are up to 42,000 incident cases of RSE in the USA, annually (DeLorenzo, Pellock et al. 1995).

## **3.3. Super-refractory SE**

After 24 hours of burst suppression, the patient is weaned off of the third-line therapy. If the weaning is unsuccessful (neuronal activity has not returned to normal), the third-line agent is re-administered or a different third-line agent is started, and the patient is considered to be in super-refractory status epilepticus (SRSE) (Chapman, Smith et al. 2001; Shorvon 2011; Brophy, Bell et al. 2012). SAGE-547 is being developed as an adjunct to third-line therapy in patients in RSE who have failed standard treatment. In this protocol, the term “RSE that has failed standard treatment” is deemed to be equivalent to the term “SRSE” and the two may be used interchangeably.

### **3.3.1. Epidemiology of SRSE**

The incidence of SRSE is very poorly understood, mainly because the diagnostic codes used for SE do not generally differentiate its nature as responding or refractory to treatment. Based on the variable reporting of outcomes data, the incident cases of SRSE could represent between one and two-thirds of the RSE patients (Novy, Logroscino et al. 2010; Ferlisi and Shorvon 2012; Hocker, Britton et al. 2013; Sutter, Marsch et al. 2013). More detailed epidemiology studies are needed to better elucidate the proportion of RSE patients whose condition becomes super-refractory. A recent review of ICU discharge data in the USA suggests an annual incidence of approximately 35,000, based on patients who required at least three days in the ICU for SE [Sage data on file].

### **3.3.2. Outcomes of SRSE**

SE has varying degrees of mortality depending on the underlying etiologies. Table 4 outlines the acute mortality in patients with SE by etiology (Neligan and Shorvon 2010). The mortality rate of SRSE is estimated to be 30% to 50% using current standard of care.

The causes of death from SE (and therefore SRSE) are heterogeneous, resulting from neuronal cell death, complications of underlying medical conditions, or adverse effects of the current standard treatments. Prognosis worsens and mortality increases with longer duration of SE, i.e. with SE that develops into RSE or SRSE (Neligan and Shorvon 2010), and with longer duration of medically-induced coma (Ferlisi and Shorvon 2012). There is an obvious unmet medical need to improve upon the current standard of care treatment regimens.

Morbidity is high and survivors have outcomes ranging from poor function to vegetative state (Shorvon 2011). Approximately one third of patients with RSE and SRSE will recover, but with chronic neurologic or other deficits (Neligan and Shorvon 2010; Hocker, Britton et al. 2013). In all, it is estimated that less than 25-30% of all SRSE patients have a favorable functional outcome.

**Table 4: Approximate Mortality of Status Epilepticus in Different Etiologies**

Underlying Etiology	Associated Acute Mortality in Patients with SE (%)
Drug reduction/withdrawal, poor AED compliance, or low AED levels	0-10
Cerebrovascular Disease	20-60
Metabolic Disorders	10-35
Acute CNS Infection	0-30
Anoxia	60-100
Alcohol Abuse	0-10
Head Trauma	0-25
Drug Overdose/Toxicity	10-25
Brain Tumors	0-20
Cryptogenic/Idiopathic	5-20

### 3.3.3. Unmet Medical Need in Super-refractory Status Epilepticus

Treatment approaches for SRSE consist of diagnosis and treatment of underlying medical conditions, adding and changing anti-seizure drugs, and repeated attempts at weaning from IV anesthetic agents. Treatment of SRSE has three aims:

- to prevent excitotoxicity, which begins within 24 hours of SE onset;
- to prevent cerebral damage by initiating neuroprotective burst suppression;
- to prevent the complications of extended periods of anesthesia or unconsciousness (Shorvon 2011).

Currently, there are no therapies that have been specifically approved for RSE or SRSE. The primary drugs used to induce coma are continuously infused IV anesthetics such as propofol, midazolam, or pentobarbital/thiopental, known as third-line agents. Use of these drugs to control SRSE has only been studied in small retrospective reviews or small prospective studies without

controls (Hocker, Britton et al. 2013) therefore there is no agreement on which drug is optimal nor on an optimal dosing regimen for the treatments that are used.

The most common adverse effect of the third-line agents is hemodynamic instability; in addition, they are not universally effective, with breakthrough seizures and withdrawal seizures requiring dose adjustments and changes in third-line agent(s). The drug thought to be most effective in SRSE, pentobarbital, is also associated with the most toxic adverse effect profile, comprising decreased blood pressure and cardiorespiratory collapse (Claassen, Hirsch et al. 2002). The ability to wean patients successfully off the third-line agents as quickly as possible is therefore paramount, and an adjunct to SRSE treatment that enhances the success of the third-line agents and supports their successful weaning in a short timeframe would be an important addition to the therapeutic armamentarium. Preliminary clinical data show that SAGE-547 has been a successful adjunct to third-line therapy in this regard.

### 3.4. SAGE-547 Injection

Allopregnanolone is an endogenous, naturally occurring neuroactive steroid formed in the corpus luteum of the ovary, adrenal cortex and central nervous system (CNS) (Holzbauer, Birmingham et al. 1985; Paul and Purdy 1992; Ottander, Poromaa et al. 2005). It is a metabolite of progesterone created by the actions of 5- $\alpha$  reductase and 3- $\alpha$  hydroxy-steroid dehydrogenase. Allopregnanolone is a potent positive allosteric modulator of both synaptic and extra-synaptic GABA<sub>A</sub> receptors.

SAGE-547 Injection (allopregnanolone aqueous formulation in Captisol<sup>®</sup>) is being developed for the treatment of patients in RSE who have not responded to standard treatment. SAGE-547 Injection is a solution of 5 mg/mL allopregnanolone in Sterile Water for Injection (SWFI), USP and 250 mg/mL betadex sulfobutyl-ether sodium, NF. It is further diluted with Sterile Water for Injection, USP (SWFI) in IV bags to achieve an allopregnanolone concentration of approximately 1.67 mg/mL in an approximately isotonic solution and will be administered intravenously.

#### 3.4.1. Scientific Rationale for SAGE-547 in SRSE

Ineffective recruitment of inhibitory neurotransmission, together with excessive neuronal excitation, likely plays a role in the initiation and propagation of the electrical disturbance occurring in SE. GABA ( $\gamma$ -aminobutyric acid), the major inhibitory neurotransmitter in the central nervous system (CNS), is released from GABAergic neurons and binds to several types of GABA receptors (GABA<sub>A</sub>, GABA<sub>B</sub>, and GABA<sub>C</sub>) on target neurons. GABA<sub>A</sub> receptors are macromolecular proteins that form a chloride ion channel complex and contain specific binding sites for GABA and a number of allosteric regulators, including barbiturates, benzodiazepines, and some anesthetic agents. GABA receptor-mediated inhibition contributes significantly to the normal termination of a seizure (Kapur and Macdonald 1997). SAGE-547 is a positive allosteric modulator of the GABA<sub>A</sub> receptor.

The importance of terminating seizure activity as soon as possible is underpinned by a growing body of evidence from research and clinical observation that SE becomes more difficult to control as its duration increases. It has been postulated that this occurs due to a mechanistic shift from inadequate GABAergic inhibitory receptor-mediated transmission to excessive N-methyl-D-aspartic acid (NMDA) excitatory receptor-mediated transmission (Kapur and Macdonald 1997). As prolonged epileptiform bursting results in a reduction of GABA<sub>A</sub>-mediated synaptic

inhibition, antiepileptic treatments which rely on enhancing intrasynaptic GABA<sub>A</sub> neurotransmission become less effective the longer SE continues.

Furthermore, the constitutive process of synaptic GABA<sub>A</sub> receptor internalization is accelerated by the increased neuronal activity associated with seizures. These findings suggest that the rate of GABA<sub>A</sub> receptor internalization is regulated by neuronal activity, and its acceleration contributes to the reduction of inhibitory transmission observed during prolonged seizures (Kapur and Macdonald 1997). Of note is that SAGE-547 binds to extrasynaptic as well as intrasynaptic GABA<sub>A</sub> receptors; extrasynaptic receptors remain active with ongoing seizure activity, resulting in a putative mode of action for SAGE-547 in SRSE.

Status epilepticus induces cerebral damage that includes neuronal cell necrosis, gliosis, and network reorganization. The major cause of cell death in cerebral damage is excitotoxicity, which is initiated by glutaminergic receptor over-activation, causing calcium to flood the cell, thereby leading to apoptosis and necrosis. This process is initiated within a few hours of the start of seizure activity, and provides the medical imperative to terminate SE as quickly as possible. To prevent the consequences of the excitotoxicity cascade, it is recommended that anesthesia be initiated within 1-2 hours of onset of seizures at doses designed to induce EEG burst suppression (Shorvon and Ferlisi 2011).

### **3.4.2. SAGE-547 Clinical Program in the Treatment of SRSE**

The current SAGE-547 development program includes:

- a completed Phase 2 open-label trial, Study 547-SSE-201;
- this proposed Phase 3 randomized, double-blind, placebo-controlled trial, Study 547-SSE-301;
- an ongoing open-label, expanded access protocol, Study 547-SSE-302;
- a number of EINDs for SAGE-547 in patients with SRSE.

The designs of these studies are all similar, with a five to six day infusion of SAGE-547 (or placebo), during which time attempts are made to wean the subject off all third-line agents. In the Phase 3 studies, those subjects who cannot be weaned off third-line agents while being administered SAGE-547 (or placebo) may be eligible for a second open-label infusion of SAGE-547 at a higher dose. Follow up of subjects is for 21 – 30 days after the first infusion of study medication.

### **3.4.3. Data from the SAGE-547 Development Program**

The data from 30 subjects included in the on-going clinical evaluation of SAGE-547 for the treatment of adults and children with SRSE clearly offers preliminary evidence that SAGE-547 could provide substantial and clinically significant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate. These subjects comprise 20 from the ongoing Phase 2 trial (71% success rate in 12/17 evaluable subjects) and 10 subjects who received EIND treatments (78% success rate in 7/9 evaluable subjects).

Successful therapy of SRSE has been defined as “the SE is completely controlled by the therapy, without breakthrough of withdrawal seizures, or discontinuation due to side effects or death during therapy,” (Ferlisi and Shorvon 2012). By this definition, which is in accord with the

efficacy assessments used in the overall clinical evaluation of SAGE-547, 19 of the 26 (73%) subjects with SRSE who completed the SAGE-547 infusion were treatment successes. As data collection is ongoing, this information is preliminary and subject to change upon further monitoring.

Published reports on RSE and SRSE have stated mortality rate ranges from 35% to 65%. The underlying etiologies of SE in the 547-SAGE-201 study and EINDs are heterogeneous, and each one conveys a different risk of mortality and longer term morbidity. However, the death rate in subjects who have received SAGE-547, 6 out of 30 (20%) subjects, appears to be lower than the published rates. None of the deaths were considered related to SAGE-547: brain tumor, organophosphate toxicity, respiratory failure, respiratory arrest due to ventilator support withdrawal, and breast cancer.

In the Phase 2 study, 20 SAEs (15 non-fatal) have been reported in 13 (65%) subjects, and of these 3 events in 2 subjects (10%) were considered by the investigator to be related to SAGE-547: pulmonary emboli and tracheostomy dehiscence/infection. The Sponsor did not consider these events to be related to SAGE-547, rather to the underlying disease states. Four of the 20 subjects (20%) experienced AEs considered possibly related to SAGE-547 by the investigator, namely moderate myopathy and severe pulmonary emboli in 1 subject, moderate tracheostomy dehiscence and tracheostomy infection in 1 subject, moderate thrombocytosis in 1 subject and moderate BUN, ALT and AST elevation in 1 subject.

Review of the most current safety data from 547-SAGE-201 reveals that there were changes in serum chemistry, hematology, and urinalysis during the study, but that none of those changes were assessed as related to SAGE-547. There were also no SAGE-547-related changes to vital signs.

Despite the heterogeneity in the underlying causes of SE, the ages of the subject, comorbidities, which normally complicate the treatment of SE, and the fact that all subjects had failed current standard of care treatment, a large majority of subjects had a successful therapy outcome, with discontinuation of all third-line agents and resolution of SE.

Refer to the Investigational Brochure for further information on the pre-clinical and clinical data supporting the use of SAGE-547 in SRSE.

### **3.5. Study Rationale - SAGE-547 in SRSE**

#### **3.5.1. Justification for the Control Group**

Although SAGE-547 has demonstrated extremely promising activity in subjects with SRSE, both in the Phase 2 study and during the EINDs, these have been open-label investigations with no control data for comparison. Generally in the literature there are few data describing the success rates of wean attempts of third-line agents, and few comparative data on the effectiveness of the three main third-line agents, propofol, pentobarbital/thiopental, and midazolam.

Several options for a control group in Study 547-SSE-301 were considered:

- No control group was thought to be unacceptable since there are no reliable published data on success rates in this population that could be used for broad comparisons;
- An active control was considered but found to be impractical since none of the third-line agents are approved for their use in SRSE, no standardized dosing regimens or

treatment guidelines have been adopted for the management of SRSE, and clinicians were unlikely to agree which of the available third-line agents would be reserved for the active control arm;

- Historical controls were considered but abandoned because of the practical difficulties of obtaining high quality data, the lack of ability to prospectively match cases, and a suspicion that clinical practice in the standard of care of SRSE is evolving, mandating the use of prospective, concurrent control data;
- Comparison to standard of care alone was considered as a feasible design. However, in a field where no widely adopted treatment guidelines exist, there was a concern that knowledge of the treatment group (SAGE-547 plus standard of care versus standard of care alone) would alter the behavior of the investigators such that they could be more aggressive with weaning in the SAGE-547 group;
- Placebo control is not without its challenges since the preliminary efficacy data for SAGE-547 show that the compound exerts central pharmacological effects and is associated with positive outcomes in around 70% of patients. There is therefore a potential ethical concern about administering placebo to desperately ill patients who have often exhausted all treatment options for SRSE. This concern has been addressed in two ways: firstly all patients receive current standard of care; secondly, all subjects who fail to be weaned from their third-line agents at the end of the blinded infusion of study drug will be administered open-label SAGE-547 without un-blinding their initial treatment allocation, so treatment with the investigational product is not denied, but delayed about a week in the setting of ongoing receipt of full current standard of care.

It was therefore decided that a blinded, placebo-controlled design was appropriate for Study 547-SSE-301.

### **3.5.2. Justification for the Dose Regimen**

The standard dose regimen has been studied in 19 subjects in the 547-SSE-201 Phase 2 trial; the average peak plasma concentration of SAGE-547 at the end of the loading dose was approximately 144 ng/ml. The average plasma concentration during the maintenance infusion was approximately 70 ng/ml. At these concentrations, there were no clear safety signals although two-thirds of subjects experienced an SAE and there were four deaths, all related to the underlying comorbid conditions. The standard dosing regimen was associated with an approximate 70% successful treatment outcome. For these reasons, the standard dosing regimen has been adopted for the initial SAGE-547 infusion to be compared in a blinded fashion to placebo.

In the 547-SSE-201 trial, three subjects have thus far received the higher dose regimen. This dose regimen has also been well tolerated. The average peak plasma concentrations at the end of the loading dose for both dosing regimens will be in the same range, as the loading dose is the same for both regimens. The average plasma concentrations observed during the higher maintenance dose are 102 ng/ml (n=2). The rationale for adopting the higher dose regimen as the open-label infusion of SAGE-547 for subjects who are retreated in this 547-SSE-301 trial is that those who fail on the standard SAGE-547 dose regimen are afforded the opportunity to have access to a higher dose. The justification to also administer the higher dose regimen to failures on placebo is that the regimen has thus far been well tolerated, and this methodology preserves the blind for the initial infusion.



A five-day dosing regimen with SAGE-547 was investigated in the Phase 2 study, 547-SSE-201. There were some cases when weaning off all third-line agents was not possible within 48 hours, but weaning was completed after the end of the infusion of SAGE-547. For this reason, the duration of dosing with SAGE-547 has been increased from 120 hours (five days) in Phase 2 to 144 hours (six days) in this Phase 3 study.

### 3.5.3. Rationale for Genetic Testing Sub-study

Sage Therapeutics intends to perform genetic research in the SAGE-547 development program in order to explore how genetic variations may affect the metabolism and activity of SAGE-547. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials, and, possibly, to genetically-guided treatment strategies for optimizing decision making with respect to individual benefit:risk. Participation of subjects in genetic research as part of the overall clinical study is optional.

## 3.6. Benefit-Risk Evaluation of the Present Study

Previous reports of human administration of exogenous allopregnanolone indicate that for exposures in men and women up to 150 nM, the most commonly reported AEs were sedation (recorded as sleepiness or tiredness), feelings of intoxication (like alcohol), flushing, and mild headache (Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007). No SAEs were reported (Navarro, Kaddouz et al. 2003; Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007; Kask, Backstrom et al. 2008; Kask, Backstrom et al. 2009; Timby, Hedstrom et al. 2011a). In view of the reduced consciousness and sedation of study subjects at entry into this protocol, none of these previously-reported events are likely to impact subjects in this study.

To date, in the SAGE-547 Phase 2 study and the EIND subjects, a majority of subjects demonstrated a successful therapy outcome (>70%). The majority in the clinical trial (65%) have also experienced SAEs, but none has been considered related to SAGE-547 by the Sponsor (SAEs in 2 subjects (10%) were considered possibly related by Investigator). Five deaths have been reported in 30 subjects (20%), all related to the underlying cause of SRSE and not related to SAGE-547 – this is in the context of published mortality rates between 35% and 65%. These preliminary data suggest that SAGE-547 has the potential to provide clinically relevant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate.

The underlying etiologies of SE are heterogeneous, and each one conveys a different risk of mortality. Subjects who survive SRSE still have a high risk of severe morbidity (Neligan and Shorvon 2010). The subjects treated with SAGE-547 in Study 547-SSE-201, are heterogeneous in factors such as age and etiology of SE, factors that usually complicate treatment and can increase morbidity and mortality. Even with this heterogeneity, the preliminary efficacy and safety data for SAGE-547 are very encouraging, and the mortality rate suggests that the risk to benefit assessment of this treatment rests on the side of benefit.



## **4. ETHICS**

### **4.1. Institutional Review Board or Independent Ethics Committee**

This protocol will be reviewed and approved by the Institutional Review Board (IRB) where the study is conducted. The IRB will meet all FDA requirements governing IRBs (CFR, Title 21, Part 56).

### **4.2. Ethical Conduct of the Study**

The Sponsor, the Medical Monitor, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable ICH and GCP guidelines, and must also conduct the study in accordance with local regulations.

### **4.3. Subject Information and Informed Consent**

Subjects prospectively enrolled in this study will be unable to give consent. Therefore, consent will be given by proxy by a legally authorized representative (LAR). Written informed consent is required for each subject prior to any testing under this protocol not considered standard of care, including screening tests and evaluations. Should a subject gain the ability to sufficiently comprehend the situation and consent during the course of the study, written informed consent or verbal assent will be documented as required or recommended by the institution's IRB.

The form of consent to be obtained will depend on the condition of the subject as determined by the Principal Investigator. The informed consent form (ICF), as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50.

It is the responsibility of the Investigator to obtain consent and to provide the subject's LAR with a copy of the signed and dated informed consent form. The informed consent form for subject participation must also be available as part of the subject file for review by the site's dedicated study monitor or any authorized auditor of the Sponsor or regulatory authorities.

All ICFs used in this study must be approved by the appropriate IRB and by the Sponsor. The ICF must not be altered without the prior agreement of the relevant IRB and the Sponsor.

### **4.4. Ethical and Regulatory Considerations for Pharmacogenetic Sub-study**

#### **4.4.1. Informed Consent for Pharmacogenetics**

The genetic component of this study is optional and subjects may participate in other components of the main study without having to agree to participate in the genetic component. If subject chooses to participate in the genetic component of the study, the subject or LAR must sign and date a specific consent form for the genetic component of the study in addition to the main study consent form. The principal investigator(s) is responsible for ensuring that consent is freely given and that the subject understands that they may discontinue from the genetic aspect of the study independent of their decision to remain within or withdrawal from the main study.

#### **4.4.2. Subject Data Protection Relative to Pharmacogenomics**

Sage Therapeutics will not provide individual genotype results to subjects, their family members, their general physician, their employer or any insurance company unless required to do so by law. While extra precautions will be taken to preserve confidentiality and to prevent genetic data from being linked to an individual's identity outside of a restricted access site, in certain exceptional situations (e.g. in case of a medical emergency or as a consequence of a specific regulatory need), certain individuals may see both genetic data and the personal identifiers of a subject; however in all cases a subject's medical information and genetic files will remain physically separated.

### **5. STUDY OBJECTIVES**

#### **5.1. Primary Objective**

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult and pediatric subjects with SRSE, and for the response to endure at least 24 hours after cessation of the SAGE-547 or placebo infusion (primary response).

#### **5.2. Secondary Objectives**

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in Clinical Global Impression Scale between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

#### **5.3. Safety Objectives**

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

## **5.4. Other Objectives**

1. To evaluate the impact of treatment with a higher dose SAGE-547 infusion;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;
6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS) (age  $\geq 17$  years).

## **6. ENDPOINTS**

### **6.1. Primary Endpoint**

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### **6.2. Secondary Endpoints**

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) and to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;

6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### **6.3. Safety Endpoints**

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.

### **6.4. Other Endpoints**

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who are treated with a higher dose of SAGE-547;
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS) (age  $\geq 17$  years).

## **7. INVESTIGATIONAL PLAN**

### **7.1. Overview of Study Design**

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

Figure 1 provides an overview of the study design and Figure 2 gives the details of treatment and follow-up on the active treatment arm. Patients will follow one of three paths to entry to the study. The first path is for patients who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst suppression with a third-line agent. These patients will be consented for the study after admission to the intensive care unit, but before any third-line agents are administered for burst suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental

incapacity from the status epilepticus, and so consent will be obtained from their LAR. Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours. Once burst suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned during the QW will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The second path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst suppression pattern on the EEG. These patients may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The third path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These patients may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within six hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third line agent wean attempts prior to randomization (one vs two or more).

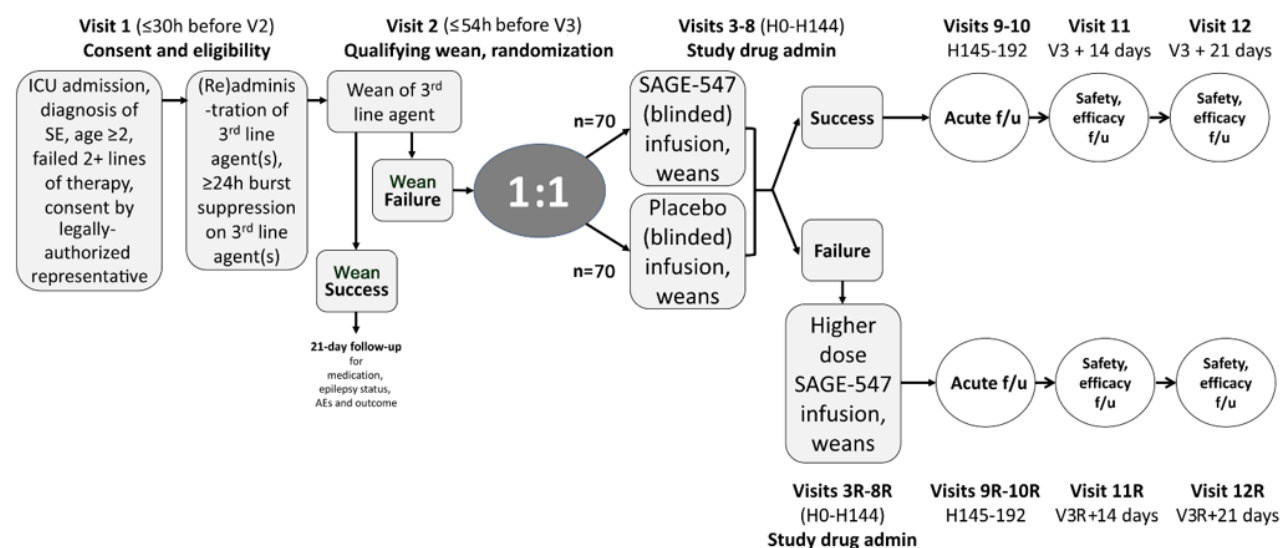
The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as the ability to wean the subject off all third-line agents before the end of the first infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication. Subjects must also have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) at the end of the primary endpoint assessment period as determined by EEG in order to be deemed a success. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#), [Table 2](#) and [Table 3](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion may be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. Eligibility for the open-label treatment must be confirmed in writing by the medical monitor prior to the open-label infusion starting. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo may all subsequently be eligible to be administered SAGE-547 at the higher dose.

**Figure 1: Study Design**



## 7.2. Trial Conduct

This study will be conducted according to the principles of the World Medical Association Declaration of Helsinki and most recent amendment, and in compliance with the protocol

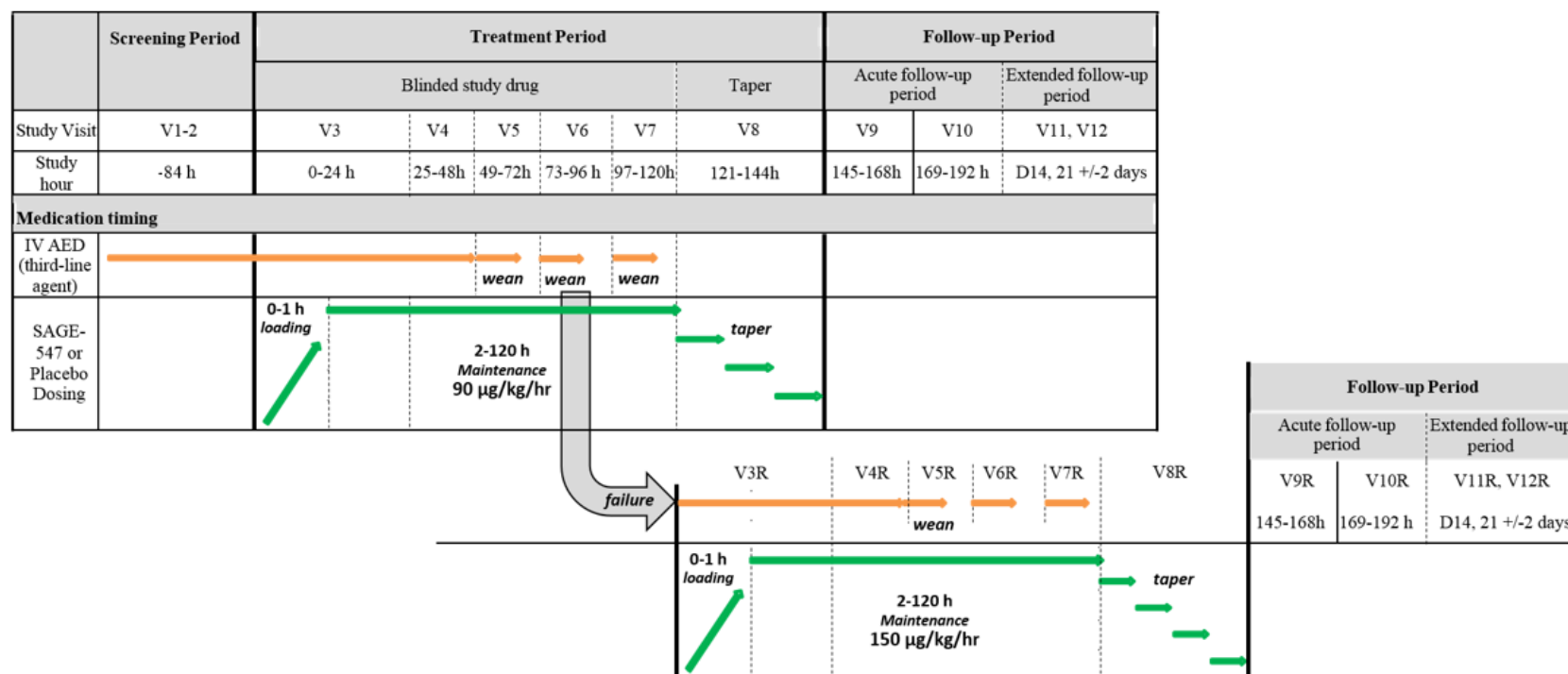
approved by the IRBs/Independent Ethics Committees (IECs), and in accordance with ICH Guidelines on GCP standards.

### **7.3. Blinding and Randomization**

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo). Details of the dynamic randomization process will be included in the SAP.

The randomized portion of the study will be blinded, with the two treatment products (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

The second infusion of SAGE-547 will be administered on an open-label basis to subjects who meet the criteria for open-label treatment.

**Figure 2: Details of Treatment Administration and Follow-up**



## 8. SELECTION AND WITHDRAWAL OF SUBJECTS

The study will randomize 140 patients at up to 180 sites. All subjects deemed eligible to enroll must have written Medical Monitor approval on a case-by-case basis prior to undertaking the qualifying wean.

### 8.1. Inclusion Criteria

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects two (2) years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; *or* who have previously failed one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst suppression pattern; *or* who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst suppression pattern.

### 8.2. Exclusion Criteria

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy.
4. Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing underlying neurological disorder.
5. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis but for whatever reason, dialysis that would adequately remove Captisol® is not planned;
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the experience of the investigator, is less than 30 days;

- e. a do not resuscitate (DNR) order.
- 6. Subjects who are being administered more than three third-line agents concomitantly or for whom the qualifying wean cannot be completed within 24 hours or who are being administered a third-line agent for indications such as raised intra-cranial pressure that would preclude weaning according to this protocol.
- 7. Subjects with a living will that does not allow heroic measure.
- 8. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
- 9. Subjects who have been treated or randomized in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not have received study drug/placebo and then re-enroll).

### **8.3. Selection and Consent of Subjects for Pharmacogenetic Substudy**

All subjects will be asked to participate in pharmacogenetic research; however, participation in research is voluntary and a subject can decide to decline his/her participation without penalty or loss of benefit. Participation or lack thereof will not be a cause for exclusion from any aspect of the main study. In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **8.4. Subject Withdrawal / Study Termination**

#### **8.4.1. Withdrawal/Discontinuation of Individual Subjects**

The reasons for study drug discontinuation and/or subject withdrawal from the study must be recorded in the subject's electronic case report form (eCRF). The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject has been discontinued/withdrawn due to an AE.

##### **8.4.1.1. Withdrawal from the Study**

Subjects or their LAR may withdraw subjects from the study at any time for any reason without compromising the subject's medical care. The Investigator will also withdraw subjects upon the request of Sage Therapeutics or upon termination of the study.

Subjects who withdraw from the study prior to Visit 10 (or 10R) should complete the procedures scheduled for the day of study drug taper (Hour 121-144; Visit8/8R) on the day of their withdrawal, including the SAGE-547 taper schedule, with the addition of the mortality assessment from Visit 12/12R. Subjects who withdraw from the study after Visit 10/10R should undergo study procedures as outlined for Visit 12/12R on the day of their withdrawal. In all cases, the reason for subject withdrawal will be recorded in the eCRF.

Withdrawal of subjects for any reason should be discussed with the Medical Monitor.

#### **8.4.1.2. Discontinuation of Study Drug**

If it is necessary to discontinue the study drug earlier than planned, subjects should continue to be followed per protocol to capture safety and efficacy assessments for the duration of the study period.

The investigator may withdraw the subject from the study drug for the following reasons:

- Upon subject's or LAR's request
- The subject or LAR is unwilling or unable to adhere to the protocol-specified visits
- The subject experiences an intolerable adverse event
- During the course of the study, the subject develops symptoms or conditions listed in the exclusion criteria.
- Other medical reason, at the discretion of the Investigator and/or the Medical Monitor

Subjects who discontinue the study due to an AE considered related to study drug should be followed until the event is resolved, considered stable, or the Investigator determines the event is no longer clinically significant. Study drug discontinuation due to AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

#### **8.4.2. Study Termination**

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of AEs or other findings suggesting unacceptable risk to subjects, administrative or operational reasons. In the event of study termination, Sage Therapeutics will provide written notification to the Investigator. Investigational sites must promptly notify their IRB and initiate withdrawal procedures for participating subjects.

## **9. INVESTIGATIONAL PRODUCT**

### **9.1. Identity of Investigational Product**

SAGE-547 Injection (allopregnanolone)

### **9.2. Clinical Supplies**

#### **9.2.1. SAGE-547**

Adequate supplies of SAGE-547 Injection and materials for intravenous administration will be provided to each site.

SAGE-547 Injection is a clear, colorless sterile solution of allopregnanolone intended for intravenous injection. SAGE-547 Injection is an aqueous solution of 5 mg/mL allopregnanolone in 250 mg/mL Captisol® (betadex sulfobutyl-ether sodium, NF). It is presented either un-buffered or buffered with 10 mM citrate at a pH of 6.0 in either 20 mL or 50 mL vials. SAGE-547 is further diluted according to the Pharmacy Manual to achieve an approximately isotonic solution and will be administered intravenously.

No preservatives are included in the drug product, which is intended to be used as a single-use vial. All inactive components (excipients) used in the formulation are compendial grade and conform to

current USP/EP, and include sodium citrate, citric acid and betadex sulfobutyl-ether sodium (Captisol®).

### **9.2.2. Placebo**

Placebo will be identical to SAGE-547 and presented in identical vials. Placebo will be manufactured in a similar way to SAGE-547 and comprises all excipients but no SAGE-547.

### **9.2.3. Blinding**

The vials of SAGE-547 and placebo will be identical in every way so that they are indistinguishable by the pharmacist, investigator, anyone treating or managing the patient, the monitors, and the sponsor. In this way the first infusion of study drug administered to each patient will be double-blind.

For the blinded study drug infusions, subject-specific dosing kits will be provided. These dosing kits will be pre-labelled with kit number for the first blinded infusion. For the second-infusion, open-label kits will be provided, which will require subject assignment by the pharmacy for reconciliation purposes. The study kits must be stored under refrigerated conditions (2-8 °C). IV administration bags and lines may be provided for the blinded and open-label infusions. Refer to the Pharmacy Manual for additional details.

The label for the SAGE-547 Injection vials will include standard product identification information according to the Code of Federal Regulations, 21CFR 312.6. All study labels will also contain the following statement:

Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use.

## **9.3. Preparation of SAGE-547 or Placebo Injection for Dosing**

The Pharmacy will be responsible for preparing the blinded and open-label study drug for subject dosing. The prepared admixture will be assigned a room temperature (20-25 °C) storage shelf life of 30 hours from time of compounding.

SAGE-547, which is hypertonic, will require dilution with SWFI to achieve an approximately isotonic solution according to the instructions provided in the Pharmacy Manual. Exactly the same procedures will be used to prepare the placebo admixture, so that all site staff remain blinded as to treatment allocation for the first infusion of study drug. SAGE-547 Injection is not intended to be administered to patients undiluted.

Refer to the Pharmacy Manual for specific instructions regarding infusion preparation.

## **9.4. Administration and Accountability**

The Pharmacy will maintain accurate records of all investigational product supplies. Accurate records will be kept regarding the volume of SAGE-547 Injection or placebo used for each IV preparation, as well as the required infusion rate or rates, and the date and time of preparation. Reasons for departure from the expected dosing regimen must also be recorded. To satisfy regulatory requirements regarding drug accountability, all study medication will be reconciled in full. Refer to the Pharmacy Manual for additional details.

## 10. TREATMENT OF SUBJECTS

### 10.1. Dosing Schedule (Blinded Infusions)

SAGE-547 Injection or placebo will be administered according to the dosing schedules in [Table 5](#). The infusion rates to accomplish these  $\mu\text{g/kg/h}$  doses will be calculated according to the weight of the subject obtained within the six-hour window that follows the declaration of the QW failure at V2 and prior to dosing at V3. The infusion rates will be applied to blinded study drug for the first infusion of study medication.

**Table 5: SAGE-547 or Placebo Dosing Schedule**

Hour	Type and Duration of Study Drug Infusion	Description
H1	One hour loading Infusion	300 $\mu\text{g/kg/h}$
H2 – H120	119 hour maintenance infusion	90 $\mu\text{g/kg/h}$
H121 – H128	8 hour taper	65 $\mu\text{g/kg/h}$
H129 – H136	8 hour taper	45 $\mu\text{g/kg/h}$
H137 – H144	8 hour taper	25 $\mu\text{g/kg/h}$

### 10.2. Dosing Schedule (Open-Label Infusions)

Those subjects that qualify for the open-label study drug will be administered SAGE-547 Injection according to the dosing schedule in [Table 6](#). The dose will be administered on a  $\mu\text{g/kg/h}$  basis, and the subject's weight measured prior to dosing during V10 will be used to calculate the doses. These infusion rates will be applied to SAGE-547 treatment for the open-label second infusions of study medication.

**Table 6: SAGE-547 Open-Label Dosing Schedule**

Hour	Type and Duration of SAGE-547 Infusion	Description
H1	One hour loading Infusion	300 $\mu\text{g/kg/h}$
H2 –H120	119 hour maintenance infusion	150 $\mu\text{g/kg/h}$
H121 – H126	6 hour taper	125 $\mu\text{g/kg/h}$
H127 – H132	6 hour taper	95 $\mu\text{g/kg/h}$
H133 – H138	6 hour taper	65 $\mu\text{g/kg/h}$
H139 – H144	6 hour taper	35 $\mu\text{g/kg/h}$

### 10.3. Route of Administration

SAGE-547 Injection is intended for IV administration only. The compatibility of SAGE-547 with other drugs is unknown, and the product should be administered via a dedicated peripheral IV line using any Sage-supplied study-specific IV administration bags and lines. In order to preserve blinding, these instructions also apply to the blinded placebo infusions.

## **10.4. Treatment Period**

The treatment period with double-blind SAGE-547 or placebo is six 24-hour periods (144 hours), which may encompass 6-7 calendar days. The open-label study drug treatment period is of identical duration.

## **10.5. Concomitant Medications, Procedures and Treatments**

Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. All concomitant medications, procedures, and treatments should be documented throughout the study from Screening through Visit 12/12R and recorded on the eCRF.

SAGE-547 has demonstrated inhibitory effects on cytochrome P450 isoenzyme 2C9 (CYP2C9). Therefore, AEDs such as phenytoin and phenobarbital that are primarily metabolized by CYP2C9 should be closely monitored during SAGE-547 administration to ensure target exposures are maintained.

### **10.5.1. Concomitant AEDs**

Subjects may enter the study on AEDs, and be administered AEDs during the study. All of these must be recorded on the eCRF with details including date and time of starting and stopping each AED, the route of administration, changes in doses, and frequency of administration. In addition, details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the eCRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.

### **10.5.2. Concomitant Third-Line Agents**

All third-line agents (as defined in [Section 8](#)) administered since the diagnosis of SE will be recorded on the eCRF, whatever path the patient took for entry into the study. Details will include the name of the drug, the start and stop dates and times, and, after consent, the doses with start and stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

In addition, those changes in dose that constitute a wean attempt will be marked as such on the eCRF. In this way the start and stop dates and times of all wean attempts (see [Section 11](#) for definitions) will be recorded, as will the type of wean (QW, OW, or TW) and the outcome of the wean attempt (successful, failed and dose of this third-line agent increased or failed and this third-line agent stopped and another third-line agent started). Those wean attempts that occur after the TW up to and including Visit 12/12R will be marked “AW”.

Some third-line agents (such as propofol) are also used to induce sedation to facilitate a subject’s ability to tolerate the ventilator. For subjects requiring such sedation, propofol is the preferred agent unless there are contraindications. The eCRF will make clear from the indication for the third-line agent when it is being used for burst or seizure suppression and when it is being used as ventilator support or for another purpose. The investigator will add a note to the eCRF to justify that the doses used are appropriate for sedation and not for seizure or burst suppression. The doses used for ventilator support and other similar uses are usually much lower than those used for

seizure or burst suppression, and use of these third-line agents for these other purposes does not constitute a wean failure under this protocol.

### **10.5.3. Concomitant Pressors**

The start and stop dates and times of all pressors will be recorded as well as the start and stop dates and times of all dose changes.

### **10.5.4. Other Concomitant Medications**

All other concomitant medications must be recorded on the eCRF with details including date and time of starting and stopping, the route of administration, dose, and frequency of administration.

## **11. STUDY ASSESSMENTS**

### **11.1. Efficacy Assessments**

#### **11.1.1. Primary Efficacy**

Success or failure will be determined, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo infusion and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the blinded (first) infusion of SAGE-547 or placebo. In addition, subjects must have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) to be deemed to be successes. All subjects who fail to complete their infusion of randomized treatment or do not have at least one attempt during study treatment to wean off all third-line agents will be considered as “failures” for the primary endpoint.

##### **11.1.1.1. Weaning**

Third-line agents are anesthetic agents that are administered in order to reach a seizure or burst suppression EEG pattern. For the purposes of this study, third-line agents are defined as continuous intravenous infusions of pentobarbital/thiopental, midazolam, propofol, and ketamine at maintenance doses alone or in combination sufficient to produce a burst suppression pattern on the EEG. The following are considered to be minimum maintenance doses of these agents that may be expected alone or in combination to achieve EEG burst suppression. If subjects are on lower doses than these and are not in EEG burst suppression for the 24 hours prior to the QW or the first 12 hours of the blinded study drug infusion, they will be considered to be screen failures/protocol violators and will exit the study.

- Pentobarbital: 1 mg/kg/hour
- Thiopental: 3 mg/kg/hour
- Midazolam: 0.1 mg/kg/hour
- Propofol: 3 mg/kg/hour
- Ketamine 1.2 mg/kg/hour

The timing and nature of the third-line agent weans will be guided by the Clinical Standardization Guidelines for the study, and the clinical judgment of the investigator, and will always be primarily

done in the best medical interests of the subject. Advice about weaning may be sought from the Clinical Standardization Team, a group of fellow investigators with experience of performing clinical trials in subjects with SRSE. The Clinical Standardization Team will be able to discuss EEGs related to key study timepoints (qualifying wean, terminal wean, and the period after the end of the blinded study drug infusion if the terminal wean was successful) in a timely manner in order to provide advice about compliance with the Clinical Standardization Guidelines.

The following guidance for weaning applies to all weans of third-line agents undertaken during the study. Continued determined efforts to liberate subjects from sedation must be undertaken for the entire duration of the blinded study drug infusion. Each failed wean from third-line agents should be followed by a 6-24 hour period of suppression and then another wean attempt, with further optimization of the AED regimen.

Weans include the qualifying wean (QW); the terminal wean (TW), which is the wean of the third-line agent if the subject is on only one third-line agent or the wean of the last third-line agent if the subject is on more than one third-line agent; the other weans (OW), which are the weans of the third-line agents other than the TW if the subject is on more than one third-line agent. The guidance also applies to additional weans (AW), which are the weans from third-line agents that take place after the TW for the first blinded study drug infusion or the second open-label study drug infusion.

### **QW Guidance**

- Wean to be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace that third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Investigators should allow 24 hours to lapse after the end of a “successful” qualifying wean before finally declaring the QW a success. If a third-line agent needs to be re-instituted within that 24 hours, the QW is a failure, and the subject may then be randomized in the study.

### **OW Guidance**

- First OW should not begin before H49 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- If the subject is on two third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the TW. However the OW may be completed over a shorter or longer time period and may overlap if clinically indicated with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- If the subject is on three third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the wean of the second agent. The



second agent should be weaned over 24 hours and that wean completed before starting the TW. However the OWs may be completed over a shorter or longer time period and may overlap if clinically indicated with each other and with the start of the TW.

Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.

- All OWs should be completed before H96 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **TW Guidance**

- The TW is defined as the wean of the last third-line agent.
- If the subject is on one third-line agent, the TW should not begin before H49 and should begin no later than H97 after starting administration of study drug or starting the open-label infusion of SAGE-547. If the subject has had one or more OWs, the TW should ideally begin as soon as the last OW is complete but in any case not later than H97 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- The TW must be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace this third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Every effort must be made to complete the TW before H120 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547, but the TW must be complete before H144 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **AW Guidance**

- AWs will take place when medically indicated in the opinion of the investigator.
- Ideally the AW should take place over 24 hours, but completion may be over a shorter or longer time period than this. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.

#### **11.1.1.2. EEG**

Electroencephalographs (EEGs) that are representative of the intermittent or continuous EEG being used to support key investigator decisions will be collected at the following time points:

- A 24-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst suppression for the second path to eligibility, and a variable pattern for the third path to eligibility. This EEG also aims to capture the burst suppression pattern during the 24 hours that precede the QW. If the CEEG does not capture the 24 hours that precede the QW, additional EEG data collected as standard of care after the CEEG and prior to the QW may be collected to assess the depth of burst suppression prior to the QW.
- EEG will be performed to cover the qualifying wean (QWEEG). EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for up to 24 hours after the end of the QW. The duration of the QWEEG will be up to 48.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s), the decision to re-institute a third-line agent(s) at doses intended to induce burst suppression, and the decision that the QW is a success.
- EEG will be performed from three hours prior to the start of the blinded infusion to 12 hours after the start of the blinded infusion. This will be called the BIEEG. The intent of this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG and to assess the depth of burst suppression in the first 12 hours of blinded study drug infusion.
- EEG will be performed to cover the final or terminal wean of third-line agent (TWEEG). The TW is the wean of the final third-line agent during the blinded administration of study drug or the open-label infusion of SAGE-547; if the subject was on one third-line agent, the TW is the wean of that agent. If the subject was on three third-line agents, the TW is the wean of the third and final agent. EEG recording will start 30 minutes prior to the start of the TW, continue for up to 24 hours during the TW, and then continue for the one hour after the end of the TW. The duration of the TWEEG will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the final third-line agent or the decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity could not be managed using intermittent bolus doses of AEDs.
- EEG will be performed during the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 (TAEED). The TAEED is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the start of the taper (at Hour 119.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours during the taper, and then continue for the one hour after the end of the taper (to Hour 145 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547). The duration of the TAEED will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity seen during the taper could not be managed using intermittent bolus doses of AEDs.

- EEG will be obtained to cover the end of the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 and the ensuing 24-hour period, during which the primary endpoint is assessed (PAEEG). The PAEEG is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the end of taper (at Hour 143.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours after the end of the blinded administration of study treatment or the open-label infusion of SAGE-547, and then continue for the one hour after the end of the 24-hour assessment period (to Hour 169 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547). The duration of the PAEEG will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to reinstitute a third-line agent at doses intended to induce burst suppression because any seizure activity seen in the 24 hours following the end of the blinded administration of study treatment or the open-label infusion of SAGE-547 that could not be managed using intermittent bolus doses of AEDs.

In practice, most subjects are on continuous EEG monitoring or long periods of intermittent EEG monitoring. However, this protocol does not mandate continuous EEG monitoring and breaks from EEG monitoring to provide relief to the scalp from the irritating effects of the electrodes are advised, particularly in children, according to local practice. If a break in EEG monitoring is mandated by local practice guidelines at a time when one of the protocolled EEG segments is to be collected, the break in EEG monitoring will take precedence, with the reason for missing the EEG reading noted on the eCRF. The EEGs obtained for the study are therefore part of the existing EEG record rather than being obtained de-novo at each timepoint. For timepoints where there might be some ambiguity, such as the TWEEG, the final EEG record is that of the final attempt to wean the last third-line agent, even if earlier attempts to wean that agent took place. In some cases (the TAEED and PAEEG, for instance), the EEG records will overlap, but different cuts are taken to service the different EEG record requirements.

The electronic EEG file will be de-identified, the date and time of the start and stop of the EEG and the subject number will be attached to the file, and the study time point will be indicated (CEEG, QWEEG, BIEEG, TWEEG, TAEED, and PAEEG). The PI will indicate on the eCRF what the EEG shows, as follows:

- For the CEEG, the PI will describe the EEG pattern that determined which path to eligibility the subject was on.
- For the QWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure or success on the qualifying wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the qualifying wean constitutes a failure); the QWEEG will extend to cover the 24 hours after the end of third line agents in order to confirm that the QW was a success.
- For the BIEEG, the PI will note the date and time of the start of the EEG and the pattern seen on the EEG.
- For the TWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure on the

terminal wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the terminal wean).

- For the TAEED, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst suppression before the end of the SAGE-547 infusion).
- For the PAEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst suppression in the 24 hours following the end of the SAGE-547 infusion).

A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm the depth of burst suppression prior to the QW and during the first 12 hours of the blinded study drug infusion, the PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period (average EEG power at the end of Visit 9 of more than two microvolts):

- All subjects will have the CEEG and QWEEG collected and stored, and the CEEG and QWEEG read;
- Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;
- Those subjects randomized who are not administered the open-label study drug will have the QWEEG, BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the BIEEG, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read;
- Those subjects randomized who later undergo the open-label infusion will have the QWEEG, BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion and the TWEEG, TAEED, and PAEEG related to the open-label study drug infusion collected and stored, and the BIEEG, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read.

All EEG records may be subject to quantitative EEG analysis.

### **11.1.2. Secondary Efficacy**

#### **11.1.2.1. Clinical Global Impression Scale (CGI)**

The clinical global impression scales are often utilized in clinical trials to allow clinicians to integrate several sources of information into a single rating of the subject's condition. Both the CGI-Severity (Question 1, CGI-S) and the CGI-Improvement (Question 2, CGI-I) employ a 7-point Likert scale measuring severity of the disease state in the subject and improvement, respectively. All severity assessments after initiation of SAGE-547 treatment should consider the general state of the subject over the preceding week. The third question on the scale will not be

employed in this trial, and where the scale states “mental illness”, this means “physical illness” in this trial.

The CGI-S will be evaluated at Visit 1 and at the last visit, Visit 12 or 12R. The CGI-I will be evaluated at Visit 12 or 12R.

#### **11.1.2.2. Epilepsy Status**

At Visit 1, the diagnosis of epilepsy will be documented as a no/yes question. If there was a previous diagnosis of epilepsy, further details will be documented, including:

- Date of diagnosis;
- Details of anti-epileptic drugs currently being taken;
- Type of epilepsy;
- Seizure frequency in the past month.

Information about the current (index) episode of status epilepticus will be obtained at Visit 1:

- Date of onset
- Date of failure to respond to first line agent(s) and the name(s) of the agent(s)
- Date of failure to respond to second line agent(s) and the name(s) of the agent(s)
- Any previous treatment with third line agents and the response to those agents (details of the third line agent drugs and previous wean attempts will be recorded on the Third Line Agent Medication CRF)
- The cause of the index episode of status epilepticus
- If the subject was transferred from another hospital or from within the hospital, the reason for the transfer will be recorded (such as for study enrollment, due to lack of medical options at original hospital or unit, due to lack of beds at the original hospital or unit, family request, other)

Previous (non-index) diagnosis of status epilepticus will be documented as a no/yes question. If SE did occur in the past 12 months, further information will be gathered, including:

- SE, RSE, or SRSE diagnosis, whichever was the most severe diagnosis for each episode;
- Cause;
- Treatment, including experimental treatments and need for intubation/ventilation;
- Dates of onset and duration.

At Visit 12 or Visit 12R, the following information will be gathered:

- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of SE up to and including Visit 12 or Visit 12R;
- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of seizures (convulsive and non-convulsive) up to and including Visit 12 or Visit 12R;

- Number of separate episodes of SE after H144 at the end of Visit 8 or Visit 8R (no/yes); if yes,
  - SE, RSE, or SRSE diagnosis;
  - Cause;
  - Treatment, including experimental treatments and need for intubation/ventilation;
  - Dates of onset and duration.

Note that a separate episode of SE is defined as an episode of SE separated from other periods of status epilepticus by at least 24 hours.

- Diagnosis of epilepsy since Visit 11 or Visit 11R will be documented as a no/yes question. If a diagnosis of epilepsy has been made, further details will be documented, including:
  - Status as ongoing or new epilepsy since Visit 11 or Visit 11R after initiation of SAGE-547 treatment;
  - Details of anti-epileptic drugs currently being taken;
  - Type of epilepsy and seizure frequency in the past week.

## **11.2. Safety Assessments**

The safety and tolerability of SAGE-547 will be assessed using adverse events, clinical laboratory measures, vital signs, ECG intervals and morphology, and mortality. All safety assessments should be performed per hospital standard of care and will be collected periodically throughout the study according to [Table 1](#), [Table 2](#), and [Table 3](#) (Schedules of Assessments).

### **11.2.1. Adverse Events**

AEs will be collected after informed consent has been signed and prior to study-specific screening procedures not considered standard of care, during subject preparation for SAGE-547 administration and through Visit 12 or Visit 12R. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™) coding system (current version). See [Section 14](#) for additional details.

### **11.2.2. Clinical Laboratory Tests**

Blood samples will be taken for hematology, and serum chemistry and GFR will be calculated at:

- Visit 1 and then at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.
- Blood samples will be taken at Visit 11 or Visit 11R for serum chemistry (renal panel only).

Urine samples (20 ml) will be taken for urinalysis and urine NAG analysis at:

- Visit 1 and at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.

For adults and children  $\geq 30$  kg, these samples will be analyzed at a central laboratory; hour-to-hour medical decisions will be based on sampling for laboratory testing done outside the protocol as part of normal standard of care. GFR will be calculated by the central laboratory. For children under 30 kg, results of local laboratory testing undertaken at the protocolled timepoints may be sent to the central laboratory for inclusion in the central study laboratory database; this obviates the need for additional blood sampling for central laboratory testing.

Any out-of-range values will be flagged by the laboratory; the investigator will add a comment about whether the abnormality is clinically significant. Clinical significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

#### **11.2.2.1. Hematology and Serum Chemistry**

Hematology will include complete blood count (CBC) white blood cell count with differential, platelet count and red blood cell (RBC) count, hemoglobin and hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose. In addition triglycerides will be measured in serum chemistry samples (to aid assessment of lipemia in pharmacokinetic samples).

#### **11.2.2.2. Pregnancy Test**

Females of child-bearing potential will be tested for pregnancy by serum pregnancy test at Visit 1. In this study, since an accurate history of menstruation in girls and menopause in older women may not be available at Visit 1, “child-bearing potential” is taken to mean any female aged 10 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy. Female subjects with a positive pregnancy test will be ineligible for study participation.

#### **11.2.2.3. Urinalysis**

Urinalysis will include assessment of protein, blood, leukocytes, glucose, ketones, urobilinogen, pH, and specific gravity.

#### **11.2.3. Vital Signs**

Blood pressure, heart rate, and temperature will be recorded at the following time points relative to the first infusion of study drug, and to the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547:

- Visit 1;
- At 0, +30, +60 minutes (+/-15 minutes) and +2, +4 and +8 hours (+/- 30 minutes) after the start of the infusion;
- At +24, +48, +72, +96, +120, +144, +168, and +192 hours (+/- 2 hours) after the start of the infusion.

**11.2.4. Weight and Height**

Weight and height will be measured at Visit 1. Weight will also be obtained at V2, within the six hour window that follows the declaration of the QW failure and prior to the initiation of the blinded infusion loading dose at H0 of V3, and will be used to calculate the infusion rates throughout the entire blinded treatment course. If a subject qualifies for open-label study drug, the infusion rates for the open-label infusion will be calculated using the subject's weight measured prior to dosing during V10.

If it is not possible to obtain an actual weight at the above-referenced time points, permission from the Clinical Monitor must be obtained to use another method to obtain the subject's weight (such as information from the LAR or estimating using an established local protocol).

In addition, a daily weight will be obtained and recorded if this is easily obtained, such as the use of a scale bed.

**11.2.5. ECG**

12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours. If it is not possible to perform ECG immediately after the collection of PK samples up to 160 hours, ECG must be performed within 15 minutes prior to the collection of PK samples up to 160 hours; at other times the allowed time window for ECGs is +/- 2 hours:

- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +128, +136, +144, +152, +160, and +192 hours after the start of the blinded (first) study drug infusion
- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +126, +132, +138, +144, +152, +160, and +192 hours after the start of the open-label (second) study drug

The heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm.

**11.2.6. Mortality**

Mortality will be recorded on the Visit 12 or Visit 12R case report form. If the subject has died, the following information will be collected:

- Date of death;
- Cause of death.

As accurate as possible cause of death will be collected, which will be further categorized as due to one of the following causes:

- SE;
- complications of long term intubation and third-line agent infusions;
- underlying cause of qualifying SE;
- co-morbidity existing at the time of the qualifying SE;
- new co-morbidity or trauma;
- study drug;



- other (specify).

### 11.2.7. Pharmacogenetic Samples

If a subject's LAR consents to pharmacogenetic sampling, a blood sample for genetic research will be collected at Visit 1 in order to avoid the possible introduction of bias through the exclusion of patients who may withdraw from study due to an AE (a subject population that may be of specific interest for subsequent genetic analysis). If for any reason a sample cannot be taken prior to treatment, a sample can be drawn at any point prior to completion with the restriction that no more than one genetic sample be taken per subject.

The objective of this research is to collect and store blood samples for possible DNA extraction and exploratory research into how genes or specific genetic variation may influence response (i.e. distribution, safety, tolerability, and efficacy) to SAGE-547. Specific genetic variations of interest include but are not limited to: classes of metabolizing enzymes (e.g. Cytochrome P450 supra-family genes), genes encoding enzymes involved in the production and metabolism of allopregnanolone (e.g. AKR1C4 (3a-hydroxysteroid dehydrogenase)), genes associated with the GABA receptor (e.g. GABRA1-A6, GABRB1-B3, GABRD, GABRE, GABRG1-3) and genes associated with the production and degradation of GABA.

Future research may suggest other genes or gene categories as candidates for influencing not only response to SAGE-547 but also susceptibility to disorders for which SAGE-547 is being evaluated. Thus, the genetic research may involve study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.

#### 11.2.7.1. Biological Sampling and Coding Procedures (Pharmacogenetics)

To ensure patient confidentiality, utmost care will be taken in the coding and storage of pharmacogenetic samples.

*Extraction and coding:* DNA will be extracted from the blood sample and the DNA sample will be assigned a unique number replacing information from sampling tube. The assigned DNA number will be used to identify the sample and its corresponding information within Sage Therapeutics or at any designated contract laboratory for the purpose of sequencing of other DNA specific analysis. No personal details sufficient for individual identification will be available to any person (internal or external to Sage Therapeutics) working with the DNA.

*Genotype/Phenotype Analysis:* Samples and data from genetic analysis will be coded. The link between subject enrollment / randomization code and DNA number will be maintained and stored in a secure environment with restricted access. The established link will be used to identify relevant DNA samples for analysis, facilitated correlation of genotype results with clinical data, allow regulatory audit, and to trace samples for destruction in case of withdrawal of consent.

#### 11.2.7.2. Retention of Biological Samples for Pharmacogenetic Analysis

Extracted DNA is a finite research that is destroyed in the process of being analyzed. Primary blood samples from which DNA can be extracted will be stored and used until no further analyses are possible, a maximum storage period of 25 years from time of last subject last visit has been reached, or an individual or LAR withdraws his/her or their consent.

## 11.2.8. Other Outcomes

### 11.2.8.1. Pharmacokinetic Data

Formal plasma analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS)). In addition, all samples will be analyzed for important SAGE-547 metabolites (if and when these are identified) and Captisol® concentrations.

#### Plasma Analysis

Plasma will be collected to assay for SAGE-547 concentrations at the following time points relative to the start of each infusion of study drug:

- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion.
- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open-label SAGE-547 study drug infusion.
- All samples will also be analyzed for plasma concentrations of important metabolites of SAGE-547 if and when these are identified.
- All samples will also be analyzed for plasma concentrations of Captisol®.

The plasma samples will be drawn from the arm contralateral to that used for drug administration. Drawing samples from peripheral arterial or venous lines or from a central line is permissible. PK collection times should be adhered to as strictly as possible. The allowed time window for all samples is: pre-dose in the two hours prior to starting the infusion of study drug; samples up to and including 1h, +/- 5 minutes; subsequent samples, +/- 15 minutes. Subject-specific PK kits for sampling including instructions on collection and processing methods, and storage and shipping conditions, will be provided separately. To maintain the blind, all subjects will have samples taken as outlined above: subjects receiving SAGE-547 will have all samples analyzed for all analytes. Subjects on placebo may have samples analyzed to investigate endogenous allopregnanolone and metabolite concentrations, as well as Captisol® concentrations; experience with the plasma concentration data will determine if and which placebo samples are analyzed.

Each blood sample will be 3 ml in volume for adults and children weighing 30 kg or more, and 1 ml in volume for children weighing less than 30 kg. Separate aliquots will be obtained from each sample to service the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum blood draw for PK analysis for a subject having two infusions of study drug will be 99 ml (33 ml for children weighing less than 30 kg).

Plasma PK parameters for SAGE-547 will be calculated where appropriate (e.g.,  $C_{max}$ ,  $C_{min}$ ,  $t_{max}$ ,  $AUC_{last}$ ,  $AUC_{\infty}$ ,  $CL_s$ ). In addition, similar PK parameters will be calculated for Captisol®. PK

parameters for important metabolites of SAGE-547 may be calculated. An evaluation will be made of the feasibility of adopting a population-PK approach to assess drug-drug-interactions with SAGE-547 as victim of AEDs.

In addition, the Visit 9 sample may be analyzed for plasma concentrations of third-line agents.

#### Other Analysis

If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations. The minimum volume of cerebrospinal fluid for analysis is 100 microlitres.

Full details of all pharmacokinetic analyses will be described in the Pharmacokinetic Analysis Plan.

#### **11.2.8.2. Correlation of QT/QTc Changes and Plasma Concentrations of SAGE-547**

An analysis will be performed to determine whether there is any correlation between changes in QT/QTc interval and plasma concentrations of SAGE-547, in order to investigate any effect that SAGE-547 may have on QT/QTc interval.

#### **11.2.8.3. Pharmacoeconomic Data**

At Visit 12 or Visit 12R, the following information will be collected: number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital. If the subject dies before Visit 12 or Visit 12R, data will be collected up to the date of death. The definition of “hospital” is the institution that the subject was initially treated in. If the subject is transferred to another hospital, that hospital would be the “discharge destination from the hospital” and the “number of days in hospital” would be the number of days in the initial treating hospital.

For those subjects discharged from hospital before Visit 12/12R, the following questions will be asked:

- On what study day was the subject discharged from hospital?
- What type of facility was the subject discharged to (another hospital, a rehabilitation center, a supported care facility, home, other)?
- How many days did the subject stay in this facility?

The following questions will be answered regarding the stay in the ICU and hospital:

- Was the subject still in the ICU at the end of Visit 10/10R?
- If the FOUR Score was  $\geq 12$  at Visit 10/10R and the subject was in the ICU at Visit 10/10R, what was the reason for the subject not being discharged from the ICU (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, other)?
- Was the subject still an in-patient in the hospital at the end of Visit 12/12R?
- If the FOUR Score was  $\geq 15$  at Visit 12/12R and the subject was in the hospital at Visit 12/12R, what was the reason for the subject not being discharged from the hospital?

(underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, unsuitable home circumstances, other)?

#### **11.2.8.4. STESS**

The STESS will be assessed during Visit 1 in order to assess the severity of the status epilepticus.

#### **11.2.8.5. FOUR Score**

The Full Outline of UnResponsiveness or FOUR Score is designed to assess conscious level and unlike other scores, is suitable for subjects who are intubated. It assesses four domains of neurological function (eye responses, motor responses, brainstem reflexes, and breathing pattern).

The FOUR Score will be collected at the following time points relative to each infusion of study drug (the initial blinded infusion and the second open-label infusion if this is administered):

- baseline, +24, +48, +72, +96, +120, +144, +168, and +192 hours (all +/- 2 hours) after the start of the infusion, and at Visit 11/11R and Visit 12/12R.

#### **11.2.8.6. Glasgow Outcome Scale (GOS)**

The GOS is a relatively common assessment scale used to standardize descriptions of the objective degree of recovery from brain injury such as cerebral trauma, or in this case SRSE. It was first used in 1975 ([Jennett and Bond 1975](#)) and allows a prediction of the long-term course of rehabilitation to return to work and everyday life. The scale classifies subjects into 5 groups:

- Death
- Persistent vegetative state
- Severe disability
- Moderate disability
- Good recovery

The GOS will be assessed at Visit 12 or Visit 12R.

#### **11.2.8.7. Supervision Rating Scale (SRS)**

The Supervision Rating (SRS) measures the level of supervision that a patient/subject receives from caregivers. The SRS rates level of supervision on a 13-point ordinal scale that can optionally be grouped into five ranked categories (Independent, Overnight Supervision, Part-Time Supervision, Full-Time Indirect Supervision, and Full-Time Direct Supervision). The SRS was designed to be rated by a clinician based on interviews with the subject and an informant who has observed at first hand the level of supervision received by the subject ([Boake 2000](#)). Scoring is a one-step procedure in which the clinician assigns the rating that is closest to the subject's level. Ratings are based on the level of supervision received, not on how much supervision a subject is judged or predicted to need.

The SRS will be assessed at Visit 1 and Visit 12 or Visit 12R. The Visit 1 assessment will be a retrospective assessment of the supervision required by the subject immediately prior to the admission that included the index episode of status epilepticus.

### 11.2.8.8. Modified Rankin Scale – 9Q (mRS-9Q)

The Modified Rankin Scale (mRS) is a commonly used scale to determine disability and functional dependence due to neurological insult such as stroke in adults. The 7-point scale (0 – 6) denotes functional capacity from no symptoms (0) to severe disability (5) and death (6). The Modified Rankin Scale – 9Q is a shortened version consisting of 9 questions that reliably determines the mRS score and was developed to both simplify the assessment and expand the rater base to non- medically trained personnel (Patel, Rao et al. 2012). The assessment is a web-based tool in the public domain with automatic score calculation and error checking found at [www.modifiedrankin.com](http://www.modifiedrankin.com).

The mRS will be assessed at Visit 1 and at Visit 12 or Visit 12R in subjects  $\geq 17$  years of age. The baseline assessment will be a retrospective assessment of the disability and dependence of the subject immediately prior to the admission that included the index episode of status epilepticus.

## 12. STUDY PROCEDURES

The study procedures listed below by study day reflect the required data collection times for this protocol. When a time window is necessary, this is specified below. If no time window is specified, the test may be performed at any time within the specified 24-hour period.

### 12.1. Visit 1 (V2- $\leq 30$ h)

The baseline period will be up to approximately 84 hours prior to starting blinded study treatment and should include the assessments/procedures listed below and summarized in [Table 1 and Table 2 \(for open-label treatment\)](#), the Schedules of Events.

- Informed consent
- Eligibility checklist
- Verification of inclusion/exclusion criteria.
- Demographic information and medical history obtained by proxy and confirmed by the subject when possible.
- SE and wean history
- Blood will be collected from female subjects 10 years to 55 years for a serum pregnancy test unless they are known to be pre-menstrual or post-menopausal or to have had a hysterectomy.
- Blood and urine samples collected for clinical laboratory testing.
- Pharmacogenetic sample will be collected from consenting/eligible subjects.
- Vital signs
- Height
- Weight
- An ECG reading taken.
- Administration of the STESS.

- Administration of the FOUR Score.
- Administration of SRS.
- Administration of the mRS-9Q assessment.
- Assessment of the CGI scale.
- Evaluation of epilepsy status.
- Administration of continuous IV third-line agents.
- Perform EEG.
- Recording of adverse events.
- Recording of previous and concomitant anti-epileptic drugs.
- Recording of previous and concomitant third-line agents.
- Recording of concomitant pressors.
- Recording of other concomitant medications, procedures, and treatments.

## **12.2. Visit 2 (V3-≤54h)**

- Recording of adverse events.
- Recording of concomitant anti-epileptic drugs.
- Recording of concomitant third-line agents.
- Recording of concomitant pressors.
- Recording of other concomitant medications, procedures, and treatments.
- Wean of continuous third-line agent (QW):
  - If wean is successful, subject is followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (these subjects are Qualifying Wean Success subjects or QWS subjects);
  - If wean is not successful, there is ongoing intravenous administration of at least one continuous IV third-line agent and EEG is performed and the subject is randomized.
- Weight
  - Subject weight will be obtained within the six-hour period from the declaration of failure of QW and prior to the initiation of the blinded infusion loading dose at H0 of V3. This weight will be the dosing weight used to determine the infusion rate for the entire blinded infusion treatment course.

## **12.3. SAGE-547 Treatment Period**

### **12.3.1. Visit 3/3R (0-24 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.

- Vital signs will be recorded at:
  - 0, +30, +60 minutes (+/-15 minutes) and +2, +4, +8 (+/- 30 minutes) and +24 hours (+/- 2 hours) after the start of the infusion
- ECG readings will be recorded immediately after PK sampling, or within 15 minutes prior to PK sampling, at the following time points:
  - 0 (pre-dose) and at +0.5, +1, +3, +6, +12, and +24 hours after the start of the blinded study drug infusion.
- A blood sample for PK analysis should be collected at the following time points (all +/- 15 minutes except where otherwise stated):
  - 0 (pre-dose, within two hours of the start of the infusion) and at +0.5, +1 (+/- 5 minutes), +3, +6, +12, and +24 hours after the start of the blinded study drug infusion.
- Completion of the FOUR Score
  - +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the final declaration of QW success)
- Ongoing intravenous administration of a continuous IV third-line agent.
- Study drug administration in loading (Hour 0-1) and maintenance infusions (at completion of Hour 1).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.3.2. Visit 4/4R (25-48 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +48 hours (+/- 2 hours) after the start of the infusion
- An ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +48 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +48 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +48 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent.

- Ongoing study drug maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.3. Visit 5/5R (49-72 hours)**

- Weight if easily obtained
- Vital signs should be recorded at:
  - +72 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +72 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +72 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +72 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.4. Visit 6/6R (73-96 hours)**

- Weight if easily obtained
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +96 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +96 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +96 hours (+/- 15 minutes) after the start of study drug infusion.



- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +96 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Perform EEG.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.5. Visit 7/7R (97-120 hours)**

- Weight if easily obtained
- Vital signs should be recorded at:
  - +120 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at the following time point:
  - +120 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +120 hours (+/- 15 minutes) after the start of study drug infusion, immediately prior to the end of the maintenance infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +120 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled. Complete wean by 120 hours if at all possible.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.4. SAGE-547 Taper Period**

#### **12.4.1. Visit 8/8R (121-144 hours)**

- Weight if easily obtained

- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +144 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after each PK sampling, or within 15 minutes prior to PK sampling at the following time points:
  - +128, +136 hours and +144 hours after the start of the study drug infusion
  - During the open-label study drug phase of the study ECG readings at: +126, +132, +138 hours and +144 hours after the start of the open-label study drug infusion
- A blood sample for PK analysis should be collected (+/- 15 minutes unless otherwise stated):
  - +128 (immediately prior to the end of the first taper step), +136 hours (+/- 5 minutes, immediately prior to the end of the second taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of study drug infusion.
  - During the open-label study drug phase of the study PK blood draws at: +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 hours (+/- 5 minutes, immediately prior to the end of the third taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of the study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +144 hours (+/- 2 hours) after the start of the infusion
- Complete wean of third line agents by H144 if not completed by H120.
- Perform EEG.
- Taper of SAGE-547 infusion begins at hour 121.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## **12.5. Follow-up Period**

### **12.5.1. Visit 9/9R (145-168 hours)**

- Vital signs should be recorded at:
  - +168 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling, or within 15 minutes prior to PK sampling at + 152 hours:
  - +152, +160 hours (+/- 2 hours) after the start of the study drug infusion
- A blood sample for PK analysis should be collected:

- +152 and +160 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +168 hours (+/- 2 hours) after the start of the infusion
- Perform EEG.
- Assessment of the presence of physiologic brain activity using EEG.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.2. Visit 10/10R (169-192 hours)**

- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +192 hours (+/- 2 hours) after the start of the infusion
- At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine eligibility for the open-label treatment with the higher dose of study drug. This determination may occur at any point during Visit 10: the higher dose open-label infusion must begin within the Visit 10 window. All patients receiving the higher dose open-label treatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.
- Weight if the subject qualifies for the open-label study drug (Visit 10 only, not Visit 10R).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.3. Visit 11/11R (Visit 3/3R + 14d (±2))**

- Blood samples collected for clinical laboratory testing (renal panel only).
- Completion of the FOUR Score (QWS subjects also).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

**12.5.4. Visit 12/12R (Visit 3/3R + 21d ( $\pm 2$ ))**

- All assessments also performed for QWS subjects.
- Completion of the FOUR Score.
- Administration of the GOS.
- Administration of the SRS.
- Administration of the mRS-9Q assessment.
- Evaluation of epilepsy status (see [Section 11.1.2.2](#) for details).
- Assessment of the CGI Scale.
- Recording of adverse events.
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications.
- Collection of pharmacoeconomic data.
- Mortality will be assessed throughout the study period.

**13. STATISTICS****13.1. Statistical Plan**

Complete details for the analysis and reporting of data from this study will be contained in the Statistical Analysis Plan (SAP).

**13.1.1. Interim Analysis**

When approximately 50% of subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

**13.1.2. Study Populations**

The **Safety Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to actual treatment. This analysis population will be used for all safety analyses.

The **Intent to Treat Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to randomized treatment. This analysis population will be used for all efficacy analyses.

The **Modified Intent to Treat Population** is defined as all subjects who:

1. complete their initial course of blinded SAGE-547 or placebo treatment unless the non-completion was due a drug-related adverse event; and
2. have at least one attempt to wean from third-line agents prior to the end of blinded study treatment infusion unless the failure to wean was because seizures were not controlled.

Subjects will be classified according to randomized treatment. This analysis population will be used for sensitivity analyses of the primary endpoint and select secondary efficacy endpoints.

Narratives will be prepared for all subjects who do not complete the infusion of blinded study medication or were not subjected to any wean attempts. Narratives will include details of the cause of SE, the comorbid conditions, the adverse event(s), and reasons for non-completion of the infusion or failure to attempt weaning. This blinded narrative will be reviewed by the medical monitors and the patient adjudicated as MITT eligible or ineligible. Acceptable reasons for defining a subject as MITT ineligible include death or withdrawal of consent due to progression of the underlying cause of SE or comorbid conditions, unless the cause of death or progression of disease were thought by the investigator, sponsor, or DSMB to be related to study drug.

The **Per-Protocol (PP) Population** is defined as a subset of the MITT population but will exclude data from all subjects with significant protocol violations or deviations. Subjects will be classified according to actual treatment received. This data set will be used for sensitivity analyses to examine the robustness of results for the primary and key secondary efficacy endpoints.

The **Pharmacokinetics Population** is defined as all subjects who at least had an infusion of blinded SAGE-547 initiated and have at least one pharmacokinetic sample collected.

The **Pharmacogenetic Population** is defined all subjects who consent to being included in the pharmacogenetic assessment and provide a pharmacogenetic sample.

Summary statistics of all data collected will be presented for subjects who were QW successes.

### 13.1.3. General Aspects

Tabular displays of descriptive statistics will be provided for all variables. Summary tables will include n, mean, standard deviation, minimum and maximum for continuous variable and frequency and percentage for categorical variables.

### 13.1.4. Analysis of Primary Endpoint

The analysis of response to treatment (see [Section 11.1.1](#) for definition of primary endpoint) between SAGE-547 treated subjects and placebo treated subjects will be performed on the ITT population using a Cochran-Mantel-Haenszel (CMH) test with variables for treatment, concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). The CMH general association statistic and its associated p-value will be presented. The comparison of treatment response rates will be conducted at the 5% level of significance. To confirm the CMH results, a permutation test will also be conducted.

An additional analysis of the primary endpoint will also be performed on the MITT population. In addition sensitivity analyses of the primary endpoint will be performed using the ITT population based on:

- the number of third-line agents (one, two, or three) subjects were administered post-randomization; and
- which third line agent was the subject of the first TW.

**13.1.5. Analysis of Secondary Efficacy Endpoints**

Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section (Section 6). Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. The analysis of the secondary endpoints will also be performed on the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

**13.1.6. Analysis of Other Endpoints**

Safety and “Other” endpoints will only be summarized by treatment group. Summaries of safety endpoints will be based on the overall Safety Population.

**13.1.7. Epilepsy and SRSE Status**

Diagnosis of epilepsy and recurrence of RSE or SRSE will be documented as the percentage of subjects by time point and overall. Kaplan-Meier curves may be plotted if sufficient data are available.

Utilization of AEDs during follow-up and during recurrence will be summarized.

**13.1.8. Questionnaires**

The data collected from each questionnaire will be interpreted according to the standard methodology for that questionnaire. There will be no adjustment for missing values.

**13.1.9. Pharmacokinetic Data Analysis**

Details of the pharmacokinetic data analysis will be described in detail in a separate Pharmacokinetic Analysis Plan.

**13.1.10. Pharmacogenetic Data Analysis**

Any genotype data generated in this study will be stored within a secured database within Sage Therapeutics and / or a third party contracted to work with Sage Therapeutics to analyze the samples. Because the number of subjects agreeing to participate in the genetic research component of the study is unknown, it is not possible to establish, a priori, whether sufficient samples will be obtained to support formal statistical evaluation of data. As a consequence a Pharmacogenetic Analysis Plan will only be prepared where appropriate and the results obtained from any genetic research will be reported in a report separate from the main study CSR.

### **13.1.11. Open-Label Study Drug Subjects**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are treated with SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo.

### **13.1.12. EEG-Responders**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who are classified as EEG-responders/non-responders based on the independent assessment of the PAEEG. Summaries will be derived for the two randomized treatment groups.

### **13.1.13. QT/QTc Assessment**

An analysis of the correlation between changes in QT/QTc intervals and SAGE-547 plasma levels will be performed to investigate if there is a potential effect that SAGE-547 may have on QT/QTc interval. A detailed description of the QT/QTc assessment will be included in the SAP.

### **13.1.14. Quantitative EEG**

The nine EEG records for each subject may be subjected to exploratory quantitative EEG analysis, the details of which will be included in the EEG Analysis Plan. In summary the following comparisons may be made, SAGE-547 versus placebo: the QWEEG versus the TWEEG (main analysis); the CEEG versus PAEEG (subsidiary analysis); and TAEED versus PAEEG (exploratory analysis).

## **13.2. Determination of Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between treatment groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

## **13.3. Statistical Analysis Plan**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

## **14. ADVERSE EVENTS**

The safety procedures in this study will be detailed in a Safety Management Plan, which will be agreed and signed before the first subject is randomized in the study. [Section 14.1](#) summarizes Investigator responsibilities regarding the identification and documentation of AEs, the classification of AEs for relationship to study drug and severity, and the reporting of AE information to the Sponsor and the IRB.

[Section 14.2](#) summarizes Sponsor/Medical Monitor Responsibilities regarding monitoring of AE data and reporting relevant safety information to FDA.

[Section 14.3](#) lists important AE definitions.

## 14.1. Investigator Responsibilities

### 14.1.1. Identification and Documentation of Adverse Events by Investigator

Subjects will be evaluated and questioned generally (if possible) to identify AEs during the course of the study. AEs will be collected from the signature of the consent form through Visit 12/12R. Adverse events that occur prior to completion of screening will be captured on the Medical History eCRF. Adverse events that occur after completion of screening will be recorded on the Adverse Event eCRF.

All AEs revealed by observation, other diagnostic procedures, or spontaneously reported by the subject and/or in response to an open question from study personnel will be recorded on the Adverse Event Form. Any clinically significant deterioration in laboratory assessments or other clinical findings are considered an AE and must be recorded on the Adverse Event Form, unless otherwise stated. AE information recorded will be entered into the database on an ongoing basis.

AEs with a relationship considered related to study drug (probable, possible) should be followed until the event is resolved or the Investigator determines the event is stable or no longer clinically significant. AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

For SAEs, an electronic Serious Adverse Event eCRF must be completed with as much information as possible and submitted in the time frame described below in [Section 14.1.3](#). When new significant information is obtained as well as when the outcome of an event is known, the electronic SAE eCRF should be updated within 24 hours. If the subject was an outpatient at the time of the SAE and was re-hospitalized due to the SAE, a copy of relevant hospital records (e.g., admission report, laboratory test results, discharge summary, etc.) may be requested to be included as part of the subject medical file.

All SAEs will be followed until resolved or until a stable status has been achieved.

### 14.1.2. Adverse Event Classification

#### 14.1.2.1. Relationship to Investigational Drug

None:	No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state.
Possible:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject, but this is not known for sure.
Probable:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.



**14.1.2.2. Severity**

Mild	Discomfort noticed, but no disruption to daily activity.  For subjects that are unconscious, this may be a slight or minor change in a lab result or clinical sign or symptom that does not require immediate corrective action.
Moderate	Discomfort sufficient to reduce or affect normal daily activity, but is not hazardous to health; prescription drug therapy may be employed to treat the AE.  For subjects that are unconscious, this may be a clinically meaningful change that may require immediate corrective action.
Severe	Inability to work or perform normal daily activity and represented a definite hazard to health; prescription drug therapy and/or hospitalization may be employed to treat the AE.  For unconscious subjects, this may be a significant clinical change that requires immediate corrective action.

**14.1.2.3. Action Taken with Investigational Drug**

None	Study medication was continued without change.
Discontinued	Study medication was terminated.
Dose adjusted	Study medication dose/infusion rate was changed and then continued per protocol.
Interrupted	Study medication was interrupted and then continued per protocol.
Unknown	The action taken with regard to study medication is unknown.
Not applicable	Administration of study medication was not ongoing.

**14.1.2.4. Assessment of Outcome**

Ongoing	At the end of the study, the event has not resolved or stabilized.
Ongoing and stable	The event is ongoing but has stabilized and is unlikely to change
Resolved	The event has resolved or the subject recovered without sequelae.
Resolved with sequelae	The event has at least one secondary outcome that may result in permanent disability and/or functional limitation.
Unknown	The status of the event is unknown.
Death	The subject has expired.

**14.1.3. Investigator Reporting to Sponsor and Sponsor Emergency Contact**

All new SAEs that come to the Investigator and/or Sponsor's notice during the course of the study (up to and including the last study visit) must be reported by the Investigator on the designated electronic report form within 24 hours of the point in time when the Investigator becomes aware of the SAE. As additional information becomes available, the designated electronic report form must be updated within 24 hours.

Investigators must report any SAE, whether or not considered drug related. The report must include an assessment of whether there is a reasonable possibility that the drug caused the event.

In a medical emergency (ie, an event that requires immediate attention regarding the treatment of a subject, operation of the clinical study, and/or the use of investigational drug), study site staff will apply appropriate medical intervention according to current standards of care, and contact the Medical Monitor.

**14.1.4. Medical Monitor and Emergency Contact Information**

[REDACTED], MD  
[REDACTED]

**14.1.5. SAE Reporting Contact Information**

Contact information and reporting instructions are provided in the Safety Management Plan.

**14.1.6. Reporting to Institutional Review Boards (IRBs)**

It is the responsibility of the Investigator to promptly notify the institution's IRB of all serious and unexpected suspected adverse reactions (see [Section 14.3](#) for definitions).

**14.2. Sponsor/Medical Monitor Responsibilities****14.2.1. Monitoring of Adverse Event Data**

The Medical Monitor will review any newly reported adverse events in an ongoing basis. If the aggregate assessment indicates that an event is occurring more frequently than would normally be expected in this population, or as previously observed, and the sponsor believes that the events are causally related to the administration of SAGE-547, the Sponsor will then report that information in an IND safety report.

**14.2.2. Data Safety Monitoring Board**

An independent DSMB will monitor the clinical, PK and PD data for safety signals throughout the study and will be asked to assess the placebo response rate at the time of the interim analysis to determine final sample size. In order to perform their monitoring function the DSMB will have access to un-blinded safety data as necessary.

The composition and procedures for the board will be described in a separate DSMB Charter.

### **14.2.3. Reporting to FDA**

The Sponsor must report in an IND safety report any suspected adverse reaction to study treatment that is both serious and unexpected (21 CFR 312.32(c)(1)(i)). Before submitting an IND safety report, the Sponsor will ensure the event meets all three of the definitions: (1) suspected adverse reaction, (2) serious, (3) unexpected. If the AE does not meet all three of the definitions, it should not be submitted as an IND safety report. The Sponsor should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the adverse event and, therefore, that the event meets the definition of a suspected adverse reaction.

If there is a serious and unexpected suspected adverse reaction, the Sponsor will notify the appropriate regulatory agency(ies) and all appropriate parties on an expedited basis. In addition, Sponsors must submit expedited reports of an increased rate of occurrence or severity of serious suspected adverse reactions over that listed in the protocol or Investigational Brochure.

SUSARs will be unblinded prior to reporting to FDA. Unless it is necessary to unblind for the safety of the patient, the investigator will not be informed of the unblinding of the subject.

Under 21 CFR 312.32, Sponsors should identify in the protocol SAEs that it does not plan to report individually in an expedited manner, because they are known consequences of the disease or otherwise common in the study population. Given the grave condition and prognosis of SRSE being studied, individual occurrences of seizures or seizure activity will not be reported expeditiously in this study. Regardless of which events are reported in an expedited manner, all adverse events will be closely monitored throughout the study.

## **14.3. Adverse Event Definitions**

### **14.3.1. Adverse Event**

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

### **14.3.2. Suspected Adverse Reaction**

Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

### **14.3.3. Life-Threatening**

An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

### **14.3.4. Serious**

An AE or suspected adverse reaction is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death

- A life-threatening AE – see definition above
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disability
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

#### **14.3.5. Unexpected**

An AE or suspected adverse reaction is considered “unexpected”:

- If it is not listed in the Investigational Brochure or is not listed at the specificity or severity that has been observed, or
- If an Investigational Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigational Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigational Brochure listed only cerebral vascular accidents.

“Unexpected,” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigational Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

#### **14.4. Emergency Identification of Study Medication**

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject’s treatment in the study via the IVRS; this normally requires prior approval by the medical monitor. However, if the subject is at immediate risk and the Investigator believes that immediate knowledge of the study treatment will alter medical management, discussion with the medical monitor may take place after unblinding. The Investigator will not unblind the medical monitor during that discussion. The process of unblinding will ensure that only the investigator is unblinded; the medical monitor, study management team, and data management team will not be made aware of the treatment allocation of an individual subject. All cases of emergency unblinding will be fully documented in a way that does not unblind the medical monitor, study management team, and data management team.

## **15. STUDY ADMINISTRATIVE CONSIDERATIONS**

### **15.1. Quality Control and Quality Assurance**

The Investigators and institutions will permit trial related monitoring, audits, IRB review, and regulatory inspections as requested by FDA, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed informed consent forms, etc.) in addition to case report forms.

Quality assurance and quality control systems with written standard operating procedures (SOPs) will be followed to ensure this trial will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The site's dedicated study monitor will arrange to visit the Investigator at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be identified and resolved. The study monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality assurance officers named by Sage Therapeutics or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements, made by the Sponsor with the Investigator/institution and any other parties involved with the clinical trial, will be in writing in a separate agreement.

### **15.2. Data Handling and Recordkeeping**

#### **15.2.1. Data Handling**

Procedures for data handling (including electronic data) used in this protocol will be documented in a Data Management Plan.

#### **15.2.2. Case Report Form Completion**

eCRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of demographics, study drug administration, study procedures, AEs, questionnaire completion, efficacy assessments and subject status, including survival.

The Investigator will maintain copies of the eCRFs at the study site. For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate eCRF.

**15.2.3. Retention of Study Records**

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval and until there are no pending or contemplated marketing applications or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to an appropriate person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

**15.3. Confidentiality**

To maintain subject privacy, all eCRFs, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available trial registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by Sage Therapeutics to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

**15.4. Publication Policy**

All information concerning SAGE-547 is considered confidential and shall remain the sole property of Sage Therapeutics. The Investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval from Sage Therapeutics. No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between Sage Therapeutics and the Investigator.

**15.5. Protocol Amendments**

Changes to the conduct of the study should be prepared as a protocol amendment by the Sponsor. Protocol amendments should receive written IRB/IEC approval prior to implementation at the investigative site, except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the trial (eg, change of monitor, telephone numbers). In this case, Sage Therapeutics will amend and implement the protocol change and subsequently notify the regulatory authorities and the Investigative sites who will notify the respective IRB, as appropriate.

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**APPENDIX 1. APPENDIX 1: FOUR SCORE****FOUR score****Full Outline of UnResponsiveness****Eye response**

- E4: eyelids open or opened, tracking, or blinking to command
- E3: eyelids open but not tracking
- E2: eyelids closed but open to loud voice
- E1: eyelids closed but open to pain
- E0: eyelids remain closed with pain

**Motor response**

- M4: thumbs-up, fist or peace sign
- M3: localizing to pain
- M2: flexion response to pain
- M1: extension response to pain
- M0: no response to pain or generalized myoclonus status

**Brainstem reflexes**

- B4: pupil and corneal reflexes present
- B3: one pupil wide and fixed
- B2: pupil or corneal reflexes absent
- B1: pupil and corneal reflexes absent
- B0: absent pupil, corneal and cough reflex

**Respiration pattern**

- R4: not intubated, regular breathing pattern
- R3: not intubated, Cheyne-Stokes breathing pattern
- R2: not intubated, irregular breathing
- R1: breathes above ventilatory rate
- R0: breathes at ventilator rate or apnea

Reference ([Iyer, Hoel et al. 2009](#)).

**APPENDIX 2. GLASGOW OUTCOME SCALE (GOS)****GLASGOW  
OUTCOME  
SCALE**

Patient Name: \_\_\_\_\_  
 Rater Name: \_\_\_\_\_  
 Date: \_\_\_\_\_

*Note:* The scale presented here is based on the original article by Jennett and Bond. It has become common practice in clinical trial administration, however, to use a modified version that places the scores in reverse order (i.e., "good recovery" = 1, "moderate disability" =2, etc.).

Score	Description
1	DEATH
2	PERSISTENT VEGETATIVE STATE Patient exhibits no <i>obvious cortical</i> function.
3	SEVERE DISABILITY (Conscious but disabled). Patient depends upon others for daily support due to mental or physical disability or both.
4	MODERATE DISABILITY (Disabled but independent). Patient is independent as far as daily life is concerned. The disabilities found include varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes.
5	GOOD RECOVERY Resumption of normal activities even though there may be minor neurological or psychological deficits.

**TOTAL (1-5):** \_\_\_\_\_

Reference ([Jennett and Bond 1975](#)).

## APPENDIX 3. SUPERVISION RATING SCALE (SRS)

### SUPERVISION RATING SCALE (SRS)

**Instructions:** Circle the rating that is closest to the amount of supervision that the patient *actually receives*. "Supervision" means that someone is responsible for being with the patient.

<u>Rating</u>	<u>Description</u>
<b>Level 1: INDEPENDENT</b>	
1	The patient lives alone or independently. Other persons can live with the patient, but they cannot take responsibility for supervision (for example, a child or elderly person).
2	The patient is unsupervised overnight. The patient lives with one or more persons who <i>could</i> be responsible for supervision (for example, a spouse or roommate), but they are <i>all</i> sometimes absent overnight.
<b>Level 2: OVERNIGHT SUPERVISION</b>	
3	The patient is only supervised overnight. One or more supervising persons are always present overnight but they are <i>all</i> sometimes absent for the rest of the day.
<b>Level 3: PART-TIME SUPERVISION</b>	
4	The patient is supervised overnight and part-time during waking hours, but is allowed on independent outings. One or more supervising persons are always present overnight and are also present during part of waking hours every day. However, the patient is sometimes allowed to leave the residence without being accompanied by someone who is responsible for supervision.
5	The patient is supervised overnight and part-time during waking hours, but is unsupervised during working hours. Supervising persons are <i>all</i> sometimes absent for enough time for them to work full-time outside the home.
6	The patient is supervised overnight and during most waking hours. Supervising persons are <i>all</i> sometimes absent for periods longer than one hour, but less than the time needed to hold a full-time job away from home.
7	The patient is supervised overnight and during almost all waking hours. Supervising persons are <i>all</i> sometimes absent for periods shorter than one hour.
<b>Level 4: FULL-TIME INDIRECT SUPERVISION</b>	
8	The patient is under full-time indirect supervision. At least one supervising person is <i>always</i> present, but the supervising person does not check on the patient more than once every 30 minutes.
9	Same as #8 plus requires overnight safety precautions (for example, a deadbolt on outside door).
<b>Level 5: FULL-TIME DIRECT SUPERVISION</b>	
10	The patient is under full-time direct supervision. At least one supervising person is always present and the supervising person checks on the patient more than once every thirty minutes.
11	The patient lives in a setting in which the exits are physically controlled by others (for example, a locked ward).
12	Same as #11 plus a supervising person is designated to provide full-time line-of-sight supervision (for example, an escape watch or suicide watch).
13	The patient is in physical restraints.

3/12/93

Corwin Boake, Ph.D., TIRR, 1333 Moursund, Houston, TX 77030-3405, 713/799-6990

## APPENDIX 4. MODIFIED RANKIN SCALE – LEVEL OF FUNCTION SURVEY (mRS-9Q)

1. Do you have any symptoms that are bothering you? (For example, trouble with reading or writing, trouble speaking, problems with vision, numbness, weakness, balance trouble, or problems with swallowing?)	YES <input type="radio"/>	NO <input type="radio"/>
2. Are you able to do the same work as before?	YES <input type="radio"/>	NO <input type="radio"/>
3. Are you able to keep up with your hobbies?	YES <input type="radio"/>	NO <input type="radio"/>
4. Have you maintained your ties to friends and family?	YES <input type="radio"/>	NO <input type="radio"/>
5. Do you need help making a simple meal, doing household chores, or balancing a checkbook?	YES <input type="radio"/>	NO <input type="radio"/>
6. Do you need help with shopping or traveling close to home?	YES <input type="radio"/>	NO <input type="radio"/>
7. Do you need another person to help you walk?	YES <input type="radio"/>	NO <input type="radio"/>
8. Do you need help with eating, going to the toilet, or bathing?	YES <input type="radio"/>	NO <input type="radio"/>
9. Do you stay in bed most of the day and need constant nursing care?	YES <input type="radio"/>	NO <input type="radio"/>

## APPENDIX 5. CLINICAL GLOBAL IMPRESSION (CGI)

### Clinical Global Impression (CGI)

#### 1. Severity of illness

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- |                             |   |
|-----------------------------|---|
| 0 = Not assessed            | 4 = Moderately ill                        |
| 1 = Normal, not at all ill  | 5 = Markedly ill                          |
| 2 = Borderline mentally ill | 6 = Severely ill                          |
| 3 = Mildly ill              | 7 = Among the most extremely ill patients |

#### 2. Global improvement: Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.

Compared to his condition at admission to the project, how much has he changed?

- |                        |                     |
|------------------------|---------------------|
| 0 = Not assessed       | 4 = No change       |
| 1 = Very much improved | 5 = Minimally worse |
| 2 = Much improved      | 6 = Much worse      |
| 3 = Minimally improved | 7 = Very much worse |

#### 3. Efficacy index: Rate this item on the basis of drug effect only.

Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.

EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect		Side effects			
		None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
<b>Marked</b>	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
<b>Moderate</b>	Decided improvement. Partial remission of symptoms	05	06	07	08
<b>Minimal</b>	Slight improvement which doesn't alter status of care of patient	09	10	11	12
<b>Unchanged or worse</b>		13	14	15	16
Not assessed = 00					

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

**APPENDIX 6. STATUS EPILEPTICUS SEVERITY SCORE (STESS)**

Outcome Predictor	Feature	Score
Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type (prior to first treatment)	Simple-partial, complex-parial, absence, myoclonic (complicating idiopathic generalized epilepsy)	0
	Generalized-convulsive	1
	Nonconvulsive status epilepticus in coma	2
Age	< 65 years	0
	≥ 65 years	2
History of previous seizures	Yes	0
	No or unknown	1
Summed Total		

**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY  
TO EVALUATE THE EFFICACY AND SAFETY OF SAGE-547 INJECTION  
IN THE TREATMENT OF SUBJECTS WITH SUPER-REFRACTORY  
STATUS EPILEPTICUS**

**PROTOCOL NUMBER: 547-SSE-301**

**IND NUMBER: 117901**

**EudraCT Number: 2015-002142-31**

Product: SAGE-547 Injection (allopregnanolone)

Sponsor Contact: [REDACTED], MD

[REDACTED]  
Sage Therapeutics  
215 First Street  
Cambridge, MA 02142

Medical Monitor: [REDACTED], MD

Date of Protocol: 09 March 2015  
Date of Amendment One 27 May 2015  
Date of Amendment Two 04 February 2016  
(Italy Specific)

**Confidentiality Statement**

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

**PROTOCOL NUMBER: 547-SSE-301**

Sponsor [REDACTED]:

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]:

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

CRO [REDACTED]:

[REDACTED]



## 1. SIGNATURE PAGE

Title of Protocol:

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus

Protocol No: 547-SSE-301

### Sponsor Approval

  
 MD

19 Feb 2016

Date (dd/mmm/yyyy)

Sage Therapeutics

### Investigator Agreement

By signing this page I attest that I have read and understand the contents of Clinical Protocol 547-SSE-301 and any current amendments. I agree to adhere to the design, conduct, and reporting requirements of the study as stated in the clinical protocol and to my obligations to the Sponsor as described in the protocol and executed contracts between myself, my Institution, and the Sponsor. I also agree to adhere to any subsequent amendments to the clinical protocol.

Investigator's Signature: \_\_\_\_\_

Investigator's Name: \_\_\_\_\_

Institution: \_\_\_\_\_

Date: \_\_\_\_\_

## 2. SYNOPSIS

<b>Name of Sponsor:</b> Sage Therapeutics 215 First Street Cambridge, MA 02142		
<b>Protocol No.</b> 547-SSE-301	<b>Phase:</b> 3	
<b>Name of Investigational Product:</b> SAGE-547 Injection		
<b>Name of Active Ingredient:</b> Allopregnanolone		
<b>Title of the Protocol:</b> A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus		
<b>Dosing Regimen: SAGE-547 or Placebo Dosing Schedule</b>		
<b>Hour</b>	<b>Type and Duration of SAGE-547 Infusions</b>	<b>Dose</b>
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	90 µg/kg/h
H121 – H128	8 hour taper	65 µg/kg/h
H129 – H136	8 hour taper	45 µg/kg/h
H137 – H144	8 hour taper	25 µg/kg/h
<b>Dosing Regimen: SAGE-547 Open Label Dosing Schedule</b>		
<b>Hour</b>	<b>Type and Duration of SAGE-547 Infusion</b>	<b>Dose</b>
H1	One hour loading infusion	300 µg/kg/h
H2 –H120	119 hour maintenance infusion	150 µg/kg/h
H121 – H126	6 hour taper	125 µg/kg/h
H127 – H132	6 hour taper	95 µg/kg/h
H133 – H138	6 hour taper	65 µg/kg/h
H139 – H144	6 hour taper	35 µg/kg/h
<b>Study Sites</b> Up to 180 sites in the USA, Europe, and Canada.		
<b>Number of Subjects</b>		

The study will randomize 140 subjects at up to 180 sites.

### Study Population

Subjects will be aged two years or more, in SRSE<sup>1</sup> (as defined in the Inclusion Criteria [Section 8.1](#)), and being managed in an intensive care setting. Pediatric patients (those < 14 years of age) will be managed in a pediatric intensive care setting.

### Duration of Subject Involvement

Individual subject participation will be up to 30 days.

### Study Design

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

Patients will follow one of three paths to entry to the study. The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst suppression with a third-line agent. These subjects will be consented for the study after admission to the intensive care unit, but before any third-line agents are administered for burst suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their legally authorized representative (LAR). Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours. Once burst suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The second path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst suppression pattern on the EEG. These subjects may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

<sup>1</sup> In this study, the term Super-Refractory Status Epilepticus or SRSE is equivalent to “Refractory Status Epilepticus (RSE) that has failed standard treatment” and the two terms are used interchangeably.

The third path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These subjects may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 treatment or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within six hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo).

The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that subjects, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as both the ability to wean the subject off all third-line agents before the end of the infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication infusion, and concurrent signs of physiologic brain activity as determined by EEG. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#) and [Error! Not a valid result for table.](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo will all subsequently be eligible to be administered SAGE-547 at the higher dose.

## Visit Schedule

The visit schedule and an overview of events at each visit is provided in Table 1, **Error! Not a valid result for table.** and Table 3 Schedule of Assessments.

## Study Objectives

### *Primary objective:*

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult and pediatric subjects with SRSE, and for the response to endure at least 24 hours after the end of the SAGE-547 or placebo infusion (primary response).

### *Secondary objectives:*

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in the Clinical Global Impression scale (CGI) between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### *Safety objectives:*

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

### *Other objectives:*

1. To evaluate the impact of retreatment with a higher dose SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;

2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;
6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS) (age  $\geq 17$  years).

## Endpoints

### *Primary endpoint:*

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### *Secondary endpoints:*

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### *Safety endpoints:*

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;

## 5. Mortality.

**Other endpoints:**

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who fail to respond to their randomized double blind treatment and are retreated with a higher dose of SAGE-547.
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol<sup>®</sup> and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS) (age  $\geq 17$  years).

**Inclusion Criteria**

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects two (2) years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst suppression pattern; or who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst suppression pattern.

**Exclusion Criteria**

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone or any excipients in SAGE-547.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy.

4. Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing underlying neurological disorder.
5. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis for whatever reason, but dialysis is not planned or non-continuous dialysis is planned (that would not adequately remove Captisol®);
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the opinion of the investigator, of less than 30 days;
  - e. a do not resuscitate (DNR) order.
6. Subjects who are being administered more than three third-line agents concomitantly or in whom the qualifying wean cannot be completed within 24 hours, or who are being administered a third-line agent for other indications such as management of raised intra-cranial pressure that would preclude weaning according to this protocol.
7. Subjects with a living will that does not allow heroic measures.
8. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
9. Subjects who have been enrolled in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not withdraw or complete and then re-enroll).

### **Pharmacogenetic Research**

In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **Statistical Analysis**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

### **Interim Analysis**

When approximately 50% of the subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### **Analysis of Primary Endpoint**



The analysis of response to treatment between SAGE-547 treated subjects and placebo treated subjects will be performed using a Cochran-Mantel-Haenszel test with variables for treatment, concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). In this analysis, a treatment responder is a subject who is successfully weaned off all third-line agents and blinded study medication prior to the end of study treatment infusion and remains off third-line agents for at least 24 hours following cessation of the blinded study medication, and who has concurrent signs of physiologic brain activity as determined by EEG. The analysis will be based on the ITT Population. The comparison of treatment response rates will be conducted at the 5% level of significance.

### **Analysis of Secondary Efficacy Endpoints**

The primary analysis will be repeated for the MITT population. Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section. Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. Secondary analyses will be repeated for the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from Baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third-line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

Summaries of safety endpoints will be based on the overall Safety Population which is defined as all subjects who at least initiated the infusion with blinded study treatment.

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are retreated with SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo. Summary statistics will be presented for subjects who were QW successes.

### **Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

**Table 1: Schedule of Assessments for Protocol 547-SSE-301: One Infusion of Study Drug (blinded)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical/SE/Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X		X	X	X	X	X	X				
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X		X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X		X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X		X	X		X		X		X		
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X			
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>o</sup>											X
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV 3rd-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>p</sup>				
EEG	X	X				X		X	X			
Randomization		X										
Study Drug Administration <sup>q</sup>			X	X	X	X	X	X				
TW Outcome & Retreat Decision										X <sup>r</sup>		
Physiologic Brain Activity									X			
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

**Table 2: Schedule of Assessments for Protocol 547-SSE-301: Two Infusions of Study Drug (one blinded, one open-label)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V3R
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	0-24h
Eligibility Checklist	X										S
Informed Consent <sup>a</sup>	X										E
Inclusion/Exclusion Criteria	X										E
Demography <sup>b</sup>	X										
Medical and SE and Wean History <sup>c</sup>	X										T
Height	X										A
Weight <sup>d</sup>	X		X	X	X	X	X	X			B
Serum Pregnancy Test <sup>e</sup>	X										L
Hematology <sup>f</sup>	X		X	X		X		X		X	E
Serum Chemistry and GFR <sup>g</sup>	X		X	X		X		X		X	
Urinalysis <sup>h</sup>	X		X	X		X		X		X	E
Pharmacogenetic sample	X										X
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X	T
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X	E
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X		N
STESS	X										I
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	O
Glasgow Outcome Score (GOS)											N
Supervision Rating Scale (SRS)	X <sup>o</sup>										
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>										
Epilepsy Status	X										N
Clinical Global Impression (CGI)	X										E
Continuous IV Third-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>p</sup>			X
EEG	X	X				X		X	X		T
Randomization		X									
Study Drug Administration <sup>q</sup>			X	X	X	X	X	X			
TW Outcome and Retreat Decision										X <sup>r</sup>	P
Physiologic Brain Activity									X		
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	A
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	G
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	E
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X	
Pharmacoeconomic Data											
Mortality											

Table 2 continued

	V3R	V4R	V5R	V6R	V7R	V8R	V9R	V10R	V11R	V12R
	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3R+14d (±2d)	V3R+21d (±2d)
Weight <sup>d</sup>	X	X	X	X	X	X				
Serum Pregnancy Test <sup>e</sup>										
Hematology <sup>f</sup>	X	X		X		X		X		
Serum Chemistry and GFR <sup>g</sup>	X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X	X		X		X		X		
Vital Signs <sup>i</sup>	X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>	X	X	X	X	X	X	X			
STESS										
FOUR Score <sup>m</sup>	X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)										X
Supervision Rating Scale (SRS)										X
Modified Rankin Score (mRS) <sup>n</sup>										X
Epilepsy Status										X
Clinical Global Impression Scale (CGI)										X
Continuous IV Third-Line Agent(s)	X	X	Wean	Wean	Wean	Wean <sup>p</sup>				
EEG			X			X	X			
Randomization										
Study Drug Administration <sup>q</sup>	X	X	X	X	X	X				
TW Success and Physiologic Brain Activity							X			
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data										X
Mortality										X

**Table 3: Schedule of Assessments for Protocol 547-SSE-301: Qualifying Wean Successes**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical and SE and Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X											
Serum Pregnancy Test <sup>c</sup>	X											
Hematology <sup>f</sup>	X											
Serum Chemistry and GFR <sup>f</sup>	X											
Urinalysis <sup>h</sup>	X											
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X											
ECG <sup>j</sup>	X											
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>o</sup>											X
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV Third-Line Agent(s)	X	Wean										
EEG	X	X										
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

<sup>a</sup> Written informed consent by proxy (LAR) will be obtained prior to starting any study-related procedures not considered standard of care.

<sup>b</sup> Demographic information will be obtained by proxy and confirmed by the subject when possible.

<sup>c</sup> Medical history will be obtained by proxy and confirmed by the subject when possible. All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Dosing changes with the third-line agent(s) that constitute a wean attempt will be marked as such on the CRF, and the start/stop dates and times of all wean attempts prior to V3 will be recorded, as well as the outcome of the wean attempt.

<sup>d</sup> Weight will be collected at Screening (V1) and once during each 24 hour period of the initial study drug infusion period (V3-V8) and second infusion period (V3R-V8R, if applicable). Daily weight will be used to determine the appropriate infusion rate of each dose.

<sup>e</sup> Serum pregnancy test for females aged 10 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy.

<sup>f</sup> Blood samples will be taken for hematology and serum chemistry and GFR calculation at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will document whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

<sup>g</sup> Blood samples will be taken at V11 or V11R for serum chemistry (renal panel only).

<sup>h</sup> Urine samples will be taken for urinalysis and NAG at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will add a comment about whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

<sup>i</sup> Vital signs will be recorded at the following time points relative to the start of each infusion of study drug: Screening (V1), at 0, 30, 60 minutes ( $\pm 15$  minutes), at 2, 4, and 8 hours ( $\pm 30$  minutes), and at 24, 48, 72, 96, 120, 144, 168, and 192 hours ( $\pm 2$  hours).

<sup>j</sup> ECG (12-lead) should be performed at Screening (V1) and at the following times relative to the start of study drug infusion. For the blinded (first) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 128, 136, 144, 152, 160, and 192 hours ( $\pm 2$  hours). For the open label SAGE-547 (second) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 126, 132, 138, 144, 152, 160, and 192 hours ( $\pm 2$  hours). Heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours.

<sup>k</sup> Plasma will be collected to assay for study drug concentrations at the following time points relative to the start of each infusion of study drug: For the blinded (first) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion. For the open label SAGE-547 (second) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open label SAGE-547 study drug infusion. Pre-dose samples may be taken within two hours before starting the infusion of study drug; timepoints up to and including 1h will have a time window of  $\pm 5$  minutes; all other timepoints will have a window of  $\pm 15$  minutes.

<sup>m</sup> FOUR Score assessments will be performed at Screening (V1), 24, 48, 72, 96, 120, 144, 168, and 192 hours (all  $\pm 2$  hours) relative to the start of each infusion of study drug, and at V11 or V11R, and at V12 or V12R.

<sup>n</sup> Modified Rankin Score (mRS) applicable for subjects  $\geq 17$  years old only.

<sup>o</sup> SRS at V1 will be a retrospective assessment of the supervision required by the subject immediately prior to admission that includes the index episode of the SE, and mRS at V1 will be a retrospective assessment of the disability and dependence of the subject immediately prior to admission that includes the index episode of the SE.

<sup>p</sup> Target for complete wean of all continuous IV third-line agents by 144 hours at V8/V8R if not completed by 120 hours at V7/V7R.

<sup>q</sup> Study drug infusion is intended for IV administration only with a dedicated peripheral IV line using Sage-approved IV administration bags and lines.

<sup>r</sup> At V10 only a decision to re-treat at a higher dose of SAGE-547 will be made by the Investigator if the continuous IV third-line agent wean has failed or the third-line agent requires re-introduction during V9. Subjects who become eligible for re-treatment at a higher dose of SAGE-547 will discontinue the planned visit schedule at V10, then repeat V3 (V3R) and all applicable subsequent visits.

<sup>s</sup> AEs will be collected from the time Informed Consent is obtained and prior to the start of study-specific screening procedures not considered standard of care. Collection of AEs will continue throughout the study from V1 through V12 or V12R.

<sup>t</sup> Subjects may enter the study on AEDs and be administered AEDs during the study. All Concomitant AEDs must be recorded on the CRF with details including date and time of starting/stopping each AED, the route of administration, changes in doses, and frequency of administration. Details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the CRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.

<sup>u</sup> All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Details will include the name of the drug, the start/stop dates and times, and, after consent, the doses with start/stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

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**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
AE	adverse event
AED	anti-epileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the time-concentration curve
AW	additional weans
BDZ	benzodiazepine
BIEEG	blinded infusion electroencephalogram
BUN	blood urea nitrogen
CBC	complete blood count
CEEG	consent electroencephalogram
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
C <sub>max</sub>	maximum plasma concentration
C <sub>min</sub>	minimum plasma concentration
CNS	central nervous system
CRF	case report form
CSR	clinical study report
CYP2C9	cytochrome P450 enzyme involved in drug metabolism
DNR	do not resuscitate
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EEG	electroencephalogram
EIND	Emergency Use Investigational New Drug Application
EP	European Pharmacopeia
ESETT	Established Status Epilepticus Treatment Trial
FDA	Food and Drug Administration
FOUR	Full Outline of UnResponsiveness
GABA	$\gamma$ -aminobutyric acid
GABA <sub>A</sub>	$\gamma$ -aminobutyric acid-gated chloride channel

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GOS	Glasgow Outcome Scale
H	hour
HPLC	high performance liquid chromatography
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent to Treat
IV	intravenous
IVRS	Interactive Voice Randomization System
LAR	legally authorized representative
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent to Treat
mRS-9Q	Modified Rankin Score - 9Q
MS/MS	tandem mass spectrometry
nM	nanomolar
NMDA	n-methyl-D-aspartic acid
OW	other weans
PAEEG	primary endpoint electroencephalogram
PD	pharmacodynamics
PK	pharmacokinetic
QOL	quality of life
QW	qualifying wean
QWEEG	qualifying wean electroencephalogram
RBC	red blood cell

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
RSE	refractory status epilepticus
SAE	serious adverse event
SAP	Statistical Analysis Plan
SE	status epilepticus
SOP	standard operating procedure
SRS	Severity Rating Scale
SRSE	Super-refractory status epilepticus
SSRI	Selective serotonin re-uptake inhibitors
STESS	Status Epilepticus Severity Score
SUSAR	Suspected Unexpected Serious Adverse Reactions
SWFI	Sterile Water for Injection
TAEEG	taper electroencephalogram
T <sub>max</sub>	time at maximum plasma concentration
TW	terminal wean
TWEEG	terminal wean electroencephalogram
US	United States
USP	United States Pharmacopeia



### 3. INTRODUCTION AND RATIONALE

#### 3.1. Status Epilepticus

Status epilepticus (SE) is a life-threatening seizure condition in which the brain is in a state of persistent seizure triggered by neuronal hyperexcitability. The Neurocritical Care Society defines SE as one continuous unremitting seizure lasting longer than five minutes or recurrent seizures without regaining consciousness between seizures for greater than five minutes (Brophy, Bell et al. 2012). Common causes of SE include preexisting epilepsy, cerebrovascular disease (in adults), electrolyte and metabolic disturbances, anoxia, encephalopathies, head trauma, high fever (in children, especially in the first year of life) and drug or substance intoxication. SE is associated with substantial morbidity and mortality.

##### 3.1.1. Epidemiology of SE

Geography, sex, age, and race influence the epidemiology of SE, whose incidence has a bimodal distribution, peaking in infants/young children and the elderly (Hauser 1990; DeLorenzo, Pellock et al. 1995; Wu, Shek et al. 2002). The incidence of SE in the elderly population is at least twice that in the general population. Concurrent medical conditions often exist in the elderly population, which can complicate therapy and worsen the prognosis of SE (Chapman, Smith et al. 2001).

The annual incidence of SE in the US is generally quoted to be within the range of 18/100,000 to 61/100,000, based on a 19-year retrospective study in Rochester, Minnesota (Hesdorffer, Logroscino et al. 1998) and a 2-year prospective study in Richmond, Virginia (DeLorenzo, Pellock et al. 1995), respectively. Two studies from Europe give annual incidences of a similar magnitude, ranging between 9.9/100,000 and 15.8/100,000 (Coeytaux, Jallon et al. 2000; Knake, Rosenow et al. 2001). It is thus estimated that in the United States each year there are as many as 150,000 cases of SE (DeLorenzo, Pellock et al. 1995).

#### 3.2. Refractory SE

When a patient begins to seize, the emergency medical technician will administer a first-line intravenous (IV) benzodiazepine (BDZ), such as diazepam, lorazepam or midazolam (Silbergleit, Durkalski et al. 2012), which is done either at the scene of the seizure or in the ambulance. If this is unsuccessful at abating the seizure, additional doses of the first-line therapy will be administered in the emergency room. Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line therapy, which is an IV anti-epileptic drug (AED) such as phenytoin or valproic acid (Novy, Logroscino et al. 2010; Shorvon 2011; Hocker, Britton et al. 2013).

Approximately 20-30% of patients refractory to first-line treatment will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to approximately 70-80% of patients who receive second-line therapy refractory to that therapy.

If a patient's SE continues after administration of BDZs and AEDs, the subject is diagnosed as having refractory status epilepticus (RSE), which must be treated quickly to terminate the seizure activity, maintain the patient's airway, and prevent cerebral damage. RSE patients are immediately admitted to the Intensive Care Unit (ICU) and placed in a medically-induced coma to stop all seizure-related activity. The drugs used to induce coma are continuously-infused IV agents,

commonly propofol, midazolam, or pentobarbital/thiopental, referred to as third-line agents (Brophy, Bell et al. 2012).

The RSE patient is continually monitored using electroencephalography (EEG) to ensure burst suppression is achieved. Burst suppression is a pattern of brain waves seen on an EEG, characterized by periods of activity alternating with periods of little or no activity in the brain, informing medical personnel of the effectiveness of the medically-induced coma. The goal of burst suppression is to allow the brain and corresponding neuronal tissue to restore function and reset to normal pre-seizure levels.

### 3.2.1. Epidemiology of RSE

Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line AED therapy. In turn, approximately 20 – 30% of these patients treated with AEDs will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to 28% of the total estimated SE patient population refractory to second-line therapy. Based on the previously-cited estimated incidence in the US, this means that there are up to 42,000 incident cases of RSE in the USA, annually (DeLorenzo, Pellock et al. 1995).

### 3.3. Super-refractory SE

After 24 hours of burst suppression, the patient is weaned off of the third-line therapy. If the weaning is unsuccessful (neuronal activity has not returned to normal), the third-line agent is re-administered or a different third-line agent is started, and the patient is considered to be in super-refractory status epilepticus (SRSE) (Chapman, Smith et al. 2001; Shorvon 2011; Brophy, Bell et al. 2012). SAGE-547 is being developed as an adjunct to third-line therapy in patients in RSE who have failed standard treatment. In this protocol, the term “RSE that has failed standard treatment” is deemed to be equivalent to the term “SRSE” and the two may be used interchangeably.

#### 3.3.1. Epidemiology of SRSE

The incidence of SRSE is very poorly understood, mainly because the diagnostic codes used for SE do not generally differentiate its nature as responding or refractory to treatment. Based on the variable reporting of outcomes data, the incident cases of SRSE could represent between one and two-thirds of the RSE patients (Novy, Logroscino et al. 2010; Ferlisi and Shorvon 2012; Hocker, Britton et al. 2013; Sutter, Marsch et al. 2013). More detailed epidemiology studies are needed to better elucidate the proportion of RSE patients whose condition becomes super-refractory. A recent review of ICU discharge data in the USA suggests an annual incidence of approximately 35,000, based on patients who required at least three days in the ICU for SE [Sage data on file].

#### 3.3.2. Outcomes of SRSE

SE has varying degrees of mortality depending on the underlying etiologies. Table 4 outlines the acute mortality in patients with SE by etiology (Neligan and Shorvon 2010). The mortality rate of SRSE is estimated to be 30% to 50% using current standard of care.

The causes of death from SE (and therefore SRSE) are heterogeneous, resulting from neuronal cell death, complications of underlying medical conditions, or adverse effects of the current standard treatments. Prognosis worsens and mortality increases with longer duration of SE, i.e. with SE that develops into RSE or SRSE (Neligan and Shorvon 2010), and with longer duration of

medically-induced coma ([Ferlisi and Shorvon 2012](#)). There is an obvious unmet medical need to improve upon the current standard of care treatment regimens.

Morbidity is high and survivors have outcomes ranging from poor function to vegetative state ([Shorvon 2011](#)). Approximately one third of patients with RSE and SRSE will recover, but with chronic neurologic or other deficits ([Neligan and Shorvon 2010](#); [Hocker, Britton et al. 2013](#)). In all, it is estimated that less than 25-30% of all SRSE patients have a favorable functional outcome.

**Table 4: Approximate Mortality of Status Epilepticus in Different Etiologies**

Underlying Etiology	Associated Acute Mortality in Patients with SE (%)
Drug reduction/withdrawal, poor AED compliance, or low AED levels	0-10
Cerebrovascular Disease	20-60
Metabolic Disorders	10-35
Acute CNS Infection	0-30
Anoxia	60-100
Alcohol Abuse	0-10
Head Trauma	0-25
Drug Overdose/Toxicity	10-25
Brain Tumors	0-20
Cryptogenic/Idiopathic	5-20

### 3.3.3. Unmet Medical Need in Super-refractory Status Epilepticus

Treatment approaches for SRSE consist of diagnosis and treatment of underlying medical conditions, adding and changing anti-seizure drugs, and repeated attempts at weaning from IV anesthetic agents. Treatment of SRSE has three aims:

- to prevent excitotoxicity, which begins within 24 hours of SE onset;
- to prevent cerebral damage by initiating neuroprotective burst suppression;
- to prevent the complications of extended periods of anesthesia or unconsciousness ([Shorvon 2011](#)).

Currently, there are no therapies that have been specifically approved for RSE or SRSE. The primary drugs used to induce coma are continuously infused IV anesthetics such as propofol, midazolam, or pentobarbital/thiopental, known as third-line agents. Use of these drugs to control SRSE has only been studied in small retrospective reviews or small prospective studies without controls ([Hocker, Britton et al. 2013](#)) therefore there is no agreement on which drug is optimal nor on an optimal dosing regimen for the treatments that are used.

The most common adverse effect of the third-line agents is hemodynamic instability; in addition, they are not universally effective, with breakthrough seizures and withdrawal seizures requiring dose adjustments and changes in third-line agent(s). The drug thought to be most effective in SRSE, pentobarbital, is also associated with the most toxic adverse effect profile, comprising

decreased blood pressure and cardiorespiratory collapse (Claassen, Hirsch et al. 2002). The ability to wean patients successfully off the third-line agents as quickly as possible is therefore paramount, and an adjunct to SRSE treatment that enhances the success of the third-line agents and supports their successful weaning in a short timeframe would be an important addition to the therapeutic armamentarium. Preliminary clinical data show that SAGE-547 has been a successful adjunct to third-line therapy in this regard.

### 3.4. SAGE-547 Injection

Allopregnanolone is an endogenous, naturally occurring neuroactive steroid formed in the corpus luteum of the ovary, adrenal cortex and central nervous system (CNS) (Holzbauer, Birmingham et al. 1985; Paul and Purdy 1992; Ottander, Poromaa et al. 2005). It is a metabolite of progesterone created by the actions of 5- $\alpha$  reductase and 3- $\alpha$  hydroxy-steroid dehydrogenase. Allopregnanolone is a potent positive allosteric modulator of both synaptic and extra-synaptic GABA<sub>A</sub> receptors.

SAGE-547 Injection (allopregnanolone aqueous formulation in Captisol<sup>®</sup>) is being developed for the treatment of patients in RSE who have not responded to standard treatment. SAGE-547 Injection is a solution of 5 mg/mL allopregnanolone in Sterile Water for Injection (SWFI), USP and 250 mg/mL betadex sulfobutyl-ether sodium, NF. It is further diluted with Sterile Water for Injection, USP (SWFI) in IV bags to achieve an allopregnanolone concentration of approximately 1.67 mg/mL in an approximately isotonic solution and will be administered intravenously.

#### 3.4.1. Scientific Rationale for SAGE-547 in SRSE

Ineffective recruitment of inhibitory neurotransmission, together with excessive neuronal excitation, likely plays a role in the initiation and propagation of the electrical disturbance occurring in SE. GABA ( $\gamma$ -aminobutyric acid), the major inhibitory neurotransmitter in the central nervous system (CNS), is released from GABAergic neurons and binds to several types of GABA receptors (GABA<sub>A</sub>, GABA<sub>B</sub>, and GABA<sub>C</sub>) on target neurons. GABA<sub>A</sub> receptors are macromolecular proteins that form a chloride ion channel complex and contain specific binding sites for GABA and a number of allosteric regulators, including barbiturates, benzodiazepines, and some anesthetic agents. GABA receptor-mediated inhibition contributes significantly to the normal termination of a seizure (Kapur and Macdonald 1997). SAGE-547 is a positive allosteric modulator of the GABA<sub>A</sub> receptor.

The importance of terminating seizure activity as soon as possible is underpinned by a growing body of evidence from research and clinical observation that SE becomes more difficult to control as its duration increases. It has been postulated that this occurs due to a mechanistic shift from inadequate GABAergic inhibitory receptor-mediated transmission to excessive N-methyl-D-aspartic acid (NMDA) excitatory receptor-mediated transmission (Kapur and Macdonald 1997). As prolonged epileptiform bursting results in a reduction of GABA<sub>A</sub>-mediated synaptic inhibition, antiepileptic treatments which rely on enhancing intrasynaptic GABA<sub>A</sub> neurotransmission become less effective the longer SE continues.

Furthermore, the constitutive process of synaptic GABA<sub>A</sub> receptor internalization is accelerated by the increased neuronal activity associated with seizures. These findings suggest that the rate of GABA<sub>A</sub> receptor internalization is regulated by neuronal activity, and its acceleration contributes to the reduction of inhibitory transmission observed during prolonged seizures (Kapur and Macdonald 1997). Of note is that SAGE-547 binds to extrasynaptic as well as intrasynaptic GABA<sub>A</sub> receptors;

extrasynaptic receptors remain active with ongoing seizure activity, resulting in a putative mode of action for SAGE-547 in SRSE.

Status epilepticus induces cerebral damage that includes neuronal cell necrosis, gliosis, and network reorganization. The major cause of cell death in cerebral damage is excitotoxicity, which is initiated by glutaminergic receptor over-activation, causing calcium to flood the cell, thereby leading to apoptosis and necrosis. This process is initiated within a few hours of the start of seizure activity, and provides the medical imperative to terminate SE as quickly as possible. To prevent the consequences of the excitotoxicity cascade, it is recommended that anesthesia be initiated within 1-2 hours of onset of seizures at doses designed to induce EEG burst suppression ([Shorvon and Ferlisi 2011](#)).

### **3.4.2. SAGE-547 Clinical Program in the Treatment of SRSE**

The current SAGE-547 development program includes:

- an ongoing Phase 2 open-label trial, Study 547-SSE-201;
- this proposed Phase 3 randomized, double-blind, placebo-controlled trial, Study 547-SSE-301;
- a planned open-label, expanded access protocol, Study 547-SSE-302;
- a number of EINDs for SAGE-547 in patients with SRSE.

The designs of these studies are all similar, with a five to six day infusion of SAGE-547 (or placebo), during which time attempts are made to wean the subject off all third-line agents. In the Phase 3 studies, those subjects who cannot be weaned off third-line agents while being administered SAGE-547 (or placebo) will be eligible for a second open-label infusion of SAGE-547 at a higher dose, which is also being employed for the latter patients being enrolled in the Phase 2 study. Follow up of subjects is for 21 – 30 days after the first infusion of study medication.

### **3.4.3. Data from the SAGE-547 Development Program**

The data from 30 subjects included in the on-going clinical evaluation of SAGE-547 for the treatment of adults and children with SRSE clearly offers preliminary evidence that SAGE-547 could provide substantial and clinically significant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate. These subjects comprise 20 from the ongoing Phase 2 trial (71% success rate in 12/17 evaluable subjects) and 10 subjects who received EIND treatments (78% success rate in 7/9 evaluable subjects).

Successful therapy of SRSE has been defined as “the SE is completely controlled by the therapy, without breakthrough of withdrawal seizures, or discontinuation due to side effects or death during therapy,” ([Ferlisi and Shorvon 2012](#)). By this definition, which is in accord with the efficacy assessments used in the overall clinical evaluation of SAGE-547, 19 of the 26 (73%) subjects with SRSE who completed the SAGE-547 infusion were treatment successes. As data collection is ongoing, this information is preliminary and subject to change upon further monitoring.

Published reports on RSE and SRSE have stated mortality rate ranges from 35% to 65%. The underlying etiologies of SE in the 547-SAGE-201 study and EINDs are heterogeneous, and each one conveys a different risk of mortality and longer term morbidity. However, the death rate in subjects who have received SAGE-547, 6 out of 30 (20%) subjects, appears to be lower than the published

rates. None of the deaths were considered related to SAGE-547: brain tumor, organophosphate toxicity, respiratory failure, respiratory arrest due to ventilator support withdrawal, and breast cancer.

In the Phase 2 study, 20 SAEs (15 non-fatal) have been reported in 13 (65%) subjects, and of these 3 events in 2 subjects (10%) were considered by the investigator to be related to SAGE-547: pulmonary emboli and tracheostomy dehiscence/infection. The Sponsor did not consider these events to be related to SAGE-547, rather to the underlying disease states. Four of the 20 subjects (20%) experienced AEs considered possibly related to SAGE-547 by the investigator, namely moderate myopathy and severe pulmonary emboli in 1 subject, moderate tracheostomy dehiscence and tracheostomy infection in 1 subject, moderate thrombocytosis in 1 subject and moderate BUN, ALT and AST elevation in 1 subject.

Review of the most current safety data from 547-SAGE-201 reveals that there were changes in serum chemistry, hematology, and urinalysis during the study, but that none of those changes were assessed as related to SAGE-547. There were also no SAGE-547-related changes to vital signs.

Despite the heterogeneity in the underlying causes of SE, the ages of the subject, comorbidities, which normally complicate the treatment of SE, and the fact that all subjects had failed current standard of care treatment, a large majority of subjects had a successful therapy outcome, with discontinuation of all third-line agents and resolution of SE.

Refer to the Investigational Brochure for further information on the pre-clinical and clinical data supporting the use of SAGE-547 in SRSE.

### **3.5. Study Rationale - SAGE-547 in SRSE**

#### **3.5.1. Justification for the Control Group**

Although SAGE-547 has demonstrated extremely promising activity in subjects with SRSE, both in the Phase 2 study and during the EINDs, these have been open-label investigations with no control data for comparison. Generally in the literature there are few data describing the success rates of wean attempts of third-line agents, and few comparative data on the effectiveness of the three main third-line agents, propofol, pentobarbital/thiopental, and midazolam.

Several options for a control group in Study 547-SSE-301 were considered:

- No control group was thought to be unacceptable since there are no reliable published data on success rates in this population that could be used for broad comparisons;
- An active control was considered but found to be impractical since none of the third-line agents are approved for their use in SRSE, no standardized dosing regimens or treatment guidelines have been adopted for the management of SRSE, and clinicians were unlikely to agree which of the available third-line agents would be reserved for the active control arm;
- Historical controls were considered but abandoned because of the practical difficulties of obtaining high quality data, the lack of ability to prospectively match cases, and a suspicion that clinical practice in the standard of care of SRSE is evolving, mandating the use of prospective, concurrent control data;
- Comparison to standard of care alone was considered as a feasible design. However, in a field where no widely adopted treatment guidelines exist, there was a concern that knowledge of the treatment group (SAGE-547 plus standard of care versus standard of care



alone) would alter the behavior of the investigators such that they could be more aggressive with weaning in the SAGE-547 group;

- Placebo control is not without its challenges since the preliminary efficacy data for SAGE-547 show that the compound exerts central pharmacological effects and is associated with positive outcomes in around 70% of patients. There is therefore a potential ethical concern about administering placebo to desperately ill patients who have often exhausted all treatment options for SRSE. This concern has been addressed in two ways: firstly all patients receive current standard of care; secondly, all subjects who fail to be weaned from their third-line agents at the end of the blinded infusion of study drug will be administered open-label SAGE-547 without un-blinding their initial treatment allocation, so treatment with the investigational product is not denied, but delayed about a week in the setting of ongoing receipt of full current standard of care.

It was therefore decided that a blinded, placebo-controlled design was appropriate for Study 547-SSE-301.

### **3.5.2. Justification for the Dose Regimen**

The standard dose regimen has been studied in 19 subjects in the 547-SSE-201 Phase 2 trial; the average peak plasma concentration of SAGE-547 at the end of the loading dose was approximately 144 ng/ml. The average plasma concentration during the maintenance infusion was approximately 70 ng/ml. At these concentrations, there were no clear safety signals although two-thirds of subjects experienced an SAE and there were four deaths, all related to the underlying comorbid conditions. The standard dosing regimen was associated with an approximate 70% successful treatment outcome. For these reasons, the standard dosing regimen has been adopted for the initial SAGE-547 infusion to be compared in a blinded fashion to placebo.

In the 547-SSE-201 trial, three subjects have thus far received the higher dose regimen. This dose regimen has also been well tolerated. The average peak plasma concentrations at the end of the loading dose for both dosing regimens will be in the same range, as the loading dose is the same for both regimens. The average plasma concentrations observed during the higher maintenance dose are 102 ng/ml (n=2). The rationale for adopting the higher dose regimen as the open-label infusion of SAGE-547 for subjects who are retreated in this 547-SSE-301 trial is that those who fail on the standard SAGE-547 dose regimen are afforded the opportunity to have access to a higher dose. The justification to also administer the higher dose regimen to failures on placebo is that the regimen has thus far been well tolerated, and this methodology preserves the blind for the initial infusion.

A five-day dosing regimen with SAGE-547 was investigated in the Phase 2 study, 547-SSE-201. There were some cases when weaning off all third-line agents was not possible within 48 hours, but weaning was completed after the end of the infusion of SAGE-547. For this reason, the duration of dosing with SAGE-547 has been increased from 120 hours (five days) in Phase 2 to 144 hours (six days) in this Phase 3 study.

### **3.5.3. Rationale for Genetic Testing Sub-study**

Sage Therapeutics intends to perform genetic research in the SAGE-547 development program in order to explore how genetic variations may affect the metabolism and activity of SAGE-547. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials, and, possibly, to genetically-guided

treatment strategies for optimizing decision making with respect to individual benefit:risk. Participation of subjects in genetic research as part of the overall clinical study is optional.

### **3.6. Benefit-Risk Evaluation of the Present Study**

Previous reports of human administration of exogenous allopregnanolone indicate that for exposures in men and women up to 150 nM, the most commonly reported AEs were sedation (recorded as sleepiness or tiredness), feelings of intoxication (like alcohol), flushing, and mild headache (Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007). No SAEs were reported (Navarro, Kaddouz et al. 2003; Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007; Kask, Backstrom et al. 2008; Kask, Backstrom et al. 2009; Timby, Hedstrom et al. 2011a). In view of the reduced consciousness and sedation of study subjects at entry into this protocol, none of these previously-reported events are likely to impact subjects in this study.

To date, in the SAGE-547 Phase 2 study and the EIND subjects, a majority of subjects demonstrated a successful therapy outcome (>70%). The majority in the clinical trial (65%) have also experienced SAEs, but none has been considered related to SAGE-547 by the Sponsor (SAEs in 2 subjects (10%) were considered possibly related by Investigator). Five deaths have been reported in 30 subjects (20%), all related to the underlying cause of SRSE and not related to SAGE-547 – this is in the context of published mortality rates between 35% and 65%. These preliminary data suggest that SAGE-547 has the potential to provide clinically relevant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate.

The underlying etiologies of SE are heterogeneous, and each one conveys a different risk of mortality. Subjects who survive SRSE still have a high risk of severe morbidity (Neligan and Shorvon 2010). The subjects treated with SAGE-547 in Study 547-SSE-201, are heterogeneous in factors such as age and etiology of SE, factors that usually complicate treatment and can increase morbidity and mortality. Even with this heterogeneity, the preliminary efficacy and safety data for SAGE-547 are very encouraging, and the mortality rate suggests that the risk to benefit assessment of this treatment rests on the side of benefit.

## **4. ETHICS**

### **4.1. Institutional Review Board or Independent Ethics Committee**

This protocol will be reviewed and approved by the Institutional Review Board (IRB) where the study is conducted. The IRB will meet all FDA requirements governing IRBs (CFR, Title 21, Part 56).

### **4.2. Ethical Conduct of the Study**

The Sponsor, the Medical Monitor, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable ICH and GCP guidelines, and must also conduct the study in accordance with local regulations.

### **4.3. Subject Information and Informed Consent**

Subjects prospectively enrolled in this study will be unable to give consent. Therefore, consent will be given by proxy by a legally authorized representative (LAR). Written informed consent is required for each subject prior to any testing under this protocol not considered standard of care,



including screening tests and evaluations. Should a subject gain the ability to sufficiently comprehend the situation and consent during the course of the study, written informed consent or verbal assent will be documented as required or recommended by the institution's IRB.

The form of consent to be obtained will depend on the condition of the subject as determined by the Principal Investigator. The informed consent form (ICF), as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50.

It is the responsibility of the Investigator to obtain consent and to provide the subject's LAR with a copy of the signed and dated informed consent form. The informed consent form for subject participation must also be available as part of the subject file for review by the site's dedicated study monitor or any authorized auditor of the Sponsor or regulatory authorities.

All ICFs used in this study must be approved by the appropriate IRB and by the Sponsor. The ICF must not be altered without the prior agreement of the relevant IRB and the Sponsor.

#### **4.4. Ethical and Regulatory Considerations for Pharmacogenetic Sub-study**

##### **4.4.1. Informed Consent for Pharmacogenetics**

The genetic component of this study is optional and subjects may participate in other components of the main study without having to agree to participate in the genetic component. If subject chooses to participate in the genetic component of the study, the subject or LAR must sign and date a specific consent form for the genetic component of the study in addition to the main study consent form. The principal investigator(s) is responsible for ensuring that consent is freely given and that the subject understands that they may discontinue from the genetic aspect of the study independent of their decision to remain within or withdrawal from the main study.

##### **4.4.2. Subject Data Protection Relative to Pharmacogenomics**

Sage Therapeutics will not provide individual genotype results to subjects, their family members, their general physician, their employer or any insurance company unless required to do so by law. While extra precautions will be taken to preserve confidentiality and to prevent genetic data from being linked to an individual's identity outside of a restricted access site, in certain exceptional situations (e.g. in case of a medical emergency or as a consequence of a specific regulatory need), certain individuals may see both genetic data and the personal identifiers of a subject; however in all cases a subject's medical information and genetic files will remain physically separated.

## **5. STUDY OBJECTIVES**

### **5.1. Primary Objective**

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult and pediatric subjects with SRSE, and for the response to endure at least 24 hours after cessation of the SAGE-547 or placebo infusion (primary response).

## 5.2. Secondary Objectives

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in Clinical Global Impression Scale between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

## 5.3. Safety Objectives

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

## 5.4. Other Objectives

1. To evaluate the impact of retreatment with a higher dose of SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol<sup>®</sup> and identified SAGE-547 metabolite plasma concentrations;
3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;

6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS) (age  $\geq 17$  years).

## **6. ENDPOINTS**

### **6.1. Primary Endpoint**

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### **6.2. Secondary Endpoints**

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) and to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### **6.3. Safety Endpoints**

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.

## 6.4. Other Endpoints

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who fail to respond to their randomized double blind treatment and are retreated with a higher dose of SAGE-547;
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS) (age  $\geq 17$  years).

## 7. INVESTIGATIONAL PLAN

### 7.1. Overview of Study Design

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE. Pediatric patients (those < 14 years of age) will be managed in a pediatric intensive care setting.

Figure 1 provides an overview of the study design and Figure 2 gives the details of treatment and follow-up on the active treatment arm. Patients will follow one of three paths to entry to the study. The first path is for patients who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst suppression with a third-line agent. These patients will be consented for the study after admission to the intensive care unit, but before any third-line agents are administered for burst suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their LAR. Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours. Once burst suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see Table 3). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The second path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst suppression pattern on the EEG. These patients may have had one or more previous unsuccessful weans and may be on more than one third-line agent.

Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The third path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These patients may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within six hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third line agent wean attempts prior to randomization (one vs two or more).

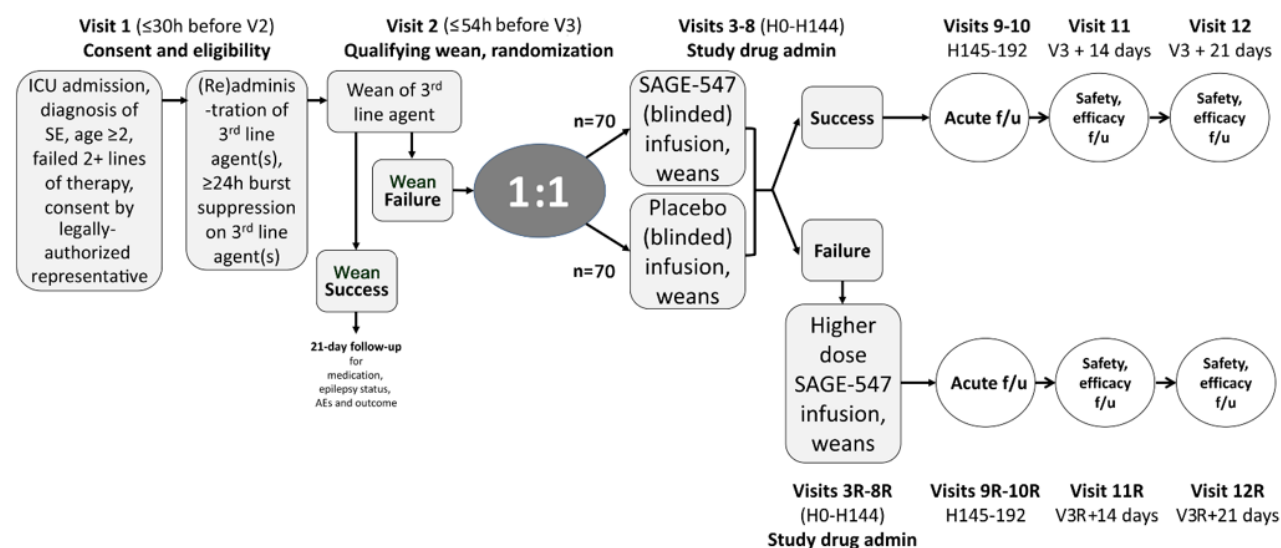
The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as the ability to wean the subject off all third-line agents before the end of the first infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication. Subjects must also have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) at the end of the primary endpoint assessment period as determined by EEG in order to be deemed a success. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#), [Table 2](#) and [Table 3](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. Eligibility for retreatment must be confirmed in writing by the medical monitor prior to the open-label infusion starting. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo will all subsequently be eligible to be administered SAGE-547 at the higher dose.

**Figure 1: Study Design**



## 7.2. Trial Conduct

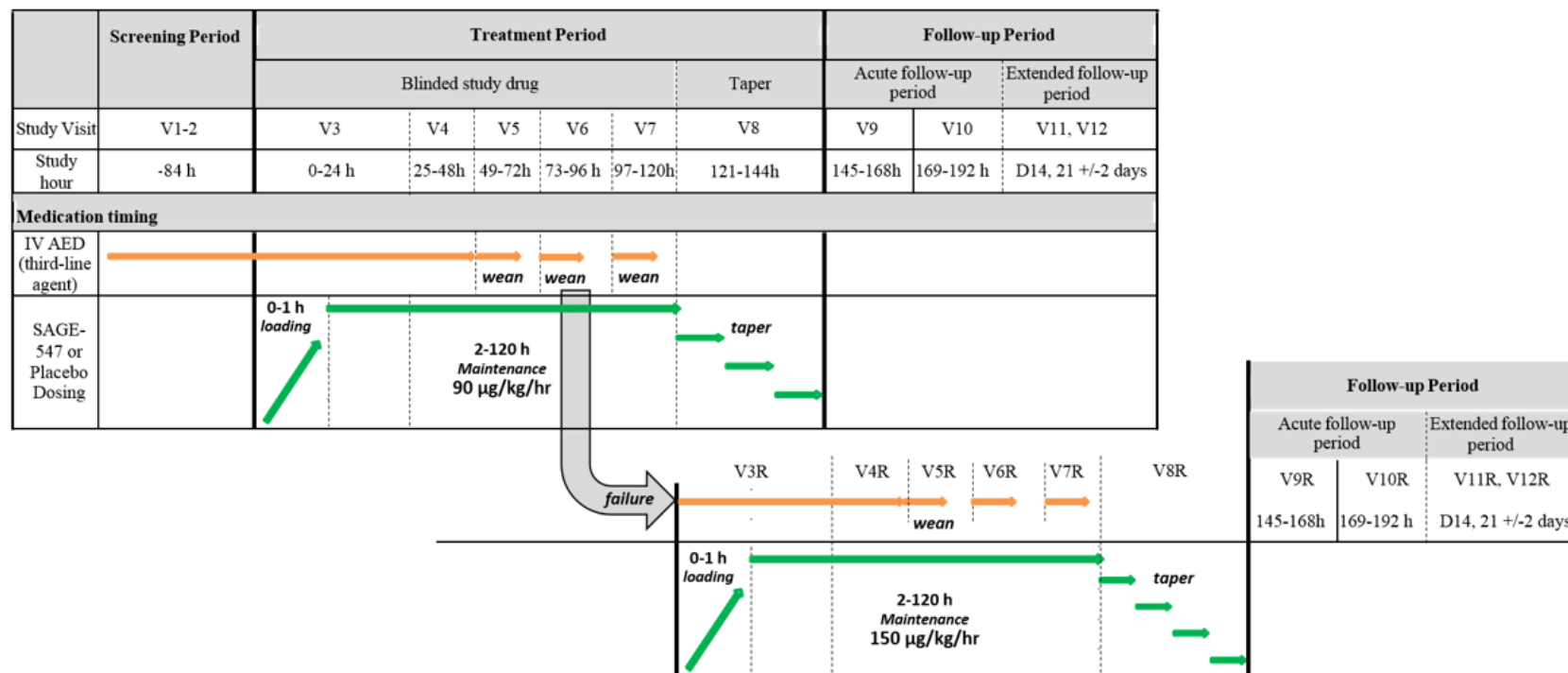
This study will be conducted according to the principles of the World Medical Association Declaration of Helsinki and most recent amendment, and in compliance with the protocol approved by the IRBs/Independent Ethics Committees (IECs), and in accordance with ICH Guidelines on GCP standards.

## 7.3. Blinding and Randomization

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo). Details of the dynamic randomization process will be included in the SAP.

The randomized portion of the study will be blinded, with the two treatment products (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

The second infusion of SAGE-547 will be administered on an open label basis to subjects who failed the primary endpoint wean.

**Figure 2: Details of Treatment Administration and Follow-up**

## 8. SELECTION AND WITHDRAWAL OF SUBJECTS

The study will randomize 140 patients at up to 180 sites. All subjects deemed eligible to enroll must have written Medical Monitor approval on a case-by-case basis prior to undertaking the qualifying wean.

### 8.1. Inclusion Criteria

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects two (2) years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; *or* who have previously failed one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst suppression pattern; *or* who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst suppression pattern.

### 8.2. Exclusion Criteria

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy.
4. Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing underlying neurological disorder.
5. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis but for whatever reason, dialysis is not planned or non-continuous dialysis planned (that would not adequately remove Captisol®);
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the experience of the investigator, is less than 30 days;
  - e. a do not resuscitate (DNR) order.



6. Subjects who are being administered more than three third-line agents concomitantly or for whom the qualifying wean cannot be completed within 24 hours or who are being administered a third-line agent for indications such as raised intra-cranial pressure that would preclude weaning according to this protocol.
7. Subjects with a living will that does not allow heroic measure.
8. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
9. Subjects who have been enrolled in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not withdraw or complete and then re-enroll).

### **8.3. Selection and Consent of Subjects for Pharmacogenetic Substudy**

All subjects will be asked to participate in pharmacogenetic research; however, participation in research is voluntary and a subject can decide to decline his/her participation without penalty or loss of benefit. Participation or lack thereof will not be a cause for exclusion from any aspect of the main study. In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **8.4. Subject Withdrawal / Study Termination**

#### **8.4.1. Withdrawal/Discontinuation of Individual Subjects**

The reasons for study drug discontinuation and/or subject withdrawal from the study must be recorded in the subject's electronic case report form (eCRF). The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject has been discontinued/withdrawn due to an AE.

##### **8.4.1.1. Withdrawal from the Study**

Subjects or their LAR may withdraw subjects from the study at any time for any reason without compromising the subject's medical care. The Investigator will also withdraw subjects upon the request of Sage Therapeutics or upon termination of the study.

Subjects who withdraw from the study prior to Visit 10 (or 10R) should complete the procedures scheduled for the day of study drug taper (hour 121-144; Visit8/8R) on the day of their withdrawal, including the SAGE-547 taper schedule, with the addition of the mortality assessment from Visit 12/12R. Subjects who withdraw from the study after Visit 10/10R should undergo study procedures as outlined for Visit 12/12R on the day of their withdrawal. In all cases, the reason for subject withdrawal will be recorded in the eCRF.

Withdrawal of subjects for any reason should be discussed with the Medical Monitor.

##### **8.4.1.2. Discontinuation of Study Drug**

If it is necessary to discontinue the study drug earlier than planned, subjects should continue to be followed per protocol to capture safety and efficacy assessments for the duration of the study period.

The investigator may withdraw the subject from the study drug for the following reasons:

- Upon subject's or LAR's request
- The subject or LAR is unwilling or unable to adhere to the protocol-specified visits
- The subject experiences an intolerable adverse event
- During the course of the study, the subject develops symptoms or conditions listed in the exclusion criteria.
- Other medical reason, at the discretion of the Investigator and/or the Medical Monitor

Subjects who discontinue the study due to an AE considered related to study drug should be followed until the event is resolved, considered stable, or the Investigator determines the event is no longer clinically significant. Study drug discontinuation due to AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

#### **8.4.2. Study Termination**

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of AEs or other findings suggesting unacceptable risk to subjects, administrative or operational reasons. In the event of study termination, Sage Therapeutics will provide written notification to the Investigator. Investigational sites must promptly notify their IRB and initiate withdrawal procedures for participating subjects.

## **9. INVESTIGATIONAL PRODUCT**

### **9.1. Identity of Investigational Product**

SAGE-547 Injection (allopregnanolone)

### **9.2. Clinical Supplies**

#### **9.2.1. SAGE-547**

Adequate supplies of SAGE-547 Injection and materials for intravenous administration will be provided to each site.

SAGE-547 Injection is a clear, colorless sterile solution of allopregnanolone intended for intravenous injection. SAGE-547 Injection is an aqueous solution of 5 mg/mL allopregnanolone in 250 mg/mL Captisol® (betadex sulfobutyl-ether sodium, NF). It is presented either un-buffered or buffered with 10 mM citrate at a pH of 6.0 in either 20 mL or 50 mL vials. SAGE-547 is further diluted according to the Pharmacy Manual to achieve an approximately isotonic solution and will be administered intravenously.

No preservatives are included in the drug product, which is intended to be used as a single-use vial. All inactive components (excipients) used in the formulation are compendial grade and conform to current USP/EP, and include sodium citrate, citric acid and betadex sulfobutyl-ether sodium (Captisol®).

### **9.2.2. Placebo**

Placebo will be identical to SAGE-547 and presented in identical vials. Placebo will be manufactured in a similar way to SAGE-547 and comprises all excipients but no SAGE-547.

### **9.2.3. Blinding**

The vials of SAGE-547 and placebo will be identical in every way so that they are indistinguishable by the pharmacist, investigator, anyone treating or managing the patient, the monitors, and the sponsor. In this way the first infusion of study drug administered to each patient will be double-blind.

For the blinded study drug infusions, subject-specific dosing kits will be provided. These dosing kits will be pre-labelled with kit number for the first blinded infusion. For the second-infusion, open-label kits will be provided, which will require subject assignment by the pharmacy for reconciliation purposes. The study kits must be stored under refrigerated conditions (2-8 °C). IV administration bags and lines may be provided for the blinded and open-label infusions. Refer to the Pharmacy Manual for additional details.

The label for the SAGE-547 Injection vials will include standard product identification information according to the Code of Federal Regulations, 21CFR 312.6. All study labels will also contain the following statement:

Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use.

## **9.3. Preparation of SAGE-547 or Placebo Injection for Dosing**

The Pharmacy will be responsible for preparing the blinded and open-label study drug for subject dosing. The prepared admixture will be assigned a room temperature (20-25 °C) storage shelf life of 30 hours from time of compounding.

SAGE-547, which is hypertonic, will require dilution with SWFI to achieve an approximately isotonic solution according to the instructions provided in the Pharmacy Manual. Exactly the same procedures will be used to prepare the placebo admixture, so that all site staff remain blinded as to treatment allocation for the first infusion of study drug. SAGE-547 Injection is not intended to be administered to patients undiluted.

Refer to the Pharmacy Manual for specific instructions regarding infusion preparation.

## **9.4. Administration and Accountability**

The Pharmacy will maintain accurate records of all investigational product supplies. Accurate records will be kept regarding the volume of SAGE-547 Injection or placebo used for each IV preparation, as well as the required infusion rate or rates, and the date and time of preparation. Reasons for departure from the expected dosing regimen must also be recorded. To satisfy regulatory requirements regarding drug accountability, all study medication will be reconciled in full. Refer to the Pharmacy Manual for additional details.

## 10. TREATMENT OF SUBJECTS

### 10.1. Dosing Schedule (Blinded Infusions)

SAGE-547 Injection or placebo will be administered according to the dosing schedules in Table 5. The infusion rates to accomplish these  $\mu\text{g/kg/h}$  doses will be calculated according to the weight of the subject. The infusion rates will be applied to blinded study drug for the first infusion of study medication.

**Table 5: SAGE-547 or Placebo Dosing Schedule**

Hour	Type and Duration of Study Drug Infusion	Description
H1	One hour loading Infusion	300 $\mu\text{g/kg/h}$
H2 – H120	119 hour maintenance infusion	90 $\mu\text{g/kg/h}$
H121 – H128	8 hour taper	65 $\mu\text{g/kg/h}$
H129 – H136	8 hour taper	45 $\mu\text{g/kg/h}$
H137 – H144	8 hour taper	25 $\mu\text{g/kg/h}$

### 10.2. Dosing Schedule (Open-Label Infusions)

If a subject fails wean from third-line agent(s) or requires re-instatement of third-line therapy within 24 hours of discontinuing the initial infusion of study drug, SAGE-547 Injection will be re-administered according to the dosing schedule in Table 6. The infusion rates to accomplish these  $\mu\text{g/kg/h}$  doses will be calculated according to the weight of the subject. These infusion rates will be applied to SAGE-547 re-treatment for the open-label second infusions of study medication.

**Table 6: SAGE-547 Open Label Dosing Schedule**

Hour	Type and Duration of SAGE-547 Infusion	Description
H1	One hour loading Infusion	300 $\mu\text{g/kg/h}$
H2 – H120	119 hour maintenance infusion	150 $\mu\text{g/kg/h}$
H121 – H126	6 hour taper	125 $\mu\text{g/kg/h}$
H127 – H132	6 hour taper	95 $\mu\text{g/kg/h}$
H133 – H138	6 hour taper	65 $\mu\text{g/kg/h}$
H139 – H144	6 hour taper	35 $\mu\text{g/kg/h}$

### 10.3. Route of Administration

SAGE-547 Injection is intended for IV administration only. The compatibility of SAGE-547 with other drugs is unknown, and the product should be administered via a dedicated peripheral IV line using any Sage-supplied study-specific IV administration bags and lines. In order to preserve blinding, these instructions also apply to the blinded placebo infusions.

### 10.4. Treatment Period

The treatment period with double-blind SAGE-547 or placebo is six 24-hour periods (144 hours), which may encompass 6-7 calendar days. The retreatment period is of identical duration.

## **10.5. Concomitant Medications, Procedures and Treatments**

Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. All concomitant medications, procedures, and treatments should be documented throughout the study from Screening through Visit 12/12R and recorded on the eCRF.

SAGE-547 has demonstrated inhibitory effects on cytochrome P450 isoenzyme 2C9 (CYP2C9). Therefore, AEDs such as phenytoin and phenobarbital that are primarily metabolized by CYP2C9 should be closely monitored during SAGE-547 administration to ensure target exposures are maintained.

### **10.5.1. Concomitant AEDs**

Subjects may enter the study on AEDs, and be administered AEDs during the study. All of these must be recorded on the eCRF with details including date and time of starting and stopping each AED, the route of administration, changes in doses, and frequency of administration. In addition, details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the eCRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.

### **10.5.2. Concomitant Third-Line Agents**

All third-line agents (as defined in [Section 8](#)) administered since the diagnosis of SE will be recorded on the eCRF, whatever path the patient took for entry into the study. Details will include the name of the drug, the start and stop dates and times, and, after consent, the doses with start and stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

In addition, those changes in dose that constitute a wean attempt will be marked as such on the eCRF. In this way the start and stop dates and times of all wean attempts (see [Section 11](#) for definitions) will be recorded, as will the type of wean (QW, OW, or TW) and the outcome of the wean attempt (successful, failed and dose of this third-line agent increased or failed and this third-line agent stopped and another third-line agent started). Those wean attempts that occur after the TW up to and including Visit 12/12R will be marked “AW”.

Some third-line agents (such as propofol) are also used to induce sedation to facilitate a subject’s ability to tolerate the ventilator. For subjects requiring such sedation, propofol is the preferred agent unless there are contraindications. The eCRF will make clear from the indication for the third-line agent when it is being used for burst or seizure suppression and when it is being used as ventilator support or for another purpose. The investigator will add a note to the eCRF to justify that the doses used are appropriate for sedation and not for seizure or burst suppression. The doses used for ventilator support and other similar uses are usually much lower than those used for seizure or burst suppression, and use of these third-line agents for these other purposes does not constitute a wean failure under this protocol.

### **10.5.3. Concomitant Pressors**

The start and stop dates and times of all pressors will be recorded as well as the start and stop dates and times of all dose changes.

#### **10.5.4. Other Concomitant Medications**

All other concomitant medications must be recorded on the eCRF with details including date and time of starting and stopping, the route of administration, dose, and frequency of administration.

### **11. STUDY ASSESSMENTS**

#### **11.1. Efficacy Assessments**

##### **11.1.1. Primary Efficacy**

Success or failure will be determined, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo infusion and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the blinded (first) infusion of SAGE-547 or placebo. In addition, subjects must have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) to be deemed to be successes. All subjects who fail to complete their infusion of randomized treatment or do not have at least one attempt during study treatment to wean off all third-line agents will be considered as “failures” for the primary endpoint.

##### **11.1.1.1. Weaning**

Third-line agents are anesthetic agents that are administered in order to reach a seizure or burst suppression EEG pattern. For the purposes of this study, third-line agents are defined as continuous intravenous infusions of pentobarbital/thiopental, midazolam, propofol, and ketamine at maintenance doses alone or in combination sufficient to produce a burst suppression pattern on the EEG. The following are considered to be minimum maintenance doses of these agents that may be expected alone or in combination to achieve EEG burst suppression. If subjects are on lower doses than these and are not in EEG burst suppression for the 24 hours prior to the QW or the first 12 hours of the blinded study drug infusion, they will be considered to be screen failures/protocol violators and will exit the study.

- Pentobarbital: 1 mg/kg/hour
- Thiopental: 3 mg/kg/hour
- Midazolam: 0.1 mg/kg/hour
- Propofol: 3 mg/kg/hour
- Ketamine 1.2 mg/kg/hour

The timing and nature of the third-line agent weans will be guided by the Clinical Standardization Guidelines for the study, and the clinical judgment of the investigator, and will always be primarily done in the best medical interests of the subject. Advice about weaning may be sought from the Clinical Standardization Team, a group of fellow investigators with experience of performing clinical trials in subjects with SRSE. The Clinical Standardization Team will be able to discuss EEGs related to key study timepoints (qualifying wean, terminal wean, and the period after the end of the blinded study drug infusion if the terminal wean was successful) in a timely manner in order to provide advice about compliance with the Clinical Standardization Guidelines.

The following guidance for weaning applies to all weans of third-line agents undertaken during the study. These weans include the qualifying wean (QW); the terminal wean (TW), which is the wean of the third-line agent if the subject is on only one third-line agent or the wean of the last third-line agent if the subject is on more than one third-line agent; the other weans (OW), which are the weans of the third-line agents other than the TW if the subject is on more than one third-line agent. The guidance also applies to additional weans (AW), which are the weans from third line agents that take place after the TW for the first blinded study drug infusion or the second open-label study drug infusion.

### **QW Guidance**

- Wean to be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace that third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Investigators should allow 24 hours to lapse after the end of a “successful” qualifying wean before finally declaring the QW a success. If a third-line agent needs to be re-instituted within that 24 hours, the QW is a failure, and the subject may then be randomized in the study.

### **OW Guidance**

- First OW should not begin before H49 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- If the subject is on two third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the TW. However the OW may be completed over a shorter or longer time period and may overlap if clinically indicated with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- If the subject is on three third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the wean of the second agent. The second agent should be weaned over 24 hours and that wean completed before starting the TW. However the OWs may be completed over a shorter or longer time period and may overlap if clinically indicated with each other and with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- All OWs should be completed before H96 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

## **TW Guidance**

- The TW is defined as the wean of the last third-line agent.
- If the subject is on one third-line agent, the TW should not begin before H49 and should begin no later than H97 after starting administration of study drug or starting the open-label infusion of SAGE-547. If the subject has had one or more OWs, the TW should ideally begin as soon as the last OW is complete but in any case not later than H97 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- The TW must be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace this third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Every effort must be made to complete the TW before H120 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547, but the TW must be complete before H144 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

## **AW Guidance**

- AWs will take place when medically indicated in the opinion of the investigator.
- Ideally the AW should take place over 24 hours, but completion may be over a shorter or longer time period than this. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.

### **11.1.1.2. EEG**

Electroencephalographs (EEGs) that are representative of the intermittent or continuous EEG being used to support key investigator decisions will be collected at the following time points:

- A 24-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst suppression for the second path to eligibility, and a variable pattern for the third path to eligibility. This EEG will capture as much as possible of the burst suppression pattern that precedes the QW.
- EEG will be performed to cover the qualifying wean (QWEEG). EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for up to 24 hours after the end of the QW. The duration of the QWEEG will be up to 48.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s), the decision to re-institute a third-line agent(s) at doses intended to induce burst suppression, and the decision that the QW is a success.



- EEG will be performed from three hours prior to the start of the blinded infusion to 12 hours after the start of the blinded infusion. This will be called the BIEEG. The intent of this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG and to assess the depth of burst suppression in the first 12 hours of blinded study drug infusion.
- EEG will be performed to cover the final or terminal wean of third-line agent (TWEEN). The TW is the wean of the final third-line agent during the blinded administration of study drug or the open-label infusion of SAGE-547; if the subject was on one third-line agent, the TW is the wean of that agent. If the subject was on three third-line agents, the TW is the wean of the third and final agent. EEG recording will start 30 minutes prior to the start of the TW, continue for up to 24 hours during the TW, and then continue for the one hour after the end of the TW. The duration of the TWEEN will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the final third-line agent or the decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity could not be managed using intermittent bolus doses of AEDs.
- EEG will be performed during the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 (TAEEG). The TAEEG is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the start of the taper (at Hour 119.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours during the taper, and then continue for the one hour after the end of the taper (to Hour 145 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547). The duration of the TAEEG will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity seen during the taper could not be managed using intermittent bolus doses of AEDs.
- EEG will be obtained to cover the end of the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 and the ensuing 24-hour period, during which the primary endpoint is assessed (PAEEG). The PAEEG is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the end of taper (at Hour 143.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours after the end of the blinded administration of study treatment or the open-label infusion of SAGE-547, and then continue for the one hour after the end of the 24-hour assessment period (to Hour 169 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547). The duration of the PAEEG will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity seen in the 24 hours following the end of the blinded administration of study treatment or the open-label infusion of SAGE-547 that could not be managed using intermittent bolus doses of AEDs.

In practice, most subjects are on continuous EEG monitoring or long periods of intermittent EEG monitoring. However, this protocol does not mandate continuous EEG monitoring and breaks from EEG monitoring to provide relief to the scalp from the irritating effects of the electrodes are advised,

particularly in children, according to local practice. If a break in EEG monitoring is mandated by local practice guidelines at a time when one of the protocolled EEG segments is to be collected, the break in EEG monitoring will take precedence, with the reason for missing the EEG reading noted on the eCRF. The EEGs obtained for the study are therefore part of the existing EEG record rather than being obtained de-novo at each timepoint. For timepoints where there might be some ambiguity, such as the TWEEG, the final EEG record is that of the final attempt to wean the last third-line agent, even if earlier attempts to wean that agent took place. In some cases (the TAEEG and PAEEG, for instance), the EEG records will overlap, but different cuts are taken to service the different EEG record requirements.

The electronic EEG file will be de-identified, the date and time of the start and stop of the EEG and the subject number will be attached to the file, and the study time point will be indicated (CEEG, QWEEG, BIEEG, TWEEG, TAEEG, and PAEEG). The PI will indicate on the eCRF what the EEG shows, as follows:

- For the CEEG, the PI will describe the EEG pattern that determined which path to eligibility the subject was on.
- For the QWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure or success on the qualifying wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the qualifying wean constitutes a failure); the QWEEG will extend to cover the 24 hours after the end of third line agents in order to confirm that the QW was a success.
- For the BIEEG, the PI will note the date and time of the start of the EEG and the pattern seen on the EEG.
- For the TWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure on the terminal wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the terminal wean).
- For the TAEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst suppression before the end of the SAGE-547 infusion).
- For the PAEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst suppression in the 24 hours following the end of the SAGE-547 infusion).

A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm the depth of burst suppression prior to the QW and during the first 12 hours of the blinded study drug infusion, the PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period (average EEG power at the end of Visit 9 of more than two microvolts):

- All subjects will have the CEEG and QWEEG collected and stored, and the CEEG and QWEEG read;
- Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;
- Those subjects randomized who are not retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the BIEEG, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read;
- Those subjects randomized who are retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion and the TWEEG, TAEED, and PAEEG related to the open-label study drug infusion collected and stored, and the BIEEG, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read.

All EEG records may be subject to quantitative EEG analysis.

### **11.1.2. Secondary Efficacy**

#### **11.1.2.1. Clinical Global Impression Scale (CGI)**

The clinical global impression scales are often utilized in clinical trials to allow clinicians to integrate several sources of information into a single rating of the subject's condition. Both the CGI-Severity (Question 1, CGI-S) and the CGI-Improvement (Question 2, CGI-I) employ a 7-point Likert scale measuring severity of the disease state in the subject and improvement, respectively. All severity assessments after initiation of SAGE-547 treatment should consider the general state of the subject over the preceding week. The third question on the scale will not be employed in this trial, and where the scale states "mental illness", this means "physical illness" in this trial.

The CGI-S will be evaluated at Visit 1 and at the last visit, Visit 12 or 12R. The CGI-I will be evaluated at Visit 12 or 12R.

#### **11.1.2.2. Epilepsy Status**

At Visit 1, the diagnosis of epilepsy will be documented as a no/yes question. If there was a previous diagnosis of epilepsy, further details will be documented, including:

- Date of diagnosis;
- Details of anti-epileptic drugs currently being taken;
- Type of epilepsy;
- Seizure frequency in the past month.

Information about the current (index) episode of status epilepticus will be obtained at Visit 1:

- Date of onset
- Date of failure to respond to first line agent(s) and the name(s) of the agent(s)
- Date of failure to respond to second line agent(s) and the name(s) of the agent(s)
- Any previous treatment with third line agents and the response to those agents (details of the third line agent drugs and previous wean attempts will be recorded on the Third Line Agent Medication CRF)

- The cause of the index episode of status epilepticus
- If the subject was transferred from another hospital or from within the hospital, the reason for the transfer will be recorded (such as for study enrollment, due to lack of medical options at original hospital or unit, due to lack of beds at the original hospital or unit, family request, other)

Previous (non-index) diagnosis of status epilepticus will be documented as a no/yes question. If SE did occur in the past, further information will be gathered, including:

- SE, RSE, or SRSE diagnosis, whichever was the most severe diagnosis for each episode;
- Cause;
- Treatment, including experimental treatments and need for intubation/ventilation;
- Dates of onset and duration if the episode of status epilepticus occurred in the past 12 months.

At Visit 12 or Visit 12R, the following information will be gathered:

- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of SE up to and including Visit 12 or Visit 12R;
- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of seizures (convulsive and non-convulsive) up to and including Visit 12 or Visit 12R;
- Number of separate episodes of SE after H144 at the end of Visit 8 or Visit 8R (no/yes); if yes,
  - SE, RSE, or SRSE diagnosis;
  - Cause;
  - Treatment, including experimental treatments and need for intubation/ventilation;
  - Dates of onset and duration.

Note that a separate episode of SE is defined as an episode of SE separated from other periods of status epilepticus by at least 24 hours.

- Diagnosis of epilepsy since Visit 11 or Visit 11R will be documented as a no/yes question. If a diagnosis of epilepsy has been made, further details will be documented, including:
  - Status as ongoing or new epilepsy since Visit 11 or Visit 11R after initiation of SAGE-547 treatment;
  - Details of anti-epileptic drugs currently being taken;
  - Type of epilepsy and seizure frequency in the past week.

## 11.2. Safety Assessments

The safety and tolerability of SAGE-547 will be assessed using adverse events, clinical laboratory measures, vital signs, ECG intervals and morphology, and mortality. All safety assessments should be performed per hospital standard of care and will be collected periodically throughout the study according to [Table 1](#), [Table 2](#), and [Table 3](#) (Schedules of Assessments).

### 11.2.1. Adverse Events

AEs will be collected after informed consent has been signed and prior to study-specific screening procedures not considered standard of care, during subject preparation for SAGE-547 administration and through Visit 12 or Visit 12R. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™) coding system (current version). See [Section 14](#) for additional details.

### 11.2.2. Clinical Laboratory Tests

Blood samples will be taken for hematology, and serum chemistry and GFR will be calculated at:

- Visit 1 and then at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.
- Blood samples will be taken at Visit 11 or Visit 11R for serum chemistry (renal panel only).

Urine samples (20 ml) will be taken for urinalysis and urine NAG analysis at:

- Visit 1 and at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.

For adults and children  $\geq 30$  kg, these samples will be analyzed at a central laboratory; hour-to-hour medical decisions will be based on sampling for laboratory testing done outside the protocol as part of normal standard of care. GFR will be calculated by the central laboratory. For children under 30 kg, results of local laboratory testing undertaken at the protocolled timepoints may be sent to the central laboratory for inclusion in the central study laboratory database; this obviates the need for additional blood sampling for central laboratory testing.

Any out-of-range values will be flagged by the laboratory; the investigator will add a comment about whether the abnormality is clinically significant. Clinical significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

#### 11.2.2.1. Hematology and Serum Chemistry

Hematology will include complete blood count (CBC) white blood cell count with differential, platelet count and red blood cell (RBC) count, hemoglobin and hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose. In addition triglycerides will be measured in serum chemistry samples (to aid assessment of lipemia in pharmacokinetic samples).

#### 11.2.2.2. Pregnancy Test

Females of child-bearing potential will be tested for pregnancy by serum pregnancy test at Visit 1. In this study, since an accurate history of menstruation in girls and menopause in older women may not be available at Visit 1, “child-bearing potential” is taken to mean any female aged 10 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had

a hysterectomy. Female subjects with a positive pregnancy test will be ineligible for study participation.

#### **11.2.2.3. Urinalysis**

Urinalysis will include assessment of protein, blood, leukocytes, glucose, ketones, urobilinogen, pH, and specific gravity.

#### **11.2.3. Vital Signs**

Blood pressure, heart rate, and temperature will be recorded at the following time points relative to the first infusion of study drug, and to the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547:

- Visit 1;
- At 0, +30, +60 minutes (+/-15 minutes) and +2, +4 and +8 hours (+/- 30 minutes) after the start of the infusion;
- At +24, +48, +72, +96, +120, +144, +168, and +192 hours (+/- 2 hours) after the start of the infusion.

#### **11.2.4. Weight and Height**

Weight and height will be measured at Visit 1 and weight will also be measured once during each 24 hour period of the first infusion of study drug, and of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547. These daily weights will be used to modify the dose of SAGE-547 if required. If it is not possible to weigh the subject daily, an actual weight must be obtained prior to starting the blinded study drug, and that weight used to calculate the dose of study drug to be administered. If this is not possible, permission from the Monitor must be obtained to use another method to obtain the subject's weight (such as information from the LAR or estimating using an established local protocol).

#### **11.2.5. ECG**

12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours; at other times the allowed time window for ECGs is +/- 2 hours:

- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +128, +136, +144, +152, +160, and +192 hours after the start of the blinded (first) study drug infusion
- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +126, +132, +138, +144, +152, +160, and +192 hours after the start of the open-label (second) study drug

The heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm.

#### **11.2.6. Mortality**

Mortality will be recorded on the Visit 12 or Visit 12R case report form. If the subject has died, the following information will be collected:

- Date of death;

- Cause of death.

As accurate as possible cause of death will be collected, which will be further categorized as due to one of the following causes:

- SE;
- complications of long term intubation and third-line agent infusions;
- underlying cause of qualifying SE;
- co-morbidity existing at the time of the qualifying SE;
- new co-morbidity or trauma;
- study drug;
- other (specify).

#### **11.2.7. Pharmacogenetic Samples**

If a subject's LAR consents to pharmacogenetic sampling, a blood sample for genetic research will be collected at Visit 1 in order to avoid the possible introduction of bias through the exclusion of patients who may withdraw from study due to an AE (a subject population that may be of specific interest for subsequent genetic analysis). If for any reason a sample cannot be taken prior to treatment, a sample can be drawn at any point prior to completion with the restriction that no more than one genetic sample be taken per subject.

The objective of this research is to collect and store blood samples for possible DNA extraction and exploratory research into how genes or specific genetic variation may influence response (i.e. distribution, safety, tolerability, and efficacy) to SAGE-547. Specific genetic variations of interest include but are not limited to: classes of metabolizing enzymes (e.g. Cytochrome P450 supra-family genes), genes encoding enzymes involved in the production and metabolism of allopregnanolone (e.g. AKR1C4 (3 $\alpha$ -hydroxysteroid dehydrogenase)), genes associated with the GABA receptor (e.g. GABRA1-A6, GABRB1-B3, GABRD, GABRE, GABRG1-3) and genes associated with the production and degradation of GABA.

Future research may suggest other genes or gene categories as candidates for influencing not only response to SAGE-547 but also susceptibility to disorders for which SAGE-547 is being evaluated. Thus, the genetic research may involve study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.

##### **11.2.7.1. Biological Sampling and Coding Procedures (Pharmacogenetics)**

To ensure patient confidentiality, utmost care will be taken in the coding and storage of pharmacogenetic samples.

*Extraction and coding:* DNA will be extracted from the blood sample and the DNA sample will be assigned a unique number replacing information from sampling tube. The assigned DNA number will be used to identify the sample and its corresponding information within Sage Therapeutics or at any designated contract laboratory for the purpose of sequencing of other DNA specific analysis. No personal details sufficient for individual identification will be available to any person (internal or external to Sage Therapeutics) working with the DNA.

*Genotype/Phenotype Analysis:* Samples and data from genetic analysis will be coded. The link between subject enrollment / randomization code and DNA number will be maintained and stored in a secure environment with restricted access. The established link will be used to identify relevant DNA samples for analysis, facilitated correlation of genotype results with clinical data, allow regulatory audit, and to trace samples for destruction in case of withdrawal of consent.

#### **11.2.7.2. Retention of Biological Samples for Pharmacogenetic Analysis**

Extracted DNA is a finite research that is destroyed in the process of being analyzed. Primary blood samples from which DNA can be extracted will be stored and used until no further analyses are possible, a maximum storage period of 25 years from time of last subject last visit has been reached, or an individual or LAR withdraws his/her or their consent.

#### **11.2.8. Other Outcomes**

##### **11.2.8.1. Pharmacokinetic Data**

Formal plasma analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS)). In addition, all samples will be analyzed for important SAGE-547 metabolites (if and when these are identified) and Captisol<sup>®</sup> concentrations.

##### Plasma Analysis

Plasma will be collected to assay for SAGE-547 concentrations at the following time points relative to the start of each infusion of study drug:

- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion.
- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open label SAGE-547 study drug infusion.
- All samples will also be analyzed for plasma concentrations of important metabolites of SAGE-547 if and when these are identified.
- All samples will also be analyzed for plasma concentrations of Captisol<sup>®</sup>.

The plasma samples will be drawn from the arm contralateral to that used for drug administration. Drawing samples from peripheral arterial or venous lines or from a central line is permissible. PK collection times should be adhered to as strictly as possible. The allowed time window for all samples is: pre-dose in the two hours prior to starting the infusion of study drug; samples up to and including 1h, +/- 5 minutes; subsequent samples, +/- 15 minutes. Subject-specific PK kits for sampling including instructions on collection and processing methods, and storage and shipping conditions, will be provided separately. To maintain the blind, all subjects will have samples taken as outlined above: subjects receiving SAGE-547 will have all samples analyzed for all analytes.



Subjects on placebo may have samples analyzed to investigate endogenous allopregnanolone and metabolite concentrations, as well as Captisol® concentrations; experience with the plasma concentration data will determine if and which placebo samples are analyzed.

Each blood sample will be 3 ml in volume for adults and children weighing 30 kg or more, and 1 ml in volume for children weighing less than 30 kg. Separate aliquots will be obtained from each sample to service the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum blood draw for PK analysis for a subject having two infusions of study drug will be 99 ml (33 ml for children weighing less than 30 kg).

Plasma PK parameters for SAGE-547 will be calculated where appropriate (e.g.,  $C_{max}$ ,  $C_{min}$ ,  $t_{max}$ ,  $AUC_{last}$ ,  $AUC_{\infty}$ ,  $CL_s$ ). In addition, similar PK parameters will be calculated for Captisol®. PK parameters for important metabolites of SAGE-547 may be calculated. An evaluation will be made of the feasibility of adopting a population-PK approach to assess drug-drug-interactions with SAGE-547 as victim of AEDs.

In addition, the Visit 9 sample may be analyzed for plasma concentrations of third-line agents.

#### Other Analysis

If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations. The minimum volume of cerebrospinal fluid for analysis is 100 microlitres.

Full details of all pharmacokinetic analyses will be described in the Pharmacokinetic Analysis Plan.

#### **11.2.8.2. Correlation of QT/QTc Changes and Plasma Concentrations of SAGE-547**

An analysis will be performed to determine whether there is any correlation between changes in QT/QTc interval and plasma concentrations of SAGE-547, in order to investigate any effect that SAGE-547 may have on QT/QTc interval.

#### **11.2.8.3. Pharmacoeconomic Data**

At Visit 12 or Visit 12R, the following information will be collected: number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital. If the subject dies before Visit 12 or Visit 12R, data will be collected up to the date of death. The definition of “hospital” is the institution that the subject was initially treated in. If the subject is transferred to another hospital, that hospital would be the “discharge destination from the hospital” and the “number of days in hospital” would be the number of days in the initial treating hospital.

For those subjects discharged from hospital before Visit 12/12R, the following questions will be asked:

- On what study day was the subject discharged from hospital?
- What type of facility was the subject discharged to (another hospital, a rehabilitation center, a supported care facility, home, other)?
- How many days did the subject stay in this facility?

The following questions will be answered regarding the stay in the ICU and hospital:

- Was the subject still in the ICU at the end of Visit 10/10R?
- If the FOUR Score was  $\geq 12$  at Visit 10/10R and the subject was in the ICU at Visit 10/10R, what was the reason for the subject not being discharged from the ICU (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, other)?
- Was the subject still an in-patient in the hospital at the end of Visit 12/12R?
- If the FOUR Score was  $\geq 15$  at Visit 12/12R and the subject was in the hospital at Visit 12/12R, what was the reason for the subject not being discharged from the hospital (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, unsuitable home circumstances, other)?

#### **11.2.8.4. STESS**

The STESS will be assessed during Visit 1 in order to assess the severity of the status epilepticus.

#### **11.2.8.5. FOUR Score**

The Full Outline of UnResponsiveness or FOUR Score is designed to assess conscious level and unlike other scores, is suitable for subjects who are intubated. It assesses four domains of neurological function (eye responses, motor responses, brainstem reflexes, and breathing pattern).

The FOUR Score will be collected at the following time points relative to each infusion of study drug (the initial blinded infusion and the second open-label infusion if this is administered):

- baseline, +24, +48, +72, +96, +120, +144, +168, and +192 hours (all +/- 2 hours) after the start of the infusion, and at Visit 11/11R and Visit 12/12R.

#### **11.2.8.6. Glasgow Outcome Scale (GOS)**

The GOS is a relatively common assessment scale used to standardize descriptions of the objective degree of recovery from brain injury such as cerebral trauma, or in this case SRSE. It was first used in 1975 ([Jennett and Bond 1975](#)) and allows a prediction of the long-term course of rehabilitation to return to work and everyday life. The scale classifies subjects into 5 groups:

- Death
- Persistent vegetative state
- Severe disability
- Moderate disability
- Good recovery

The GOS will be assessed at Visit 12 or Visit 12R.

#### **11.2.8.7. Supervision Rating Scale (SRS)**

The Supervision Rating (SRS) measures the level of supervision that a patient/subject receives from caregivers. The SRS rates level of supervision on a 13-point ordinal scale that can optionally be grouped into five ranked categories (Independent, Overnight Supervision, Part-Time Supervision, Full-Time Indirect Supervision, and Full-Time Direct Supervision). The SRS was designed to be rated by a clinician based on interviews with the subject and an informant who has observed at first hand the level of supervision received by the subject ([Boake 2000](#)). Scoring is a one-step procedure

in which the clinician assigns the rating that is closest to the subject's level. Ratings are based on the level of supervision received, not on how much supervision a subject is judged or predicted to need.

The SRS will be assessed at Visit 1 and Visit 12 or Visit 12R. The Visit 1 assessment will be a retrospective assessment of the supervision required by the subject immediately prior to the admission that included the index episode of status epilepticus.

#### **11.2.8.8. Modified Rankin Scale – 9Q (mRS-9Q)**

The Modified Rankin Scale (mRS) is a commonly used scale to determine disability and functional dependence due to neurological insult such as stroke in adults. The 7-point scale (0 – 6) denotes functional capacity from no symptoms (0) to severe disability (5) and death (6). The Modified Rankin Scale – 9Q is a shortened version consisting of 9 questions that reliably determines the mRS score and was developed to both simplify the assessment and expand the rater base to non- medically trained personnel (Patel, Rao et al. 2012). The assessment is a web-based tool in the public domain with automatic score calculation and error checking found at [www.modifiedrankin.com](http://www.modifiedrankin.com).

The mRS will be assessed at Visit 1 and at Visit 12 or Visit 12R in subjects  $\geq 17$  years of age. The baseline assessment will be a retrospective assessment of the disability and dependence of the subject immediately prior to the admission that included the index episode of status epilepticus.

## 12. STUDY PROCEDURES

The study procedures listed below by study day reflect the required data collection times for this protocol. When a time window is necessary, this is specified below. If no time window is specified, the test may be performed at any time within the specified 24-hour period.

### 12.1. Visit 1 (V2-≤30h)

The baseline period will be up to approximately 84 hours prior to starting blinded study treatment and should include the assessments/procedures listed below and summarized in Table 1 and Table 2 (for retreatment), the Schedules of Events.

- Informed consent
- Eligibility checklist
- Verification of inclusion/exclusion criteria.
- Demographic information and medical history obtained by proxy and confirmed by the subject when possible.
- SE and wean history
- Blood will be collected from female subjects 10 years to 55 years for a serum pregnancy test unless they are known to be pre-menstrual or post-menopausal or to have had a hysterectomy.
- Blood and urine samples collected for clinical laboratory testing.
- Pharmacogenetic sample will be collected from consenting/eligible subjects.
- Vital signs
- Height
- Weight
- An ECG reading taken.
- Administration of the STESS.
- Administration of the FOUR Score.
- Administration of SRS.
- Administration of the mRS-9Q assessment.
- Assessment of the CGI scale.
- Evaluation of epilepsy status.
- Administration of continuous IV third-line agents.
- Perform EEG.
- Recording of adverse events.
- Recording of previous and concomitant anti-epileptic drugs.
- Recording of previous and concomitant third-line agents.
- Recording of concomitant pressors.

- Recording of other concomitant medications, procedures, and treatments.

## **12.2. Visit 2 (V3-≤54h)**

- Recording of adverse events.
- Recording of concomitant anti-epileptic drugs.
- Recording of concomitant third-line agents.
- Recording of concomitant pressors.
- Recording of other concomitant medications, procedures, and treatments.
- Wean of continuous third-line agent:
  - If wean is successful, subject is followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (these subjects are Qualifying Wean Success subjects or QWS subjects);
  - If wean is not successful, there is ongoing intravenous administration of at least one continuous IV third-line agent and EEG is performed and the subject is randomized.

## **12.3. SAGE-547 Treatment Period**

### **12.3.1. Visit 3/3R (0-24 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs will be recorded at:
  - 0, +30, +60 minutes (+/-15 minutes) and +2, +4, +8 (+/- 30 minutes) and +24 hours (+/- 2 hours) after the start of the infusion
- ECG readings will be recorded immediately after PK sampling at:
  - 0 (pre-dose) and at +0.5, +1, +3, +6, +12, and +24 hours after the start of the blinded study drug infusion.
- A blood sample for PK analysis should be collected at the following time points (all +/- 15 minutes except where otherwise stated):
  - 0 (pre-dose, within two hours of the start of the infusion) and at +0.5, +1 (+/- 5 minutes), +3, +6, +12, and +24 hours after the start of the blinded study drug infusion.
- Completion of the FOUR Score
  - +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the end of the 24 hour observation period following the QW)
- Ongoing intravenous administration of a continuous IV third-line agent.

- Study drug administration in loading (Hour 0-1) and maintenance infusions (at completion of Hour 1).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.3.2. Visit 4/4R (25-48 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +48 hours (+/- 2 hours) after the start of the infusion
- An ECG reading taken immediately after PK sampling:
  - +48 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +48 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +48 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent.
- Ongoing study drug maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.3.3. Visit 5/5R (49-72 hours)**

- Weight
- Vital signs should be recorded at:
  - +72 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +72 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +72 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +72 hours (+/- 2 hours) after the start of the infusion

- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.4. Visit 6/6R (73-96 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +96 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +96 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +96 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +96 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Perform EEG.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.5. Visit 7/7R (97-120 hours)**

- Weight
- Vital signs should be recorded at:
  - +120 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +120 hours after the start of the study drug infusion

- A blood sample for PK analysis should be collected:
  - +120 hours (+/- 15 minutes) after the start of study drug infusion, immediately prior to the end of the maintenance infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +120 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled. Complete wean by 120 hours if at all possible.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## 12.4. SAGE-547 Taper Period

### 12.4.1. Visit 8/8R (121-144 hours)

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +144 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after each PK sampling:
  - +128, +136 hours and +144 hours after the start of the study drug infusion
  - During the open-label retreatment phase of the study ECG readings at: +126, +132, +138 hours and +144 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected (+/- 15 minutes unless otherwise stated):
  - +128 (immediately prior to the end of the first taper step), +136 hours (+/- 5 minutes, immediately prior to the end of the second taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of study drug infusion.
  - During the open-label retreatment phase of the study PK blood draws at: +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 hours (+/- 5 minutes, immediately prior to the end of the third taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of the study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +144 hours (+/- 2 hours) after the start of the infusion



- Complete wean of third line agents by H144 if not completed by H120.
- Perform EEG.
- Taper of SAGE-547 infusion begins at hour 121.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## **12.5. Follow-up Period**

### **12.5.1. Visit 9/9R (145-168 hours)**

- Vital signs should be recorded at:
  - +168 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +152, +160 hours (+/- 2 hours) after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +152 and +160 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +168 hours (+/- 2 hours) after the start of the infusion
- Perform EEG.
- Assessment of the presence of physiologic brain activity using EEG.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.5.2. Visit 10/10R (169-192 hours)**

- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +192 hours (+/- 2 hours) after the start of the infusion
- At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine eligibility for retreatment with the higher dose of study drug. This determination may occur at any point

during Visit 10: the retreatment infusion must begin within the Visit 10 window. All patients for retreatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.

- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.3. Visit 11/11R (Visit 3/3R + 14d (±2))**

- Blood samples collected for clinical laboratory testing (renal panel only).
- Completion of the FOUR Score (QWS subjects also).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.4. Visit 12/12R (Visit 3/3R + 21d (±2))**

All assessments also performed for QWS subjects.

- Completion of the FOUR Score.
- Administration of the GOS.
- Administration of the SRS.
- Administration of the mRS-9Q assessment.
- Evaluation of epilepsy status (see [Section 11.1.2.2](#) for details).
- Assessment of the CGI Scale.
- Recording of adverse events.
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications.
- Collection of pharmacoeconomic data.
- Mortality will be assessed throughout the study period.

## **13. STATISTICS**

### **13.1. Statistical Plan**

Complete details for the analysis and reporting of data from this study will be contained in the Statistical Analysis Plan (SAP).

#### **13.1.1. Interim Analysis**

When approximately 50% of subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment

will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### 13.1.2. Study Populations

The **Safety Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to actual treatment. This analysis population will be used for all safety analyses.

The **Intent to Treat Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to randomized treatment. This analysis population will be used for all efficacy analyses.

The **Modified Intent to Treat Population** is defined as all subjects who:

1. complete their initial course of blinded SAGE-547 or placebo treatment unless the non-completion was due a drug-related adverse event; and
2. have at least one attempt to wean from third-line agents prior to the end of blinded study treatment infusion unless the failure to wean was because seizures were not controlled.

Subjects will be classified according to randomized treatment. This analysis population will be used for sensitivity analyses of the primary endpoint and select secondary efficacy endpoints.

Narratives will be prepared for all subjects who do not complete the infusion of blinded study medication or were not subjected to any wean attempts. Narratives will include details of the cause of SE, the comorbid conditions, the adverse event(s), and reasons for non-completion of the infusion or failure to attempt weaning. This blinded narrative will be reviewed by the medical monitors and the patient adjudicated as MITT eligible or ineligible. Acceptable reasons for defining a subject as MITT ineligible include death or withdrawal of consent due to progression of the underlying cause of SE or comorbid conditions, unless the cause of death or progression of disease were thought by the investigator, sponsor, or DSMB to be related to study drug.

The **Per-Protocol (PP) Population** is defined as a subset of the MITT population but will exclude data from all subjects with significant protocol violations or deviations. Subjects will be classified according to actual treatment received. This data set will be used for sensitivity analyses to examine the robustness of results for the primary and key secondary efficacy endpoints.

The **Pharmacokinetics Population** is defined as all subjects who at least had an infusion of blinded SAGE-547 initiated and have at least one pharmacokinetic sample collected.

The **Pharmacogenetic Population** is defined all subjects who consent to being included in the pharmacogenetic assessment and provide a pharmacogenetic sample.

Summary statistics of all data collected will be presented for subjects who were QW successes.

### 13.1.3. General Aspects

Tabular displays of descriptive statistics will be provided for all variables. Summary tables will include n, mean, mean, standard deviation, minimum and maximum for continuous variable and frequency and percentage for categorical variables.

### **13.1.4. Analysis of Primary Endpoint**

The analysis of response to treatment (see Section 11.1.1 for definition of primary endpoint) between SAGE-547 treated subjects and placebo treated subjects will be performed on the ITT population using a Cochran-Mantel-Haenszel (CMH) test with variables for treatment, concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). The CMH general association statistic and its associated p-value will be presented. The comparison of treatment response rates will be conducted at the 5% level of significance. To confirm the CMH results, a permutation test will also be conducted.

An additional analysis of the primary endpoint will also be performed on the MITT population. In addition sensitivity analyses of the primary endpoint will be performed using the ITT population based on:

- the number of third-line agents (one, two, or three) subjects were administered post-randomization; and
- which third line agent was the subject of the first TW.

As requested by Italian regulators, the primary endpoint will also be summarized by the cause of status epilepticus being or not being an autoimmune disorder as defined by medical history and prior and/or concurrent medication use.

### **13.1.5. Analysis of Secondary Efficacy Endpoints**

Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section (Section 6). Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. The analysis of the secondary endpoints will also be performed on the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

### **13.1.6. Analysis of Other Endpoints**

Safety and “Other” endpoints will only be summarized by treatment group.

Summaries of safety endpoints will be based on the overall Safety Population.

### **13.1.7. Epilepsy and SRSE Status**

Diagnosis of epilepsy and recurrence of RSE or SRSE will be documented as the percentage of subjects by time point and overall. Kaplan-Meier curves may be plotted if sufficient data are available.

Utilization of AEDs during follow-up and during recurrence will be summarized.

#### **13.1.8. Questionnaires**

The data collected from each questionnaire will be interpreted according to the standard methodology for that questionnaire. There will be no adjustment for missing values.

#### **13.1.9. Pharmacokinetic Data Analysis**

Details of the pharmacokinetic data analysis will be described in detail in a separate Pharmacokinetic Analysis Plan.

#### **13.1.10. Pharmacogenetic Data Analysis**

Any genotype data generated in this study will be stored within a secured database within Sage Therapeutics and / or a third party contracted to work with Sage Therapeutics to analyze the samples. Because the number of subjects agreeing to participate in the genetic research component of the study is unknown, it is not possible to establish, a priori, whether sufficient samples will be obtained to support formal statistical evaluation of data. As a consequence a Pharmacogenetic Analysis Plan will only be prepared where appropriate and the results obtained from any genetic research will be reported in a report separate from the main study CSR.

#### **13.1.11. Retreated Subjects**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are retreated with SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo.

#### **13.1.12. EEG-Responders**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who are classified as EEG-responders/non-responders based on the independent assessment of the PAEEG. Summaries will be derived for the two randomized treatment groups.

#### **13.1.13. QT/QTc Assessment**

An analysis of the correlation between changes in QT/QTc intervals and SAGE-547 plasma levels will be performed to investigate if there is a potential effect that SAGE-547 may have on QT/QTc interval. A detailed description of the QT/QTc assessment will be included in the SAP.

#### **13.1.14. Quantitative EEG**

The six EEG records for each subject may be subjected to exploratory quantitative EEG analysis, the details of which will be included in the EEG Analysis Plan. In summary the following comparisons may be made, SAGE-547 versus placebo: the QWEEG versus the TWEEG (main analysis); the CEEG versus PAEEG (subsidiary analysis); and TAEED versus PAEEG (exploratory analysis).

### **13.2. Determination of Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to

placebo, there would be >90% power for detecting a significant difference between treatment groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

### **13.3. Statistical Analysis Plan**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

## **14. ADVERSE EVENTS**

The safety procedures in this study will be detailed in a Safety Management Plan, which will be agreed and signed before the first subject is randomized in the study. [Section 14.1](#) summarizes Investigator responsibilities regarding the identification and documentation of AEs, the classification of AEs for relationship to study drug and severity, and the reporting of AE information to the Sponsor and the IRB.

[Section 14.2](#) summarizes Sponsor/Medical Monitor Responsibilities regarding monitoring of AE data and reporting relevant safety information to FDA.

[Section 14.3](#) lists important AE definitions.

### **14.1. Investigator Responsibilities**

#### **14.1.1. Identification and Documentation of Adverse Events by Investigator**

Subjects will be evaluated and questioned generally (if possible) to identify AEs during the course of the study. AEs will be collected from the signature of the consent form through Visit 12/12R. Adverse events that occur prior to completion of screening will be captured on the Medical History eCRF. Adverse events that occur after completion of screening will be recorded on the Adverse Event eCRF.

All AEs revealed by observation, other diagnostic procedures, or spontaneously reported by the subject and/or in response to an open question from study personnel will be recorded on the Adverse Event Form. Any clinically significant deterioration in laboratory assessments or other clinical findings are considered an AE and must be recorded on the Adverse Event Form, unless otherwise stated. AE information recorded will be entered into the database on an ongoing basis.

AEs with a relationship considered related to study drug (probable, possible) should be followed until the event is resolved or the Investigator determines the event is stable or no longer clinically significant. AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

For SAEs, an electronic Serious Adverse Event eCRF must be completed with as much information as possible and submitted in the time frame described below in [Section 14.1.3](#). When new significant information is obtained as well as when the outcome of an event is known, the electronic SAE eCRF should be updated within 24 hours. If the subject was an outpatient at the time of the SAE and was re-hospitalized due to the SAE, a copy of relevant hospital records (e.g., admission report, laboratory test results, discharge summary, etc.) may be requested to be included as part of the subject medical file.

All SAEs will be followed until resolved or until a stable status has been achieved.

**14.1.2. Adverse Event Classification****14.1.2.1. Relationship to Investigational Drug**

None:	No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state.
Possible:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject, but this is not known for sure.
Probable:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

**14.1.2.2. Severity**

Mild	Discomfort noticed, but no disruption to daily activity.  For subjects that are unconscious, this may be a slight or minor change in a lab result or clinical sign or symptom that does not require immediate corrective action.
Moderate	Discomfort sufficient to reduce or affect normal daily activity, but is not hazardous to health; prescription drug therapy may be employed to treat the AE.  For subjects that are unconscious, this may be a clinically meaningful change that may require immediate corrective action.
Severe	Inability to work or perform normal daily activity and represented a definite hazard to health; prescription drug therapy and/or hospitalization may be employed to treat the AE.  For unconscious subjects, this may be a significant clinical change that requires immediate corrective action.

**14.1.2.3. Action Taken with Investigational Drug**

None	Study medication was continued without change.
Discontinued	Study medication was terminated.
Dose adjusted	Study medication dose/infusion rate was changed and then continued per protocol.
Interrupted	Study medication was interrupted and then continued per protocol.
Unknown	The action taken with regard to study medication is unknown.
Not applicable	Administration of study medication was not ongoing.



**14.1.2.4. Assessment of Outcome**

Ongoing	At the end of the study, the event has not resolved or stabilized.
Ongoing and stable	The event is ongoing but has stabilized and is unlikely to change
Resolved	The event has resolved or the subject recovered without sequelae.
Resolved with sequelae	The event has at least one secondary outcome that may result in permanent disability and/or functional limitation.
Unknown	The status of the event is unknown.
Death	The subject has expired.

**14.1.3. Investigator Reporting to Sponsor and Sponsor Emergency Contact**

All new SAEs that come to the Investigator and/or Sponsor's notice during the course of the study (up to and including the last study visit) must be reported by the Investigator on the designated electronic report form within 24 hours of the point in time when the Investigator becomes aware of the SAE. As additional information becomes available, the designated electronic report form must be updated within 24 hours.

Investigators must report any SAE, whether or not considered drug related. The report must include an assessment of whether there is a reasonable possibility that the drug caused the event.

In a medical emergency (ie, an event that requires immediate attention regarding the treatment of a subject, operation of the clinical study, and/or the use of investigational drug), study site staff will apply appropriate medical intervention according to current standards of care, and contact the Medical Monitor.

**14.1.4. Medical Monitor and Emergency Contact Information**

[REDACTED], MD  
[REDACTED]

**14.1.5. SAE Reporting Contact Information**

Contact information and reporting instructions are provided in the Safety Management Plan.

**14.1.6. Reporting to Institutional Review Boards (IRBs)**

It is the responsibility of the Investigator to promptly notify the institution's IRB of all serious and unexpected suspected adverse reactions (see [Section 14.3](#) for definitions).

## **14.2. Sponsor/Medical Monitor Responsibilities**

### **14.2.1. Monitoring of Adverse Event Data**

The Medical Monitor will review any newly reported adverse events in an ongoing basis. If the aggregate assessment indicates that an event is occurring more frequently than would normally be expected in this population, or as previously observed, and the sponsor believes that the events are causally related to the administration of SAGE-547, the Sponsor will then report that information in an IND safety report.

### **14.2.2. Data Safety Monitoring Board**

An independent DSMB will monitor the clinical, PK and PD data for safety signals throughout the study and will be asked to assess the placebo response rate at the time of the interim analysis to determine final sample size. In order to perform their monitoring function the DSMB will have access to un-blinded safety data as necessary.

The composition and procedures for the board will be described in a separate DSMB Charter.

### **14.2.3. Reporting to FDA**

The Sponsor must report in an IND safety report any suspected adverse reaction to study treatment that is both serious and unexpected (21 CFR 312.32(c)(1)(i)). Before submitting an IND safety report, the Sponsor will ensure the event meets all three of the definitions: (1) suspected adverse reaction, (2) serious, (3) unexpected. If the AE does not meet all three of the definitions, it should not be submitted as an IND safety report. The Sponsor should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the adverse event and, therefore, that the event meets the definition of a suspected adverse reaction.

If there is a serious and unexpected suspected adverse reaction, the Sponsor will notify the appropriate regulatory agency(ies) and all appropriate parties on an expedited basis. In addition, Sponsors must submit expedited reports of an increased rate of occurrence or severity of serious suspected adverse reactions over that listed in the protocol or Investigational Brochure.

SUSARs will be unblinded prior to reporting to FDA. Unless it is necessary to unblind for the safety of the patient, the investigator will not be informed of the unblinding of the subject.

Under 21 CFR 312.32, Sponsors should identify in the protocol SAEs that it does not plan to report individually in an expedited manner, because they are known consequences of the disease or otherwise common in the study population. Given the grave condition and prognosis of SRSE being studied, individual occurrences of seizures or seizure activity will not be reported expeditiously in this study. Regardless of which events are reported in an expedited manner, all adverse events will be closely monitored throughout the study.

## **14.3. Adverse Event Definitions**

### **14.3.1. Adverse Event**

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

### **14.3.2. Suspected Adverse Reaction**

Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

### **14.3.3. Life-Threatening**

An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

### **14.3.4. Serious**

An AE or suspected adverse reaction is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE – see definition above
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disability
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

### **14.3.5. Unexpected**

An AE or suspected adverse reaction is considered “unexpected”:

- If it is not listed in the Investigational Brochure or is not listed at the specificity or severity that has been observed, or
- If an Investigational Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigational Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigational Brochure listed only cerebral vascular accidents.

“Unexpected,” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigational Brochure as occurring with a class of drugs or as anticipated from

the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

#### **14.4. Emergency Identification of Study Medication**

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject's treatment in the study via the IVRS; this normally requires prior approval by the medical monitor. However, if the subject is at immediate risk and the Investigator believes that immediate knowledge of the study treatment will alter medical management, discussion with the medical monitor may take place after unblinding. The Investigator will not unblind the medical monitor during that discussion. The process of unblinding will ensure that only the investigator is unblinded; the medical monitor, study management team, and data management team will not be made aware of the treatment allocation of an individual subject. All cases of emergency unblinding will be fully documented in a way that does not unblind the medical monitor, study management team, and data management team.

### **15. STUDY ADMINISTRATIVE CONSIDERATIONS**

#### **15.1. Quality Control and Quality Assurance**

The Investigators and institutions will permit trial related monitoring, audits, IRB review, and regulatory inspections as requested by FDA, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed informed consent forms, etc.) in addition to case report forms.

Quality assurance and quality control systems with written standard operating procedures (SOPs) will be followed to ensure this trial will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The site's dedicated study monitor will arrange to visit the Investigator at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be identified and resolved. The study monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality assurance officers named by Sage Therapeutics or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements, made by the Sponsor with the Investigator/institution and any other parties involved with the clinical trial, will be in writing in a separate agreement.

## **15.2. Data Handling and Recordkeeping**

### **15.2.1. Data Handling**

Procedures for data handling (including electronic data) used in this protocol will be documented in a Data Management Plan.

### **15.2.2. Case Report Form Completion**

eCRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of demographics, study drug administration, study procedures, AEs, questionnaire completion, efficacy assessments and subject status, including survival.

The Investigator will maintain copies of the eCRFs at the study site. For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate eCRF.

### **15.2.3. Retention of Study Records**

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval and until there are no pending or contemplated marketing applications or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to an appropriate person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

## **15.3. Confidentiality**

To maintain subject privacy, all eCRFs, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available trial registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by Sage Therapeutics to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

#### **15.4. Publication Policy**

All information concerning SAGE-547 is considered confidential and shall remain the sole property of Sage Therapeutics. The Investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval from Sage Therapeutics. No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between Sage Therapeutics and the Investigator.

#### **15.5. Protocol Amendments**

Changes to the conduct of the study should be prepared as a protocol amendment by the Sponsor. Protocol amendments should receive written IRB/IEC approval prior to implementation at the investigative site, except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the trial (eg, change of monitor, telephone numbers). In this case, Sage Therapeutics will amend and implement the protocol change and subsequently notify the regulatory authorities and the Investigative sites who will notify the respective IRB, as appropriate.

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**APPENDIX 1. APPENDIX 1: FOUR SCORE****FOUR score****Full Outline of UnResponsiveness****Eye response**

- E4: eyelids open or opened, tracking, or blinking to command
- E3: eyelids open but not tracking
- E2: eyelids closed but open to loud voice
- E1: eyelids closed but open to pain
- E0: eyelids remain closed with pain

**Motor response**

- M4: thumbs-up, fist or peace sign
- M3: localizing to pain
- M2: flexion response to pain
- M1: extension response to pain
- M0: no response to pain or generalized myoclonus status

**Brainstem reflexes**

- B4: pupil and corneal reflexes present
- B3: one pupil wide and fixed
- B2: pupil or corneal reflexes absent
- B1: pupil and corneal reflexes absent
- B0: absent pupil, corneal and cough reflex

**Respiration pattern**

- R4: not intubated, regular breathing pattern
- R3: not intubated, Cheyne-Stokes breathing pattern
- R2: not intubated, irregular breathing
- R1: breathes above ventilatory rate
- R0: breathes at ventilator rate or apnea

Reference ([Iyer, Hoel et al. 2009](#)).

**APPENDIX 2. GLASGOW OUTCOME SCALE (GOS)****GLASGOW  
OUTCOME  
SCALE**

Patient Name: \_\_\_\_\_  
 Rater Name: \_\_\_\_\_  
 Date: \_\_\_\_\_

*Note:* The scale presented here is based on the original article by Jennett and Bond. It has become common practice in clinical trial administration, however, to use a modified version that places the scores in reverse order (i.e., "good recovery" = 1, "moderate disability" =2, etc.).

Score	Description
1	DEATH
2	PERSISTENT VEGETATIVE STATE Patient exhibits no <i>obvious cortical</i> function.
3	SEVERE DISABILITY (Conscious but disabled). Patient depends upon others for daily support due to mental or physical disability or both.
4	MODERATE DISABILITY (Disabled but independent). Patient is independent as far as daily life is concerned. The disabilities found include varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes.
5	GOOD RECOVERY Resumption of normal activities even though there may be minor neurological or psychological deficits.

**TOTAL (1-5):** \_\_\_\_\_

Reference ([Jennett and Bond 1975](#)).

## APPENDIX 3. SUPERVISION RATING SCALE (SRS)

### SUPERVISION RATING SCALE (SRS)

**Instructions:** Circle the rating that is closest to the amount of supervision that the patient *actually receives*. "Supervision" means that someone is responsible for being with the patient.

<u>Rating</u>	<u>Description</u>
<u>Level 1: INDEPENDENT</u>	
1	The patient lives alone or independently. Other persons can live with the patient, but they cannot take responsibility for supervision (for example, a child or elderly person).
2	The patient is unsupervised overnight. The patient lives with one or more persons who <i>could</i> be responsible for supervision (for example, a spouse or roommate), but they are <i>all</i> sometimes absent overnight.
<u>Level 2: OVERNIGHT SUPERVISION</u>	
3	The patient is only supervised overnight. One or more supervising persons are always present overnight but they are <i>all</i> sometimes absent for the rest of the day.
<u>Level 3: PART-TIME SUPERVISION</u>	
4	The patient is supervised overnight and part-time during waking hours, but is allowed on independent outings. One or more supervising persons are always present overnight and are also present during part of waking hours every day. However, the patient is sometimes allowed to leave the residence without being accompanied by someone who is responsible for supervision.
5	The patient is supervised overnight and part-time during waking hours, but is unsupervised during working hours. Supervising persons are <i>all</i> sometimes absent for enough time for them to work full-time outside the home.
6	The patient is supervised overnight and during most waking hours. Supervising persons are <i>all</i> sometimes absent for periods longer than one hour, but less than the time needed to hold a full-time job away from home.
7	The patient is supervised overnight and during almost all waking hours. Supervising persons are <i>all</i> sometimes absent for periods shorter than one hour.
<u>Level 4: FULL-TIME INDIRECT SUPERVISION</u>	
8	The patient is under full-time indirect supervision. At least one supervising person is <i>always</i> present, but the supervising person does not check on the patient more than once every 30 minutes.
9	Same as #8 plus requires overnight safety precautions (for example, a deadbolt on outside door).
<u>Level 5: FULL-TIME DIRECT SUPERVISION</u>	
10	The patient is under full-time direct supervision. At least one supervising person is always present and the supervising person checks on the patient more than once every thirty minutes.
11	The patient lives in a setting in which the exits are physically controlled by others (for example, a locked ward).
12	Same as #11 plus a supervising person is designated to provide full-time line-of-sight supervision (for example, an escape watch or suicide watch).
13	The patient is in physical restraints.

3/12/93

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## APPENDIX 4. MODIFIED RANKIN SCALE – LEVEL OF FUNCTION SURVEY (mRS-9Q)

1. Do you have any symptoms that are bothering you? (For example, trouble with reading or writing, trouble speaking, problems with vision, numbness, weakness, balance trouble, or problems with swallowing?)	YES <input type="radio"/>	NO <input type="radio"/>
2. Are you able to do the same work as before?	YES <input type="radio"/>	NO <input type="radio"/>
3. Are you able to keep up with your hobbies?	YES <input type="radio"/>	NO <input type="radio"/>
4. Have you maintained your ties to friends and family?	YES <input type="radio"/>	NO <input type="radio"/>
5. Do you need help making a simple meal, doing household chores, or balancing a checkbook?	YES <input type="radio"/>	NO <input type="radio"/>
6. Do you need help with shopping or traveling close to home?	YES <input type="radio"/>	NO <input type="radio"/>
7. Do you need another person to help you walk?	YES <input type="radio"/>	NO <input type="radio"/>
8. Do you need help with eating, going to the toilet, or bathing?	YES <input type="radio"/>	NO <input type="radio"/>
9. Do you stay in bed most of the day and need constant nursing care?	YES <input type="radio"/>	NO <input type="radio"/>

## APPENDIX 5. CLINICAL GLOBAL IMPRESSION (CGI)

### Clinical Global Impression (CGI)

#### 1. Severity of illness

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- |                             |   |
|-----------------------------|---|
| 0 = Not assessed            | 4 = Moderately ill                        |
| 1 = Normal, not at all ill  | 5 = Markedly ill                          |
| 2 = Borderline mentally ill | 6 = Severely ill                          |
| 3 = Mildly ill              | 7 = Among the most extremely ill patients |

#### 2. Global improvement: Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.

Compared to his condition at admission to the project, how much has he changed?

- |                        |                     |
|------------------------|---------------------|
| 0 = Not assessed       | 4 = No change       |
| 1 = Very much improved | 5 = Minimally worse |
| 2 = Much improved      | 6 = Much worse      |
| 3 = Minimally improved | 7 = Very much worse |

#### 3. Efficacy index: Rate this item on the basis of drug effect only.

Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.

EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect		Side effects			
		None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
<b>Marked</b>	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
<b>Moderate</b>	Decided improvement. Partial remission of symptoms	05	06	07	08
<b>Minimal</b>	Slight improvement which doesn't alter status of care of patient	09	10	11	12
<b>Unchanged or worse</b>		13	14	15	16
Not assessed = 00					

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

**APPENDIX 6. STATUS EPILEPTICUS SEVERITY SCORE (STESS)**

Outcome Predictor	Feature	Score
Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type (prior to first treatment)	Simple-partial, complex-parial, absence, myoclonic (complicating idiopathic generalized epilepsy)	0
	Generalized-convulsive	1
	Nonconvulsive status epilepticus in coma	2
Age	< 65 years	0
	≥ 65 years	2
History of previous seizures	Yes	0
	No or unknown	1
Summed Total		

**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY  
TO EVALUATE THE EFFICACY AND SAFETY OF SAGE-547 INJECTION  
IN THE TREATMENT OF SUBJECTS WITH SUPER-REFRACTORY  
STATUS EPILEPTICUS**

**PROTOCOL NUMBER: 547-SSE-301**

**IND NUMBER: 117901**

**EudraCT Number: 2015-002142-31**

Product: SAGE-547 Injection (allopregnanolone)

Sponsor Contact: [REDACTED], MD

[REDACTED]  
Sage Therapeutics  
215 First Street  
Cambridge, MA 02142  
[REDACTED]

Medical Monitor: [REDACTED], MD

Date of Protocol: 09 March 2015

Date of Amendment One 27 May 2015

Date of Amendment Two 07 December 2015  
(Adults Only, Sweden)

**Confidentiality Statement**

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

**PROTOCOL NUMBER: 547-SSE-301**

Sponsor [REDACTED]:

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]

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Sage Therapeutics

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CRO [REDACTED]:

[REDACTED]



## 1. SIGNATURE PAGE

Title of Protocol:

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus

Protocol No: 547-SSE-301

### Sponsor Approval

[Redacted Signature]

08 Dec 2015

[Redacted Name] MD

Date (dd/mmm/yyyy)

Sage Therapeutics

### Investigator Agreement

By signing this page I attest that I have read and understand the contents of Clinical Protocol 547-SSE-301 and any current amendments. I agree to adhere to the design, conduct, and reporting requirements of the study as stated in the clinical protocol and to my obligations to the Sponsor as described in the protocol and executed contracts between myself, my Institution, and the Sponsor. I also agree to adhere to any subsequent amendments to the clinical protocol.

Investigator's Signature: \_\_\_\_\_

Investigator's Name: \_\_\_\_\_

Institution: \_\_\_\_\_

Date: \_\_\_\_\_

## 2. SYNOPSIS

<b>Name of Sponsor:</b> Sage Therapeutics 215 First Street Cambridge, MA 02142		
<b>Protocol No.</b> 547-SSE-301	<b>Phase:</b> 3	
<b>Name of Investigational Product:</b> SAGE-547 Injection		
<b>Name of Active Ingredient:</b> Allopregnanolone		
<b>Title of the Protocol:</b> A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus		
<b>Dosing Regimen: SAGE-547 or Placebo Dosing Schedule</b>		
<b>Hour</b>	<b>Type and Duration of SAGE-547 Infusions</b>	<b>Dose</b>
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	90 µg/kg/h
H121 – H128	8 hour taper	65 µg/kg/h
H129 – H136	8 hour taper	45 µg/kg/h
H137 – H144	8 hour taper	25 µg/kg/h
<b>Dosing Regimen: SAGE-547 Open Label Dosing Schedule</b>		
<b>Hour</b>	<b>Type and Duration of SAGE-547 Infusion</b>	<b>Dose</b>
H1	One hour loading infusion	300 µg/kg/h
H2 –H120	119 hour maintenance infusion	150 µg/kg/h
H121 – H126	6 hour taper	125 µg/kg/h
H127 – H132	6 hour taper	95 µg/kg/h
H133 – H138	6 hour taper	65 µg/kg/h
H139 – H144	6 hour taper	35 µg/kg/h
<b>Study Sites</b> Up to 180 sites in the USA, Europe, and Canada.		
<b>Number of Subjects</b>		

The study will randomize 140 subjects at up to 180 sites.

### Study Population

Subjects will be aged 18 years or more, in SRSE<sup>1</sup> (as defined in the Inclusion Criteria [Section 8.1](#)), and being managed in an intensive care setting.

### Duration of Subject Involvement

Individual subject participation will be up to 30 days.

### Study Design

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

Patients will follow one of three paths to entry to the study. The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst suppression with a third-line agent. These subjects will be consented for the study after admission to the intensive care unit, but before any third-line agents are administered for burst suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their legally authorized representative (LAR) already appointed by the Court for their well-being, and closest relatives. Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours. Once burst suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The second path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst suppression pattern on the EEG. These subjects may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

<sup>1</sup> In this study, the term Super-Refractory Status Epilepticus or SRSE is equivalent to “Refractory Status Epilepticus (RSE) that has failed standard treatment” and the two terms are used interchangeably.

The third path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These subjects may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR and closest relatives. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 treatment or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within six hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo).

The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that subjects, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as both the ability to wean the subject off all third-line agents before the end of the infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication infusion, and concurrent signs of physiologic brain activity as determined by EEG. Details of the assessments and time points are provided in the schedule of assessments ([Table 1 and Error! Not a valid result for table.](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo will all subsequently be eligible to be administered SAGE-547 at the higher dose.

## Visit Schedule

The visit schedule and an overview of events at each visit is provided in [Table 1, Error! Not a valid result for table.](#) and [Table 3](#) Schedule of Assessments.

## Study Objectives

### *Primary objective:*

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult subjects with SRSE, and for the response to endure at least 24 hours after the end of the SAGE-547 or placebo infusion (primary response).

### *Secondary objectives:*

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in the Clinical Global Impression scale (CGI) between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### *Safety objectives:*

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

### *Other objectives:*

1. To evaluate the impact of retreatment with a higher dose SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;

2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;
6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS).

## Endpoints

### *Primary endpoint:*

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### *Secondary endpoints:*

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### *Safety endpoints:*

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;

## 5. Mortality.

**Other endpoints:**

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who fail to respond to their randomized double blind treatment and are retreated with a higher dose of SAGE-547.
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS).

**Inclusion Criteria**

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects 18 years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst suppression pattern; or who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst suppression pattern.

**Exclusion Criteria**

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone or any excipients in SAGE-547.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy.

4. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis for whatever reason, but dialysis is not planned or non-continuous dialysis is planned (that would not adequately remove Captisol<sup>®</sup>);
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. severe hepatic impairment;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the opinion of the investigator, of less than 30 days;
  - e. a do not resuscitate (DNR) order.
5. Subjects who are being administered more than three third-line agents concomitantly or in whom the qualifying wean cannot be completed within 24 hours, or who are being administered a third-line agent for other indications such as management of raised intra-cranial pressure that would preclude weaning according to this protocol.
6. Subjects with a living will that does not allow heroic measures.
7. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
8. Subjects who have been enrolled in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not withdraw or complete and then re-enroll).

### **Pharmacogenetic Research**

In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **Statistical Analysis**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

### **Interim Analysis**

When approximately 50% of the subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### **Analysis of Primary Endpoint**

The analysis of response to treatment between SAGE-547 treated subjects and placebo treated subjects will be performed using a Cochran-Mantel-Haenszel test with variables for treatment, concomitant



pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). In this analysis, a treatment responder is a subject who is successfully weaned off all third-line agents and blinded study medication prior to the end of study treatment infusion and remains off third-line agents for at least 24 hours following cessation of the blinded study medication, and who has concurrent signs of physiologic brain activity as determined by EEG. The analysis will be based on the ITT Population. The comparison of treatment response rates will be conducted at the 5% level of significance.

### **Analysis of Secondary Efficacy Endpoints**

The primary analysis will be repeated for the MITT population. Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section. Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. Secondary analyses will be repeated for the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from Baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third-line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

Summaries of safety endpoints will be based on the overall Safety Population which is defined as all subjects who at least initiated the infusion with blinded study treatment.

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are retreated with SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo. Summary statistics will be presented for subjects who were QW successes.

### **Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

**Table 1: Schedule of Assessments for Protocol 547-SSE-301: One Infusion of Study Drug (blinded)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical/SE/Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X		X	X	X	X	X	X				
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X		X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X		X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X		X	X		X		X		X		
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X			
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>n</sup>											X
Modified Rankin Score (mRS)	X <sup>n</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV 3rd-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>o</sup>				
EEG	X	X				X		X	X			
Randomization		X										
Study Drug Administration <sup>p</sup>			X	X	X	X	X	X				
TW Outcome & Retreat Decision										X <sup>q</sup>		
Physiologic Brain Activity									X			
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

**Table 2: Schedule of Assessments for Protocol 547-SSE-301: Two Infusions of Study Drug (one blinded, one open-label)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V3R
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	0-24h
Eligibility Checklist	X										S
Informed Consent <sup>a</sup>	X										E
Inclusion/Exclusion Criteria	X										E
Demography <sup>b</sup>	X										
Medical and SE and Wean History <sup>c</sup>	X										T
Height	X										A
Weight <sup>d</sup>	X		X	X	X	X	X	X			B
Serum Pregnancy Test <sup>e</sup>	X										L
Hematology <sup>f</sup>	X		X	X		X		X		X	E
Serum Chemistry and GFR <sup>f</sup>	X		X	X		X		X		X	
Urinalysis <sup>h</sup>	X		X	X		X		X		X	E
Pharmacogenetic sample	X										X
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X	T
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X	E
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X		N
STESS	X										I
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	O
Glasgow Outcome Score (GOS)											N
Supervision Rating Scale (SRS)	X <sup>n</sup>										
Modified Rankin Score (mRS)	X <sup>n</sup>										
Epilepsy Status	X										N
Clinical Global Impression (CGI)	X										E
Continuous IV Third-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>o</sup>			X
EEG	X	X				X		X	X		T
Randomization		X									
Study Drug Administration <sup>p</sup>			X	X	X	X	X	X			
TW Outcome and Retreat Decision										X <sup>q</sup>	P
Physiologic Brain Activity									X		
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X	A
Concomitant Anti-Epileptic Drugs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	G
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	E
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X	
Pharmacoeconomic Data											
Mortality											

Table 2 continued

	V3R	V4R	V5R	V6R	V7R	V8R	V9R	V10R	V11R	V12R
	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3R+14d (±2d)	V3R+21d (±2d)
Weight <sup>d</sup>	X	X	X	X	X	X				
Serum Pregnancy Test <sup>e</sup>										
Hematology <sup>f</sup>	X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X	X		X		X		X		
Vital Signs <sup>i</sup>	X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>	X	X	X	X	X	X	X			
STESS										
FOUR Score <sup>m</sup>	X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)										X
Supervision Rating Scale (SRS)										X
Modified Rankin Score (mRS)										X
Epilepsy Status										X
Clinical Global Impression Scale (CGI)										X
Continuous IV Third-Line Agent(s)	X	X	Wean	Wean	Wean	Wean <sup>o</sup>				
EEG			X			X	X			
Randomization										
Study Drug Administration <sup>p</sup>	X	X	X	X	X	X				
TW Success and Physiologic Brain Activity							X			
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data										X
Mortality										X

**Table 3: Schedule of Assessments for Protocol 547-SSE-301: Qualifying Wean Successes**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical and SE and Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X											
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X											
Serum Chemistry and GFR <sup>f</sup>	X											
Urinalysis <sup>h</sup>	X											
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X											
ECG <sup>j</sup>	X											
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>n</sup>											X
Modified Rankin Score (mRS)	X <sup>n</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV Third-Line Agent(s)	X	Wean										
EEG	X	X										
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

<sup>a</sup> Written informed consent by proxy (LAR) and closest relatives will be obtained prior to starting any study-related procedures not considered standard of care.

<sup>b</sup> Demographic information will be obtained by proxy and confirmed by the subject when possible.

<sup>c</sup> Medical history will be obtained by proxy and confirmed by the subject when possible. All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Dosing changes with the third-line agent(s) that constitute a wean attempt will be marked as such on the CRF, and the start/stop dates and times of all wean attempts prior to V3 will be recorded, as well as the outcome of the wean attempt.

- <sup>d</sup> Weight will be collected at Screening (V1) and once during each 24 hour period of the initial study drug infusion period (V3-V8) and second infusion period (V3R-V8R, if applicable). Daily weight will be used to determine the appropriate infusion rate of each dose.
- <sup>e</sup> Serum pregnancy test for females aged 18 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy.
- <sup>f</sup> Blood samples will be taken for hematology and serum chemistry and GFR calculation at V1, at 24, 48, 96, 144 and 192 hours ( $\pm$  2 hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will document whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.
- <sup>g</sup> Blood samples will be taken at V11 or V11R for serum chemistry (renal panel only).
- <sup>h</sup> Urine samples will be taken for urinalysis and NAG at V1, at 24, 48, 96, 144 and 192 hours ( $\pm$  2 hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will add a comment about whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.
- <sup>i</sup> Vital signs will be recorded at the following time points relative to the start of each infusion of study drug: Screening (V1), at 0, 30, 60 minutes ( $\pm$  15 minutes), at 2, 4, and 8 hours ( $\pm$  30 minutes), and at 24, 48, 72, 96, 120, 144, 168, and 192 hours ( $\pm$  2 hours).
- <sup>j</sup> ECG (12-lead) should be performed at Screening (V1) and at the following times relative to the start of study drug infusion. For the blinded (first) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 128, 136, 144, 152, 160, and 192 hours ( $\pm$  2 hours). For the open label SAGE-547 (second) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 126, 132, 138, 144, 152, 160, and 192 hours ( $\pm$  2 hours). Heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours.
- <sup>k</sup> Plasma will be collected to assay for study drug concentrations at the following time points relative to the start of each infusion of study drug: For the blinded (first) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion. For the open label SAGE-547 (second) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open label SAGE-547 study drug infusion. Pre-dose samples may be taken within two hours before starting the infusion of study drug; timepoints up to and including 1h will have a time window of  $\pm$  5 minutes; all other timepoints will have a window of  $\pm$  15 minutes.
- <sup>m</sup> FOUR Score assessments will be performed at Screening (V1), 24, 48, 72, 96, 120, 144, 168, and 192 hours (all  $\pm$  2 hours) relative to the start of each infusion of study drug, and at V11 or V11R, and at V12 or V12R.
- <sup>n</sup> SRS at V1 will be a retrospective assessment of the supervision required by the subject immediately prior to admission that includes the index episode of the SE, and mRS at V1 will be a retrospective assessment of the disability and dependence of the subject immediately prior to admission that includes the index episode of the SE.
- <sup>o</sup> Target for complete wean of all continuous IV third-line agents by 144 hours at V8/V8R if not completed by 120 hours at V7/V7R.
- <sup>p</sup> Study drug infusion is intended for IV administration only with a dedicated peripheral IV line using Sage-approved IV administration bags and lines.
- <sup>q</sup> At V10 only a decision to re-treat at a higher dose of SAGE-547 will be made by the Investigator if the continuous IV third-line agent wean has failed or the third-line agent requires re-introduction during V9. Subjects who become eligible for re-treatment at a higher dose of SAGE-547 will discontinue the planned visit schedule at V10, then repeat V3 (V3R) and all applicable subsequent visits.
- <sup>r</sup> AEs will be collected from the time Informed Consent is obtained and prior to the start of study-specific screening procedures not considered standard of care. Collection of AEs will continue throughout the study from V1 through V12 or V12R.
- <sup>s</sup> Subjects may enter the study on AEDs and be administered AEDs during the study. All Concomitant AEDs must be recorded on the CRF with details including date and time of starting/stopping each AED, the route of administration, changes in doses, and frequency of administration. Details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the CRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.
- <sup>t</sup> All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Details will include the name of the drug, the start/stop dates and times, and, after consent, the doses with start/stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

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**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
AE	adverse event
AED	anti-epileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the time-concentration curve
AW	additional weans
BDZ	benzodiazepine
BIEEG	blinded infusion electroencephalogram
BUN	blood urea nitrogen
CBC	complete blood count
CEEG	consent electroencephalogram
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
C <sub>max</sub>	maximum plasma concentration
C <sub>min</sub>	minimum plasma concentration
CNS	central nervous system
CRF	case report form
CSR	clinical study report
CYP2C9	cytochrome P450 enzyme involved in drug metabolism
DNR	do not resuscitate
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EEG	electroencephalogram
EIND	Emergency Use Investigational New Drug Application
EP	European Pharmacopeia
ESETT	Established Status Epilepticus Treatment Trial
FDA	Food and Drug Administration
FOUR	Full Outline of UnResponsiveness
GABA	$\gamma$ -aminobutyric acid
GABA <sub>A</sub>	$\gamma$ -aminobutyric acid-gated chloride channel

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GOS	Glasgow Outcome Scale
H	hour
HPLC	high performance liquid chromatography
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent to Treat
IV	intravenous
IVRS	Interactive Voice Randomization System
LAR	legally authorized representative
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent to Treat
mRS-9Q	Modified Rankin Score - 9Q
MS/MS	tandem mass spectrometry
nM	nanomolar
NMDA	n-methyl-D-aspartic acid
OW	other weans
PAEEG	primary endpoint electroencephalogram
PD	pharmacodynamics
PK	pharmacokinetic
QOL	quality of life
QW	qualifying wean
QWEEG	qualifying wean electroencephalogram
RBC	red blood cell

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
RSE	refractory status epilepticus
SAE	serious adverse event
SAP	Statistical Analysis Plan
SE	status epilepticus
SOP	standard operating procedure
SRS	Severity Rating Scale
SRSE	Super-refractory status epilepticus
SSRI	Selective serotonin re-uptake inhibitors
STESS	Status Epilepticus Severity Score
SUSAR	Suspected Unexpected Serious Adverse Reactions
SWFI	Sterile Water for Injection
TAEEG	taper electroencephalogram
T <sub>max</sub>	time at maximum plasma concentration
TW	terminal wean
TWEEG	terminal wean electroencephalogram
US	United States
USP	United States Pharmacopeia



### 3. INTRODUCTION AND RATIONALE

#### 3.1. Status Epilepticus

Status epilepticus (SE) is a life-threatening seizure condition in which the brain is in a state of persistent seizure triggered by neuronal hyperexcitability. The Neurocritical Care Society defines SE as one continuous unremitting seizure lasting longer than five minutes or recurrent seizures without regaining consciousness between seizures for greater than five minutes (Brophy, Bell et al. 2012). Common causes of SE include preexisting epilepsy, cerebrovascular disease (in adults), electrolyte and metabolic disturbances, anoxia, encephalopathies, head trauma, high fever (in children, especially in the first year of life) and drug or substance intoxication. SE is associated with substantial morbidity and mortality.

##### 3.1.1. Epidemiology of SE

Geography, sex, age, and race influence the epidemiology of SE, whose incidence has a bimodal distribution, peaking in infants/young children and the elderly (Hauser 1990; DeLorenzo, Pellock et al. 1995; Wu, Shek et al. 2002). The incidence of SE in the elderly population is at least twice that in the general population. Concurrent medical conditions often exist in the elderly population, which can complicate therapy and worsen the prognosis of SE (Chapman, Smith et al. 2001).

The annual incidence of SE in the US is generally quoted to be within the range of 18/100,000 to 61/100,000, based on a 19-year retrospective study in Rochester, Minnesota (Hesdorffer, Logroscino et al. 1998) and a 2-year prospective study in Richmond, Virginia (DeLorenzo, Pellock et al. 1995), respectively. Two studies from Europe give annual incidences of a similar magnitude, ranging between 9.9/100,000 and 15.8/100,000 (Coeytaux, Jallon et al. 2000; Knake, Rosenow et al. 2001). It is thus estimated that in the United States each year there are as many as 150,000 cases of SE (DeLorenzo, Pellock et al. 1995).

#### 3.2. Refractory SE

When a patient begins to seize, the emergency medical technician will administer a first-line intravenous (IV) benzodiazepine (BDZ), such as diazepam, lorazepam or midazolam (Silbergleit, Durkalski et al. 2012), which is done either at the scene of the seizure or in the ambulance. If this is unsuccessful at abating the seizure, additional doses of the first-line therapy will be administered in the emergency room. Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line therapy, which is an IV anti-epileptic drug (AED) such as phenytoin or valproic acid (Novy, Logroscino et al. 2010; Shorvon 2011; Hocker, Britton et al. 2013).

Approximately 20-30% of patients refractory to first-line treatment will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to approximately 70-80% of patients who receive second-line therapy refractory to that therapy.

If a patient's SE continues after administration of BDZs and AEDs, the subject is diagnosed as having refractory status epilepticus (RSE), which must be treated quickly to terminate the seizure activity, maintain the patient's airway, and prevent cerebral damage. RSE patients are immediately admitted to the Intensive Care Unit (ICU) and placed in a medically-induced coma to stop all seizure-related activity. The drugs used to induce coma are continuously-infused IV agents,

commonly propofol, midazolam, or pentobarbital/thiopental, referred to as third-line agents (Brophy, Bell et al. 2012).

The RSE patient is continually monitored using electroencephalography (EEG) to ensure burst suppression is achieved. Burst suppression is a pattern of brain waves seen on an EEG, characterized by periods of activity alternating with periods of little or no activity in the brain, informing medical personnel of the effectiveness of the medically-induced coma. The goal of burst suppression is to allow the brain and corresponding neuronal tissue to restore function and reset to normal pre-seizure levels.

### 3.2.1. Epidemiology of RSE

Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line AED therapy. In turn, approximately 20 – 30% of these patients treated with AEDs will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to 28% of the total estimated SE patient population refractory to second-line therapy. Based on the previously-cited estimated incidence in the US, this means that there are up to 42,000 incident cases of RSE in the USA, annually (DeLorenzo, Pellock et al. 1995).

### 3.3. Super-refractory SE

After 24 hours of burst suppression, the patient is weaned off of the third-line therapy. If the weaning is unsuccessful (neuronal activity has not returned to normal), the third-line agent is re-administered or a different third-line agent is started, and the patient is considered to be in super-refractory status epilepticus (SRSE) (Chapman, Smith et al. 2001; Shorvon 2011; Brophy, Bell et al. 2012). SAGE-547 is being developed as an adjunct to third-line therapy in patients in RSE who have failed standard treatment. In this protocol, the term “RSE that has failed standard treatment” is deemed to be equivalent to the term “SRSE” and the two may be used interchangeably.

#### 3.3.1. Epidemiology of SRSE

The incidence of SRSE is very poorly understood, mainly because the diagnostic codes used for SE do not generally differentiate its nature as responding or refractory to treatment. Based on the variable reporting of outcomes data, the incident cases of SRSE could represent between one and two-thirds of the RSE patients (Novy, Logroscino et al. 2010; Ferlisi and Shorvon 2012; Hocker, Britton et al. 2013; Sutter, Marsch et al. 2013). More detailed epidemiology studies are needed to better elucidate the proportion of RSE patients whose condition becomes super-refractory. A recent review of ICU discharge data in the USA suggests an annual incidence of approximately 35,000, based on patients who required at least three days in the ICU for SE [Sage data on file].

#### 3.3.2. Outcomes of SRSE

SE has varying degrees of mortality depending on the underlying etiologies. Table 4 outlines the acute mortality in patients with SE by etiology (Neligan and Shorvon 2010). The mortality rate of SRSE is estimated to be 30% to 50% using current standard of care.

The causes of death from SE (and therefore SRSE) are heterogeneous, resulting from neuronal cell death, complications of underlying medical conditions, or adverse effects of the current standard treatments. Prognosis worsens and mortality increases with longer duration of SE, i.e. with SE that develops into RSE or SRSE (Neligan and Shorvon 2010), and with longer duration of

medically-induced coma ([Ferlisi and Shorvon 2012](#)). There is an obvious unmet medical need to improve upon the current standard of care treatment regimens.

Morbidity is high and survivors have outcomes ranging from poor function to vegetative state ([Shorvon 2011](#)). Approximately one third of patients with RSE and SRSE will recover, but with chronic neurologic or other deficits ([Neligan and Shorvon 2010](#); [Hocker, Britton et al. 2013](#)). In all, it is estimated that less than 25-30% of all SRSE patients have a favorable functional outcome.

**Table 4: Approximate Mortality of Status Epilepticus in Different Etiologies**

Underlying Etiology	Associated Acute Mortality in Patients with SE (%)
Drug reduction/withdrawal, poor AED compliance, or low AED levels	0-10
Cerebrovascular Disease	20-60
Metabolic Disorders	10-35
Acute CNS Infection	0-30
Anoxia	60-100
Alcohol Abuse	0-10
Head Trauma	0-25
Drug Overdose/Toxicity	10-25
Brain Tumors	0-20
Cryptogenic/Idiopathic	5-20

### 3.3.3. Unmet Medical Need in Super-refractory Status Epilepticus

Treatment approaches for SRSE consist of diagnosis and treatment of underlying medical conditions, adding and changing anti-seizure drugs, and repeated attempts at weaning from IV anesthetic agents. Treatment of SRSE has three aims:

- to prevent excitotoxicity, which begins within 24 hours of SE onset;
- to prevent cerebral damage by initiating neuroprotective burst suppression;
- to prevent the complications of extended periods of anesthesia or unconsciousness ([Shorvon 2011](#)).

Currently, there are no therapies that have been specifically approved for RSE or SRSE. The primary drugs used to induce coma are continuously infused IV anesthetics such as propofol, midazolam, or pentobarbital/thiopental, known as third-line agents. Use of these drugs to control SRSE has only been studied in small retrospective reviews or small prospective studies without controls ([Hocker, Britton et al. 2013](#)) therefore there is no agreement on which drug is optimal nor on an optimal dosing regimen for the treatments that are used.

The most common adverse effect of the third-line agents is hemodynamic instability; in addition, they are not universally effective, with breakthrough seizures and withdrawal seizures requiring dose adjustments and changes in third-line agent(s). The drug thought to be most effective in SRSE, pentobarbital, is also associated with the most toxic adverse effect profile, comprising

decreased blood pressure and cardiorespiratory collapse (Claassen, Hirsch et al. 2002). The ability to wean patients successfully off the third-line agents as quickly as possible is therefore paramount, and an adjunct to SRSE treatment that enhances the success of the third-line agents and supports their successful weaning in a short timeframe would be an important addition to the therapeutic armamentarium. Preliminary clinical data show that SAGE-547 has been a successful adjunct to third-line therapy in this regard.

### 3.4. SAGE-547 Injection

Allopregnanolone is an endogenous, naturally occurring neuroactive steroid formed in the corpus luteum of the ovary, adrenal cortex and central nervous system (CNS) (Holzbauer, Birmingham et al. 1985; Paul and Purdy 1992; Ottander, Poromaa et al. 2005). It is a metabolite of progesterone created by the actions of 5- $\alpha$  reductase and 3- $\alpha$  hydroxy-steroid dehydrogenase. Allopregnanolone is a potent positive allosteric modulator of both synaptic and extra-synaptic GABA<sub>A</sub> receptors.

SAGE-547 Injection (allopregnanolone aqueous formulation in Captisol<sup>®</sup>) is being developed for the treatment of patients in RSE who have not responded to standard treatment. SAGE-547 Injection is a solution of 5 mg/mL allopregnanolone in Sterile Water for Injection (SWFI), USP and 250 mg/mL betadex sulfobutyl-ether sodium, NF. It is further diluted with Sterile Water for Injection, USP (SWFI) in IV bags to achieve an allopregnanolone concentration of approximately 1.67 mg/mL in an approximately isotonic solution and will be administered intravenously.

#### 3.4.1. Scientific Rationale for SAGE-547 in SRSE

Ineffective recruitment of inhibitory neurotransmission, together with excessive neuronal excitation, likely plays a role in the initiation and propagation of the electrical disturbance occurring in SE. GABA ( $\gamma$ -aminobutyric acid), the major inhibitory neurotransmitter in the central nervous system (CNS), is released from GABAergic neurons and binds to several types of GABA receptors (GABA<sub>A</sub>, GABA<sub>B</sub>, and GABA<sub>C</sub>) on target neurons. GABA<sub>A</sub> receptors are macromolecular proteins that form a chloride ion channel complex and contain specific binding sites for GABA and a number of allosteric regulators, including barbiturates, benzodiazepines, and some anesthetic agents. GABA receptor-mediated inhibition contributes significantly to the normal termination of a seizure (Kapur and Macdonald 1997). SAGE-547 is a positive allosteric modulator of the GABA<sub>A</sub> receptor.

The importance of terminating seizure activity as soon as possible is underpinned by a growing body of evidence from research and clinical observation that SE becomes more difficult to control as its duration increases. It has been postulated that this occurs due to a mechanistic shift from inadequate GABAergic inhibitory receptor-mediated transmission to excessive N-methyl-D-aspartic acid (NMDA) excitatory receptor-mediated transmission (Kapur and Macdonald 1997). As prolonged epileptiform bursting results in a reduction of GABA<sub>A</sub>-mediated synaptic inhibition, antiepileptic treatments which rely on enhancing intrasynaptic GABA<sub>A</sub> neurotransmission become less effective the longer SE continues.

Furthermore, the constitutive process of synaptic GABA<sub>A</sub> receptor internalization is accelerated by the increased neuronal activity associated with seizures. These findings suggest that the rate of GABA<sub>A</sub> receptor internalization is regulated by neuronal activity, and its acceleration contributes to the reduction of inhibitory transmission observed during prolonged seizures (Kapur and Macdonald 1997). Of note is that SAGE-547 binds to extrasynaptic as well as intrasynaptic GABA<sub>A</sub> receptors;

extrasynaptic receptors remain active with ongoing seizure activity, resulting in a putative mode of action for SAGE-547 in SRSE.

Status epilepticus induces cerebral damage that includes neuronal cell necrosis, gliosis, and network reorganization. The major cause of cell death in cerebral damage is excitotoxicity, which is initiated by glutaminergic receptor over-activation, causing calcium to flood the cell, thereby leading to apoptosis and necrosis. This process is initiated within a few hours of the start of seizure activity, and provides the medical imperative to terminate SE as quickly as possible. To prevent the consequences of the excitotoxicity cascade, it is recommended that anesthesia be initiated within 1-2 hours of onset of seizures at doses designed to induce EEG burst suppression ([Shorvon and Ferlisi 2011](#)).

### **3.4.2. SAGE-547 Clinical Program in the Treatment of SRSE**

The current SAGE-547 development program includes:

- an ongoing Phase 2 open-label trial, Study 547-SSE-201;
- this proposed Phase 3 randomized, double-blind, placebo-controlled trial, Study 547-SSE-301;
- a planned open-label, expanded access protocol, Study 547-SSE-302;
- a number of EINDs for SAGE-547 in patients with SRSE.

The designs of these studies are all similar, with a five to six day infusion of SAGE-547 (or placebo), during which time attempts are made to wean the subject off all third-line agents. In the Phase 3 studies, those subjects who cannot be weaned off third-line agents while being administered SAGE-547 (or placebo) will be eligible for a second open-label infusion of SAGE-547 at a higher dose, which is also being employed for the latter patients being enrolled in the Phase 2 study. Follow up of subjects is for 21 – 30 days after the first infusion of study medication.

### **3.4.3. Data from the SAGE-547 Development Program**

The data from 30 subjects included in the on-going clinical evaluation of SAGE-547 for the treatment of adults and children with SRSE clearly offers preliminary evidence that SAGE-547 could provide substantial and clinically significant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate. These subjects comprise 20 from the ongoing Phase 2 trial (71% success rate in 12/17 evaluable subjects) and 10 subjects who received EIND treatments (78% success rate in 7/9 evaluable subjects).

Successful therapy of SRSE has been defined as “the SE is completely controlled by the therapy, without breakthrough of withdrawal seizures, or discontinuation due to side effects or death during therapy,” ([Ferlisi and Shorvon 2012](#)). By this definition, which is in accord with the efficacy assessments used in the overall clinical evaluation of SAGE-547, 19 of the 26 (73%) subjects with SRSE who completed the SAGE-547 infusion were treatment successes. As data collection is ongoing, this information is preliminary and subject to change upon further monitoring.

Published reports on RSE and SRSE have stated mortality rate ranges from 35% to 65%. The underlying etiologies of SE in the 547-SAGE-201 study and EINDs are heterogeneous, and each one conveys a different risk of mortality and longer term morbidity. However, the death rate in subjects who have received SAGE-547, 6 out of 30 (20%) subjects, appears to be lower than the published

rates. None of the deaths were considered related to SAGE-547: brain tumor, organophosphate toxicity, respiratory failure, respiratory arrest due to ventilator support withdrawal, and breast cancer.

In the Phase 2 study, 20 SAEs (15 non-fatal) have been reported in 13 (65%) subjects, and of these 3 events in 2 subjects (10%) were considered by the investigator to be related to SAGE-547: pulmonary emboli and tracheostomy dehiscence/infection. The Sponsor did not consider these events to be related to SAGE-547, rather to the underlying disease states. Four of the 20 subjects (20%) experienced AEs considered possibly related to SAGE-547 by the investigator, namely moderate myopathy and severe pulmonary emboli in 1 subject, moderate tracheostomy dehiscence and tracheostomy infection in 1 subject, moderate thrombocytosis in 1 subject and moderate BUN, ALT and AST elevation in 1 subject.

Review of the most current safety data from 547-SAGE-201 reveals that there were changes in serum chemistry, hematology, and urinalysis during the study, but that none of those changes were assessed as related to SAGE-547. There were also no SAGE-547-related changes to vital signs.

Despite the heterogeneity in the underlying causes of SE, the ages of the subject, comorbidities, which normally complicate the treatment of SE, and the fact that all subjects had failed current standard of care treatment, a large majority of subjects had a successful therapy outcome, with discontinuation of all third-line agents and resolution of SE.

Refer to the Investigational Brochure for further information on the pre-clinical and clinical data supporting the use of SAGE-547 in SRSE.

### **3.5. Study Rationale - SAGE-547 in SRSE**

#### **3.5.1. Justification for the Control Group**

Although SAGE-547 has demonstrated extremely promising activity in subjects with SRSE, both in the Phase 2 study and during the EINDs, these have been open-label investigations with no control data for comparison. Generally in the literature there are few data describing the success rates of wean attempts of third-line agents, and few comparative data on the effectiveness of the three main third-line agents, propofol, pentobarbital/thiopental, and midazolam.

Several options for a control group in Study 547-SSE-301 were considered:

- No control group was thought to be unacceptable since there are no reliable published data on success rates in this population that could be used for broad comparisons;
- An active control was considered but found to be impractical since none of the third-line agents are approved for their use in SRSE, no standardized dosing regimens or treatment guidelines have been adopted for the management of SRSE, and clinicians were unlikely to agree which of the available third-line agents would be reserved for the active control arm;
- Historical controls were considered but abandoned because of the practical difficulties of obtaining high quality data, the lack of ability to prospectively match cases, and a suspicion that clinical practice in the standard of care of SRSE is evolving, mandating the use of prospective, concurrent control data;
- Comparison to standard of care alone was considered as a feasible design. However, in a field where no widely adopted treatment guidelines exist, there was a concern that knowledge of the treatment group (SAGE-547 plus standard of care versus standard of care



alone) would alter the behavior of the investigators such that they could be more aggressive with weaning in the SAGE-547 group;

- Placebo control is not without its challenges since the preliminary efficacy data for SAGE-547 show that the compound exerts central pharmacological effects and is associated with positive outcomes in around 70% of patients. There is therefore a potential ethical concern about administering placebo to desperately ill patients who have often exhausted all treatment options for SRSE. This concern has been addressed in two ways: firstly all patients receive current standard of care; secondly, all subjects who fail to be weaned from their third-line agents at the end of the blinded infusion of study drug will be administered open-label SAGE-547 without un-blinding their initial treatment allocation, so treatment with the investigational product is not denied, but delayed about a week in the setting of ongoing receipt of full current standard of care.

It was therefore decided that a blinded, placebo-controlled design was appropriate for Study 547-SSE-301.

### **3.5.2. Justification for the Dose Regimen**

The standard dose regimen has been studied in 19 subjects in the 547-SSE-201 Phase 2 trial; the average peak plasma concentration of SAGE-547 at the end of the loading dose was approximately 144 ng/ml. The average plasma concentration during the maintenance infusion was approximately 70 ng/ml. At these concentrations, there were no clear safety signals although two-thirds of subjects experienced an SAE and there were four deaths, all related to the underlying comorbid conditions. The standard dosing regimen was associated with an approximate 70% successful treatment outcome. For these reasons, the standard dosing regimen has been adopted for the initial SAGE-547 infusion to be compared in a blinded fashion to placebo.

In the 547-SSE-201 trial, three subjects have thus far received the higher dose regimen. This dose regimen has also been well tolerated. The average peak plasma concentrations at the end of the loading dose for both dosing regimens will be in the same range, as the loading dose is the same for both regimens. The average plasma concentrations observed during the higher maintenance dose are 102 ng/ml (n=2). The rationale for adopting the higher dose regimen as the open-label infusion of SAGE-547 for subjects who are retreated in this 547-SSE-301 trial is that those who fail on the standard SAGE-547 dose regimen are afforded the opportunity to have access to a higher dose. The justification to also administer the higher dose regimen to failures on placebo is that the regimen has thus far been well tolerated, and this methodology preserves the blind for the initial infusion.

A five-day dosing regimen with SAGE-547 was investigated in the Phase 2 study, 547-SSE-201. There were some cases when weaning off all third-line agents was not possible within 48 hours, but weaning was completed after the end of the infusion of SAGE-547. For this reason, the duration of dosing with SAGE-547 has been increased from 120 hours (five days) in Phase 2 to 144 hours (six days) in this Phase 3 study.

### **3.5.3. Rationale for Genetic Testing Sub-study**

Sage Therapeutics intends to perform genetic research in the SAGE-547 development program in order to explore how genetic variations may affect the metabolism and activity of SAGE-547. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials, and, possibly, to genetically-guided

treatment strategies for optimizing decision making with respect to individual benefit:risk. Participation of subjects in genetic research as part of the overall clinical study is optional.

### **3.6. Benefit-Risk Evaluation of the Present Study**

Previous reports of human administration of exogenous allopregnanolone indicate that for exposures in men and women up to 150 nM, the most commonly reported AEs were sedation (recorded as sleepiness or tiredness), feelings of intoxication (like alcohol), flushing, and mild headache (Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007). No SAEs were reported (Navarro, Kaddouz et al. 2003; Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007; Kask, Backstrom et al. 2008; Kask, Backstrom et al. 2009; Timby, Hedstrom et al. 2011a). In view of the reduced consciousness and sedation of study subjects at entry into this protocol, none of these previously-reported events are likely to impact subjects in this study.

To date, in the SAGE-547 Phase 2 study and the EIND subjects, a majority of subjects demonstrated a successful therapy outcome (>70%). The majority in the clinical trial (65%) have also experienced SAEs, but none has been considered related to SAGE-547 by the Sponsor (SAEs in 2 subjects (10%) were considered possibly related by Investigator). Five deaths have been reported in 30 subjects (20%), all related to the underlying cause of SRSE and not related to SAGE-547 – this is in the context of published mortality rates between 35% and 65%. These preliminary data suggest that SAGE-547 has the potential to provide clinically relevant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate.

The underlying etiologies of SE are heterogeneous, and each one conveys a different risk of mortality. Subjects who survive SRSE still have a high risk of severe morbidity (Neligan and Shorvon 2010). The subjects treated with SAGE-547 in Study 547-SSE-201, are heterogeneous in factors such as age and etiology of SE, factors that usually complicate treatment and can increase morbidity and mortality. Even with this heterogeneity, the preliminary efficacy and safety data for SAGE-547 are very encouraging, and the mortality rate suggests that the risk to benefit assessment of this treatment rests on the side of benefit.

## **4. ETHICS**

### **4.1. Institutional Review Board or Independent Ethics Committee**

This protocol will be reviewed and approved by the Institutional Review Board (IRB) where the study is conducted. The IRB will meet all FDA requirements governing IRBs (CFR, Title 21, Part 56).

### **4.2. Ethical Conduct of the Study**

The Sponsor, the Medical Monitor, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable ICH and GCP guidelines, and must also conduct the study in accordance with local regulations.

### **4.3. Subject Information and Informed Consent**

Subjects prospectively enrolled in this study will be unable to give consent. Therefore, consent will be given by proxy by a legally authorized representative (LAR) already appointed by the Court for their well-being, and closest relatives. According to Swedish Medicinal Products Act



(Läkemedelslagen 1992:859), consent will be obtained by both the LAR and the closest relatives of the patients. Only patients with a previously appointed LAR by the Court will be included in the study, providing also the closest relatives consent to the study. Written informed consent is required for each subject prior to any testing under this protocol not considered standard of care, including screening tests and evaluations. Should a subject gain the ability to sufficiently comprehend the situation and consent during the course of the study, written informed consent or verbal assent will be documented as required or recommended by the institution's IRB.

The form of consent to be obtained will depend on the condition of the subject as determined by the Principal Investigator. The informed consent form (ICF), as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50.

It is the responsibility of the Investigator to obtain consent and to provide the subject's LAR and closest relatives with a copy of the signed and dated informed consent form. The informed consent form for subject participation must also be available as part of the subject file for review by the site's dedicated study monitor or any authorized auditor of the Sponsor or regulatory authorities.

All ICFs used in this study must be approved by the appropriate IRB and by the Sponsor. The ICF must not be altered without the prior agreement of the relevant IRB and the Sponsor.

#### **4.4. Ethical and Regulatory Considerations for Pharmacogenetic Sub-study**

##### **4.4.1. Informed Consent for Pharmacogenetics**

The genetic component of this study is optional and subjects may participate in other components of the main study without having to agree to participate in the genetic component. If subject chooses to participate in the genetic component of the study, the subject or LAR and closest relatives must sign and date a specific consent form for the genetic component of the study in addition to the main study consent form. The principal investigator(s) is responsible for ensuring that consent is freely given and that the subject understands that they may discontinue from the genetic aspect of the study independent of their decision to remain within or withdrawal from the main study.

##### **4.4.2. Subject Data Protection Relative to Pharmacogenomics**

Sage Therapeutics will not provide individual genotype results to subjects, their family members, their general physician, their employer or any insurance company unless required to do so by law. While extra precautions will be taken to preserve confidentiality and to prevent genetic data from being linked to an individual's identity outside of a restricted access site, in certain exceptional situations (e.g. in case of a medical emergency or as a consequence of a specific regulatory need), certain individuals may see both genetic data and the personal identifiers of a subject; however in all cases a subject's medical information and genetic files will remain physically separated.

## **5. STUDY OBJECTIVES**

### **5.1. Primary Objective**

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult subjects

with SRSE, and for the response to endure at least 24 hours after cessation of the SAGE-547 or placebo infusion (primary response).

## **5.2. Secondary Objectives**

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in Clinical Global Impression Scale between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

## **5.3. Safety Objectives**

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

## **5.4. Other Objectives**

1. To evaluate the impact of retreatment with a higher dose of SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol<sup>®</sup> and identified SAGE-547 metabolite plasma concentrations;
3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;

4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;
6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS).

## **6. ENDPOINTS**

### **6.1. Primary Endpoint**

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### **6.2. Secondary Endpoints**

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) and to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### **6.3. Safety Endpoints**

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;

## 5. Mortality.

### 6.4. Other Endpoints

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who fail to respond to their randomized double blind treatment and are retreated with a higher dose of SAGE-547;
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS).

## 7. INVESTIGATIONAL PLAN

### 7.1. Overview of Study Design

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

[Figure 1](#) provides an overview of the study design and [Figure 2](#) gives the details of treatment and follow-up on the active treatment arm. Patients will follow one of three paths to entry to the study. The first path is for patients who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst suppression with a third-line agent. These patients will be consented for the study after admission to the intensive care unit, but before any third-line agents are administered for burst suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their LAR and closest relatives. Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours. Once burst suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The second path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst suppression pattern on the EEG. These patients may have

had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The third path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These patients may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR and closest relatives. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within six hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third line agent wean attempts prior to randomization (one vs two or more).

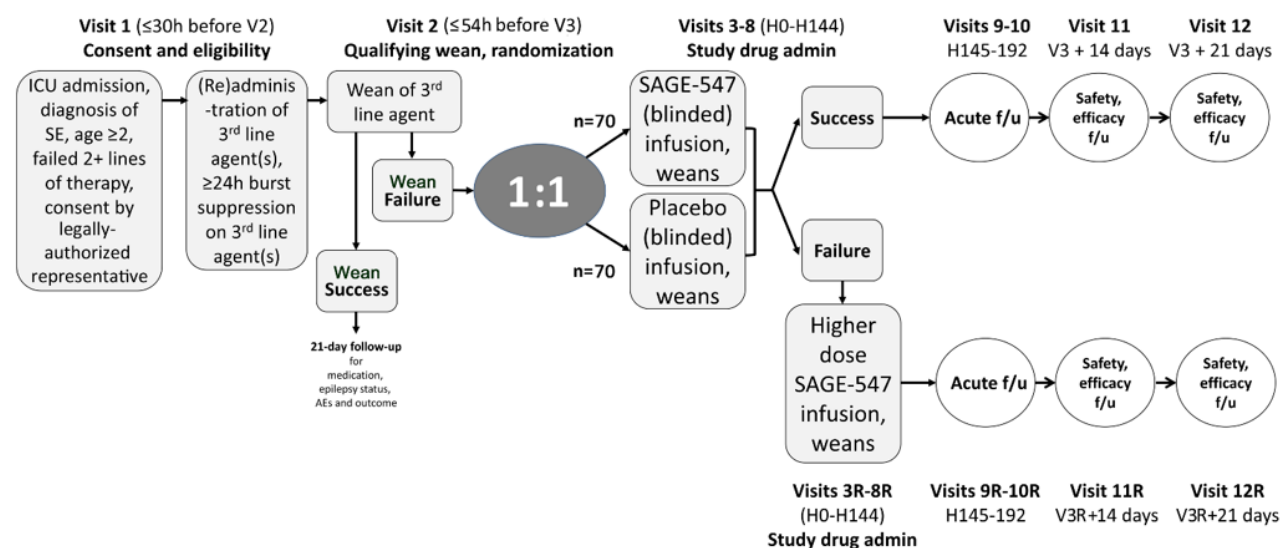
The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as the ability to wean the subject off all third-line agents before the end of the first infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication. Subjects must also have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) at the end of the primary endpoint assessment period as determined by EEG in order to be deemed a success. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#), [Table 2](#) and [Table 3](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. Eligibility for retreatment must be confirmed in writing by the medical monitor prior to the open-label infusion starting. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo will all subsequently be eligible to be administered SAGE-547 at the higher dose.

**Figure 1: Study Design**



## 7.2. Trial Conduct

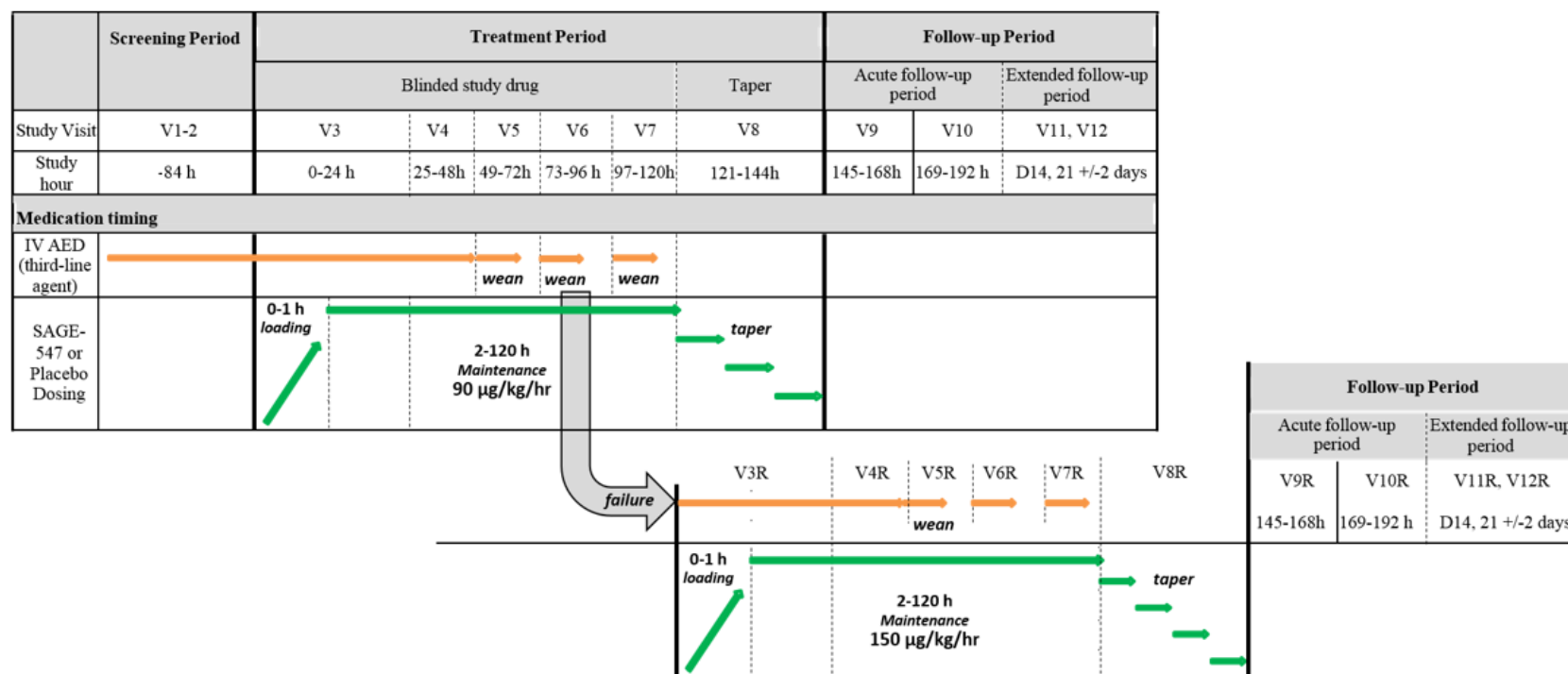
This study will be conducted according to the principles of the World Medical Association Declaration of Helsinki and most recent amendment, and in compliance with the protocol approved by the IRBs/Independent Ethics Committees (IECs), and in accordance with ICH Guidelines on GCP standards.

## 7.3. Blinding and Randomization

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo). Details of the dynamic randomization process will be included in the SAP.

The randomized portion of the study will be blinded, with the two treatment products (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

The second infusion of SAGE-547 will be administered on an open label basis to subjects who failed the primary endpoint wean.

**Figure 2: Details of Treatment Administration and Follow-up**

## 8. SELECTION AND WITHDRAWAL OF SUBJECTS

The study will randomize 140 patients at up to 180 sites. All subjects deemed eligible to enroll must have written Medical Monitor approval on a case-by-case basis prior to undertaking the qualifying wean.

### 8.1. Inclusion Criteria

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects 18 years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; *or* who have previously failed one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst suppression pattern; *or* who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst suppression pattern.

### 8.2. Exclusion Criteria

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy.
4. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis but for whatever reason, dialysis is not planned or non-continuous dialysis planned (that would not adequately remove Captisol<sup>®</sup>);
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. severe hepatic impairment;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the experience of the investigator, is less than 30 days;
  - e. a do not resuscitate (DNR) order.
5. Subjects who are being administered more than three third-line agents concomitantly or for whom the qualifying wean cannot be completed within 24 hours or who are being



administered a third-line agent for indications such as raised intra-cranial pressure that would preclude weaning according to this protocol.

6. Subjects with a living will that does not allow heroic measure.
7. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
8. Subjects who have been enrolled in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not withdraw or complete and then re-enroll).

### **8.3. Selection and Consent of Subjects for Pharmacogenetic Substudy**

All subjects will be asked to participate in pharmacogenetic research; however, participation in research is voluntary and a subject can decide to decline his/her participation without penalty or loss of benefit. Participation or lack thereof will not be a cause for exclusion from any aspect of the main study. In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **8.4. Subject Withdrawal / Study Termination**

#### **8.4.1. Withdrawal/Discontinuation of Individual Subjects**

The reasons for study drug discontinuation and/or subject withdrawal from the study must be recorded in the subject's electronic case report form (eCRF). The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject has been discontinued/withdrawn due to an AE.

##### **8.4.1.1. Withdrawal from the Study**

Subjects or their LAR may withdraw subjects from the study at any time for any reason without compromising the subject's medical care. The Investigator will also withdraw subjects upon the request of Sage Therapeutics or upon termination of the study.

Subjects who withdraw from the study prior to Visit 10 (or 10R) should complete the procedures scheduled for the day of study drug taper (hour 121-144; Visit8/8R) on the day of their withdrawal, including the SAGE-547 taper schedule, with the addition of the mortality assessment from Visit 12/12R. Subjects who withdraw from the study after Visit 10/10R should undergo study procedures as outlined for Visit 12/12R on the day of their withdrawal. In all cases, the reason for subject withdrawal will be recorded in the eCRF.

Withdrawal of subjects for any reason should be discussed with the Medical Monitor.

##### **8.4.1.2. Discontinuation of Study Drug**

If it is necessary to discontinue the study drug earlier than planned, subjects should continue to be followed per protocol to capture safety and efficacy assessments for the duration of the study period.

The investigator may withdraw the subject from the study drug for the following reasons:

- Upon subject's or LAR's request

- The subject or LAR is unwilling or unable to adhere to the protocol-specified visits
- The subject experiences an intolerable adverse event
- During the course of the study, the subject develops symptoms or conditions listed in the exclusion criteria.
- Other medical reason, at the discretion of the Investigator and/or the Medical Monitor

Subjects who discontinue the study due to an AE considered related to study drug should be followed until the event is resolved, considered stable, or the Investigator determines the event is no longer clinically significant. Study drug discontinuation due to AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

#### **8.4.2. Study Termination**

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of AEs or other findings suggesting unacceptable risk to subjects, administrative or operational reasons. In the event of study termination, Sage Therapeutics will provide written notification to the Investigator. Investigational sites must promptly notify their IRB and initiate withdrawal procedures for participating subjects.

## **9. INVESTIGATIONAL PRODUCT**

### **9.1. Identity of Investigational Product**

SAGE-547 Injection (allopregnanolone)

### **9.2. Clinical Supplies**

#### **9.2.1. SAGE-547**

Adequate supplies of SAGE-547 Injection and materials for intravenous administration will be provided to each site.

SAGE-547 Injection is a clear, colorless sterile solution of allopregnanolone intended for intravenous injection. SAGE-547 Injection is an aqueous solution of 5 mg/mL allopregnanolone in 250 mg/mL Captisol® (betadex sulfobutyl-ether sodium, NF). It is presented either un-buffered or buffered with 10 mM citrate at a pH of 6.0 in either 20 mL or 50 mL vials. SAGE-547 is further diluted according to the Pharmacy Manual to achieve an approximately isotonic solution and will be administered intravenously.

No preservatives are included in the drug product, which is intended to be used as a single-use vial. All inactive components (excipients) used in the formulation are compendial grade and conform to current USP/EP, and include sodium citrate, citric acid and betadex sulfobutyl-ether sodium (Captisol®).

#### **9.2.2. Placebo**

Placebo will be identical to SAGE-547 and presented in identical vials. Placebo will be manufactured in a similar way to SAGE-547 and comprises all excipients but no SAGE-547.

### **9.2.3. Blinding**

The vials of SAGE-547 and placebo will be identical in every way so that they are indistinguishable by the pharmacist, investigator, anyone treating or managing the patient, the monitors, and the sponsor. In this way the first infusion of study drug administered to each patient will be double-blind.

For the blinded study drug infusions, subject-specific dosing kits will be provided. These dosing kits will be pre-labelled with kit number for the first blinded infusion. For the second-infusion, open-label kits will be provided, which will require subject assignment by the pharmacy for reconciliation purposes. The study kits must be stored under refrigerated conditions (2-8 °C). IV administration bags and lines may be provided for the blinded and open-label infusions. Refer to the Pharmacy Manual for additional details.

The label for the SAGE-547 Injection vials will include standard product identification information according to the Code of Federal Regulations, 21CFR 312.6. All study labels will also contain the following statement:

Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use.

### **9.3. Preparation of SAGE-547 or Placebo Injection for Dosing**

The Pharmacy will be responsible for preparing the blinded and open-label study drug for subject dosing. The prepared admixture will be assigned a room temperature (20-25 °C) storage shelf life of 30 hours from time of compounding.

SAGE-547, which is hypertonic, will require dilution with SWFI to achieve an approximately isotonic solution according to the instructions provided in the Pharmacy Manual. Exactly the same procedures will be used to prepare the placebo admixture, so that all site staff remain blinded as to treatment allocation for the first infusion of study drug. SAGE-547 Injection is not intended to be administered to patients undiluted.

Refer to the Pharmacy Manual for specific instructions regarding infusion preparation.

### **9.4. Administration and Accountability**

The Pharmacy will maintain accurate records of all investigational product supplies. Accurate records will be kept regarding the volume of SAGE-547 Injection or placebo used for each IV preparation, as well as the required infusion rate or rates, and the date and time of preparation. Reasons for departure from the expected dosing regimen must also be recorded. To satisfy regulatory requirements regarding drug accountability, all study medication will be reconciled in full. Refer to the Pharmacy Manual for additional details.

## **10. TREATMENT OF SUBJECTS**

### **10.1. Dosing Schedule (Blinded Infusions)**

SAGE-547 Injection or placebo will be administered according to the dosing schedules in [Table 5](#). The infusion rates to accomplish these µg/kg/h doses will be calculated according to the weight of the subject. The infusion rates will be applied to blinded study drug for the first infusion of study medication.

**Table 5: SAGE-547 or Placebo Dosing Schedule**

Hour	Type and Duration of Study Drug Infusion	Description
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	90 µg/kg/h
H121 – H128	8 hour taper	65 µg/kg/h
H129 – H136	8 hour taper	45 µg/kg/h
H137 – H144	8 hour taper	25 µg/kg/h

## 10.2. Dosing Schedule (Open-Label Infusions)

If a subject fails wean from third-line agent(s) or requires re-instatement of third-line therapy within 24 hours of discontinuing the initial infusion of study drug, SAGE-547 Injection will be re-administered according to the dosing schedule in Table 6. The infusion rates to accomplish these µg/kg/h doses will be calculated according to the weight of the subject. These infusion rates will be applied to SAGE-547 re-treatment for the open-label second infusions of study medication.

**Table 6: SAGE-547 Open Label Dosing Schedule**

Hour	Type and Duration of SAGE-547 Infusion	Description
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	150 µg/kg/h
H121 – H126	6 hour taper	125 µg/kg/h
H127 – H132	6 hour taper	95 µg/kg/h
H133 – H138	6 hour taper	65 µg/kg/h
H139 – H144	6 hour taper	35 µg/kg/h

## 10.3. Route of Administration

SAGE-547 Injection is intended for IV administration only. The compatibility of SAGE-547 with other drugs is unknown, and the product should be administered via a dedicated peripheral IV line using any Sage-supplied study-specific IV administration bags and lines. In order to preserve blinding, these instructions also apply to the blinded placebo infusions.

## 10.4. Treatment Period

The treatment period with double-blind SAGE-547 or placebo is six 24-hour periods (144 hours), which may encompass 6-7 calendar days. The retreatment period is of identical duration.

## 10.5. Concomitant Medications, Procedures and Treatments

Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. All concomitant medications, procedures, and treatments should be documented throughout the study from Screening through Visit 12/12R and recorded on the eCRF.

SAGE-547 has demonstrated inhibitory effects on cytochrome P450 isoenzyme 2C9 (CYP2C9).

Therefore, AEDs such as phenytoin and phenobarbital that are primarily metabolized by CYP2C9 should be closely monitored during SAGE-547 administration to ensure target exposures are maintained. A list of drugs which are inhibitors/inducers of CYP2C9 (as well as CYP2C8, CYP2C19, CYP3A4, UGT2B7, and UGT2B17) is provided in Appendix 7. In the absence of formal drug-drug interaction studies of SAGE-547, Investigators should ensure that co-administration is performed with caution.

#### **10.5.1. Concomitant AEDs**

Subjects may enter the study on AEDs, and be administered AEDs during the study. All of these must be recorded on the eCRF with details including date and time of starting and stopping each AED, the route of administration, changes in doses, and frequency of administration. In addition, details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the eCRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.

#### **10.5.2. Concomitant Third-Line Agents**

All third-line agents (as defined in [Section 8](#)) administered since the diagnosis of SE will be recorded on the eCRF, whatever path the patient took for entry into the study. Details will include the name of the drug, the start and stop dates and times, and, after consent, the doses with start and stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

In addition, those changes in dose that constitute a wean attempt will be marked as such on the eCRF. In this way the start and stop dates and times of all wean attempts (see [Section 11](#) for definitions) will be recorded, as will the type of wean (QW, OW, or TW) and the outcome of the wean attempt (successful, failed and dose of this third-line agent increased or failed and this third-line agent stopped and another third-line agent started). Those wean attempts that occur after the TW up to and including Visit 12/12R will be marked “AW”.

Some third-line agents (such as propofol) are also used to induce sedation to facilitate a subject’s ability to tolerate the ventilator. For subjects requiring such sedation, propofol is the preferred agent unless there are contraindications. The eCRF will make clear from the indication for the third-line agent when it is being used for burst or seizure suppression and when it is being used as ventilator support or for another purpose. The investigator will add a note to the eCRF to justify that the doses used are appropriate for sedation and not for seizure or burst suppression. The doses used for ventilator support and other similar uses are usually much lower than those used for seizure or burst suppression, and use of these third-line agents for these other purposes does not constitute a wean failure under this protocol.

#### **10.5.3. Concomitant Pressors**

The start and stop dates and times of all pressors will be recorded as well as the start and stop dates and times of all dose changes.

#### **10.5.4. Other Concomitant Medications**

All other concomitant medications must be recorded on the eCRF with details including date and time of starting and stopping, the route of administration, dose, and frequency of administration.

## **11. STUDY ASSESSMENTS**

### **11.1. Efficacy Assessments**

#### **11.1.1. Primary Efficacy**

Success or failure will be determined, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo infusion and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the blinded (first) infusion of SAGE-547 or placebo. In addition, subjects must have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) to be deemed to be successes. All subjects who fail to complete their infusion of randomized treatment or do not have at least one attempt during study treatment to wean off all third-line agents will be considered as “failures” for the primary endpoint.

##### **11.1.1.1. Weaning**

Third-line agents are anesthetic agents that are administered in order to reach a seizure or burst suppression EEG pattern. For the purposes of this study, third-line agents are defined as continuous intravenous infusions of pentobarbital/thiopental, midazolam, propofol, and ketamine at maintenance doses alone or in combination sufficient to produce a burst suppression pattern on the EEG. The following are considered to be minimum maintenance doses of these agents that may be expected alone or in combination to achieve EEG burst suppression. If subjects are on lower doses than these and are not in EEG burst suppression for the 24 hours prior to the QW or the first 12 hours of the blinded study drug infusion, they will be considered to be screen failures/protocol violators and will exit the study.

- Pentobarbital: 1 mg/kg/hour
- Thiopental: 3 mg/kg/hour
- Midazolam: 0.1 mg/kg/hour
- Propofol: 3 mg/kg/hour
- Ketamine 1.2 mg/kg/hour

The timing and nature of the third-line agent weans will be guided by the Clinical Standardization Guidelines for the study, and the clinical judgment of the investigator, and will always be primarily done in the best medical interests of the subject. Advice about weaning may be sought from the Clinical Standardization Team, a group of fellow investigators with experience of performing clinical trials in subjects with SRSE. The Clinical Standardization Team will be able to discuss EEGs related to key study timepoints (qualifying wean, terminal wean, and the period after the end of the blinded study drug infusion if the terminal wean was successful) in a timely manner in order to provide advice about compliance with the Clinical Standardization Guidelines.

The following guidance for weaning applies to all weans of third-line agents undertaken during the study. These weans include the qualifying wean (QW); the terminal wean (TW), which is the wean of the third-line agent if the subject is on only one third-line agent or the wean of the last third-line agent if the subject is on more than one third-line agent; the other weans (OW), which are the weans of the third-line agents other than the TW if the subject is on more than one third-line agent. The guidance also applies to additional weans (AW), which are the weans from third line agents that take

place after the TW for the first blinded study drug infusion or the second open-label study drug infusion.

### **QW Guidance**

- Wean to be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace that third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Investigators should allow 24 hours to lapse after the end of a “successful” qualifying wean before finally declaring the QW a success. If a third-line agent needs to be re-instituted within that 24 hours, the QW is a failure, and the subject may then be randomized in the study.

### **OW Guidance**

- First OW should not begin before H49 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- If the subject is on two third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the TW. However the OW may be completed over a shorter or longer time period and may overlap if clinically indicated with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- If the subject is on three third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the wean of the second agent. The second agent should be weaned over 24 hours and that wean completed before starting the TW. However the OWs may be completed over a shorter or longer time period and may overlap if clinically indicated with each other and with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- All OWs should be completed before H96 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **TW Guidance**

- The TW is defined as the wean of the last third-line agent.
- If the subject is on one third-line agent, the TW should not begin before H49 and should begin no later than H97 after starting administration of study drug or starting the open-label infusion of SAGE-547. If the subject has had one or more OWs, the TW should ideally begin

as soon as the last OW is complete but in any case not later than H97 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

- The TW must be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace this third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Every effort must be made to complete the TW before H120 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547, but the TW must be complete before H144 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **AW Guidance**

- AWs will take place when medically indicated in the opinion of the investigator.
- Ideally the AW should take place over 24 hours, but completion may be over a shorter or longer time period than this. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.

### **11.1.1.2. EEG**

Electroencephalographs (EEGs) that are representative of the intermittent or continuous EEG being used to support key investigator decisions will be collected at the following time points:

- A 24-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst suppression for the second path to eligibility, and a variable pattern for the third path to eligibility. This EEG will capture as much as possible of the burst suppression pattern that precedes the QW.
- EEG will be performed to cover the qualifying wean (QWEEG). EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for up to 24 hours after the end of the QW. The duration of the QWEEG will be up to 48.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s), the decision to re-institute a third-line agent(s) at doses intended to induce burst suppression, and the decision that the QW is a success.
- EEG will be performed from three hours prior to the start of the blinded infusion to 12 hours after the start of the blinded infusion. This will be called the BIEEG. The intent of this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG and to assess the depth of burst suppression in the first 12 hours of blinded study drug infusion.



- EEG will be performed to cover the final or terminal wean of third-line agent (TWEEG). The TW is the wean of the final third-line agent during the blinded administration of study drug or the open-label infusion of SAGE-547; if the subject was on one third-line agent, the TW is the wean of that agent. If the subject was on three third-line agents, the TW is the wean of the third and final agent. EEG recording will start 30 minutes prior to the start of the TW, continue for up to 24 hours during the TW, and then continue for the one hour after the end of the TW. The duration of the TWEEG will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the final third-line agent or the decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity could not be managed using intermittent bolus doses of AEDs.
- EEG will be performed during the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 (TAEED). The TAEED is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the start of the taper (at Hour 119.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours during the taper, and then continue for the one hour after the end of the taper (to Hour 145 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547). The duration of the TAEED will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity seen during the taper could not be managed using intermittent bolus doses of AEDs.
- EEG will be obtained to cover the end of the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 and the ensuing 24-hour period, during which the primary endpoint is assessed (PAEED). The PAEED is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the end of taper (at Hour 143.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours after the end of the blinded administration of study treatment or the open-label infusion of SAGE-547, and then continue for the one hour after the end of the 24-hour assessment period (to Hour 169 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547). The duration of the PAEED will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity seen in the 24 hours following the end of the blinded administration of study treatment or the open-label infusion of SAGE-547 that could not be managed using intermittent bolus doses of AEDs.

In practice, most subjects are on continuous EEG monitoring or long periods of intermittent EEG monitoring. However, this protocol does not mandate continuous EEG monitoring and breaks from EEG monitoring to provide relief to the scalp from the irritating effects of the electrodes are advised according to local practice. If a break in EEG monitoring is mandated by local practice guidelines at a time when one of the protocolled EEG segments is to be collected, the break in EEG monitoring will take precedence, with the reason for missing the EEG reading noted on the eCRF. The EEGs obtained for the study are therefore part of the existing EEG record rather than being obtained de-novo at each timepoint. For timepoints where there might be some ambiguity, such as the TWEEG,

the final EEG record is that of the final attempt to wean the last third-line agent, even if earlier attempts to wean that agent took place. In some cases (the TAEED and PAEEG, for instance), the EEG records will overlap, but different cuts are taken to service the different EEG record requirements.

The electronic EEG file will be de-identified, the date and time of the start and stop of the EEG and the subject number will be attached to the file, and the study time point will be indicated (CEEG, QWEEG, BIEEG, TWEEG, TAEED, and PAEEG). The PI will indicate on the eCRF what the EEG shows, as follows:

- For the CEEG, the PI will describe the EEG pattern that determined which path to eligibility the subject was on.
- For the QWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure or success on the qualifying wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the qualifying wean constitutes a failure); the QWEEG will extend to cover the 24 hours after the end of third line agents in order to confirm that the QW was a success.
- For the BIEEG, the PI will note the date and time of the start of the EEG and the pattern seen on the EEG.
- For the TWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure on the terminal wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the terminal wean).
- For the TAEED, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst suppression before the end of the SAGE-547 infusion).
- For the PAEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst suppression in the 24 hours following the end of the SAGE-547 infusion).

A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm the depth of burst suppression prior to the QW and during the first 12 hours of the blinded study drug infusion, the PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period (average EEG power at the end of Visit 9 of more than two microvolts):

- All subjects will have the CEEG and QWEEG collected and stored, and the CEEG and QWEEG read;
- Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;

- Those subjects randomized who are not retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the BIEEG, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read;
- Those subjects randomized who are retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion and the TWEEG, TAEED, and PAEEG related to the open-label study drug infusion collected and stored, and the BIEEG, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read.

All EEG records may be subject to quantitative EEG analysis.

### **11.1.2. Secondary Efficacy**

#### **11.1.2.1. Clinical Global Impression Scale (CGI)**

The clinical global impression scales are often utilized in clinical trials to allow clinicians to integrate several sources of information into a single rating of the subject's condition. Both the CGI-Severity (Question 1, CGI-S) and the CGI-Improvement (Question 2, CGI-I) employ a 7-point Likert scale measuring severity of the disease state in the subject and improvement, respectively. All severity assessments after initiation of SAGE-547 treatment should consider the general state of the subject over the preceding week. The third question on the scale will not be employed in this trial, and where the scale states "mental illness", this means "physical illness" in this trial.

The CGI-S will be evaluated at Visit 1 and at the last visit, Visit 12 or 12R. The CGI-I will be evaluated at Visit 12 or 12R.

#### **11.1.2.2. Epilepsy Status**

At Visit 1, the diagnosis of epilepsy will be documented as a no/yes question. If there was a previous diagnosis of epilepsy, further details will be documented, including:

- Date of diagnosis;
- Details of anti-epileptic drugs currently being taken;
- Type of epilepsy;
- Seizure frequency in the past month.

Information about the current (index) episode of status epilepticus will be obtained at Visit 1:

- Date of onset
- Date of failure to respond to first line agent(s) and the name(s) of the agent(s)
- Date of failure to respond to second line agent(s) and the name(s) of the agent(s)
- Any previous treatment with third line agents and the response to those agents (details of the third line agent drugs and previous wean attempts will be recorded on the Third Line Agent Medication CRF)
- The cause of the index episode of status epilepticus
- If the subject was transferred from another hospital or from within the hospital, the reason for the transfer will be recorded (such as for study enrollment, due to lack of medical options)

at original hospital or unit, due to lack of beds at the original hospital or unit, family request, other)

Previous (non-index) diagnosis of status epilepticus will be documented as a no/yes question. If SE did occur in the past, further information will be gathered, including:

- SE, RSE, or SRSE diagnosis, whichever was the most severe diagnosis for each episode;
- Cause;
- Treatment, including experimental treatments and need for intubation/ventilation;
- Dates of onset and duration if the episode of status epilepticus occurred in the past 12 months.

At Visit 12 or Visit 12R, the following information will be gathered:

- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of SE up to and including Visit 12 or Visit 12R;
- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of seizures (convulsive and non-convulsive) up to and including Visit 12 or Visit 12R;
- Number of separate episodes of SE after H144 at the end of Visit 8 or Visit 8R (no/yes); if yes,
  - SE, RSE, or SRSE diagnosis;
  - Cause;
  - Treatment, including experimental treatments and need for intubation/ventilation;
  - Dates of onset and duration.

Note that a separate episode of SE is defined as an episode of SE separated from other periods of status epilepticus by at least 24 hours.

- Diagnosis of epilepsy since Visit 11 or Visit 11R will be documented as a no/yes question. If a diagnosis of epilepsy has been made, further details will be documented, including:
  - Status as ongoing or new epilepsy since Visit 11 or Visit 11R after initiation of SAGE-547 treatment;
  - Details of anti-epileptic drugs currently being taken;
  - Type of epilepsy and seizure frequency in the past week.

## **11.2. Safety Assessments**

The safety and tolerability of SAGE-547 will be assessed using adverse events, clinical laboratory measures, vital signs, ECG intervals and morphology, and mortality. All safety assessments should be performed per hospital standard of care and will be collected periodically throughout the study according to [Table 1](#), [Table 2](#), and [Table 3](#) (Schedules of Assessments).

### **11.2.1. Adverse Events**

AEs will be collected after informed consent has been signed and prior to study-specific screening procedures not considered standard of care, during subject preparation for SAGE-547

administration and through Visit 12 or Visit 12R. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™) coding system (current version). See [Section 14](#) for additional details.

### **11.2.2. Clinical Laboratory Tests**

Blood samples will be taken for hematology, and serum chemistry and GFR will be calculated at:

- Visit 1 and then at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.
- Blood samples will be taken at Visit 11 or Visit 11R for serum chemistry (renal panel only).

Urine samples (20 ml) will be taken for urinalysis and urine NAG analysis at:

- Visit 1 and at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.

These samples will be analyzed at a central laboratory; hour-to-hour medical decisions will be based on sampling for laboratory testing done outside the protocol as part of normal standard of care. GFR will be calculated by the central laboratory.

Any out-of-range values will be flagged by the laboratory; the investigator will add a comment about whether the abnormality is clinically significant. Clinical significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

#### **11.2.2.1. Hematology and Serum Chemistry**

Hematology will include complete blood count (CBC) white blood cell count with differential, platelet count and red blood cell (RBC) count, hemoglobin and hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose. In addition triglycerides will be measured in serum chemistry samples (to aid assessment of lipemia in pharmacokinetic samples).

#### **11.2.2.2. Pregnancy Test**

Females of child-bearing potential will be tested for pregnancy by serum pregnancy test at Visit 1. In this study, since an accurate history of menstruation in girls and menopause in older women may not be available at Visit 1, “child-bearing potential” is taken to mean any female aged 18 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy. Female subjects with a positive pregnancy test will be ineligible for study participation.

#### **11.2.2.3. Urinalysis**

Urinalysis will include assessment of protein, blood, leukocytes, glucose, ketones, urobilinogen, pH, and specific gravity.

### 11.2.3. Vital Signs

Blood pressure, heart rate, and temperature will be recorded at the following time points relative to the first infusion of study drug, and to the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547:

- Visit 1;
- At 0, +30, +60 minutes (+/-15 minutes) and +2, +4 and +8 hours (+/- 30 minutes) after the start of the infusion;
- At +24, +48, +72, +96, +120, +144, +168, and +192 hours (+/- 2 hours) after the start of the infusion.

### 11.2.4. Weight and Height

Weight and height will be measured at Visit 1 and weight will also be measured once during each 24 hour period of the first infusion of study drug, and of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547. These daily weights will be used to modify the dose of SAGE-547 if required. If it is not possible to weigh the subject daily, an actual weight must be obtained prior to starting the blinded study drug, and that weight used to calculate the dose of study drug to be administered. If this is not possible, permission from the Monitor must be obtained to use another method to obtain the subject's weight (such as information from the LAR or estimating using an established local protocol).

### 11.2.5. ECG

12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours; at other times the allowed time window for ECGs is +/- 2 hours:

- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +128, +136, +144, +152, +160, and +192 hours after the start of the blinded (first) study drug infusion
- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +126, +132, +138, +144, +152, +160, and +192 hours after the start of the open-label (second) study drug

The heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm.

### 11.2.6. Mortality

Mortality will be recorded on the Visit 12 or Visit 12R case report form. If the subject has died, the following information will be collected:

- Date of death;
- Cause of death.

As accurate as possible cause of death will be collected, which will be further categorized as due to one of the following causes:

- SE;
- complications of long term intubation and third-line agent infusions;

- underlying cause of qualifying SE;
- co-morbidity existing at the time of the qualifying SE;
- new co-morbidity or trauma;
- study drug;
- other (specify).

#### 11.2.7. Pharmacogenetic Samples

If a subject's LAR and closest relatives consent to pharmacogenetic sampling, a blood sample for genetic research will be collected at Visit 1 in order to avoid the possible introduction of bias through the exclusion of patients who may withdraw from study due to an AE (a subject population that may be of specific interest for subsequent genetic analysis). If for any reason a sample cannot be taken prior to treatment, a sample can be drawn at any point prior to completion with the restriction that no more than one genetic sample be taken per subject.

The objective of this research is to collect and store blood samples for possible DNA extraction and exploratory research into how genes or specific genetic variation may influence response (i.e. distribution, safety, tolerability, and efficacy) to SAGE-547. Specific genetic variations of interest include but are not limited to: classes of metabolizing enzymes (e.g. Cytochrome P450 supra-family genes), genes encoding enzymes involved in the production and metabolism of allopregnanolone (e.g. AKR1C4 (3 $\alpha$ -hydroxysteroid dehydrogenase)), genes associated with the GABA receptor (e.g. GABRA1-A6, GABRB1-B3, GABRD, GABRE, GABRG1-3) and genes associated with the production and degradation of GABA.

Future research may suggest other genes or gene categories as candidates for influencing not only response to SAGE-547 but also susceptibility to disorders for which SAGE-547 is being evaluated. Thus, the genetic research may involve study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.

##### 11.2.7.1. Biological Sampling and Coding Procedures (Pharmacogenetics)

To ensure patient confidentiality, utmost care will be taken in the coding and storage of pharmacogenetic samples.

*Extraction and coding:* DNA will be extracted from the blood sample and the DNA sample will be assigned a unique number replacing information from sampling tube. The assigned DNA number will be used to identify the sample and its corresponding information within Sage Therapeutics or at any designated contract laboratory for the purpose of sequencing of other DNA specific analysis. No personal details sufficient for individual identification will be available to any person (internal or external to Sage Therapeutics) working with the DNA.

*Genotype/Phenotype Analysis:* Samples and data from genetic analysis will be coded. The link between subject enrollment / randomization code and DNA number will be maintained and stored in a secure environment with restricted access. The established link will be used to identify relevant DNA samples for analysis, facilitated correlation of genotype results with clinical data, allow regulatory audit, and to trace samples for destruction in case of withdrawal of consent.

### 11.2.7.2. Retention of Biological Samples for Pharmacogenetic Analysis

Extracted DNA is a finite research that is destroyed in the process of being analyzed. Primary blood samples from which DNA can be extracted will be stored and used until no further analyses are possible, a maximum storage period of 25 years from time of last subject last visit has been reached, or an individual or LAR withdraws his/her or their consent.

### 11.2.8. Other Outcomes

#### 11.2.8.1. Pharmacokinetic Data

Formal plasma analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS)). In addition, all samples will be analyzed for important SAGE-547 metabolites (if and when these are identified) and Captisol® concentrations.

#### Plasma Analysis

Plasma will be collected to assay for SAGE-547 concentrations at the following time points relative to the start of each infusion of study drug:

- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion.
- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open label SAGE-547 study drug infusion.
- All samples will also be analyzed for plasma concentrations of important metabolites of SAGE-547 if and when these are identified.
- All samples will also be analyzed for plasma concentrations of Captisol®.

The plasma samples will be drawn from the arm contralateral to that used for drug administration. Drawing samples from peripheral arterial or venous lines or from a central line is permissible. PK collection times should be adhered to as strictly as possible. The allowed time window for all samples is: pre-dose in the two hours prior to starting the infusion of study drug; samples up to and including 1h, +/- 5 minutes; subsequent samples, +/- 15 minutes. Subject-specific PK kits for sampling including instructions on collection and processing methods, and storage and shipping conditions, will be provided separately. To maintain the blind, all subjects will have samples taken as outlined above: subjects receiving SAGE-547 will have all samples analyzed for all analytes. Subjects on placebo may have samples analyzed to investigate endogenous allopregnanolone and metabolite concentrations, as well as Captisol® concentrations; experience with the plasma concentration data will determine if and which placebo samples are analyzed.

Each blood sample will be 3 ml in volume for subjects weighing 30 kg or more, and 1 ml in volume for subjects weighing less than 30 kg. Separate aliquots will be obtained from each sample to service



the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum blood draw for PK analysis for a subject having two infusions of study drug will be 99 ml (33 ml for subjects weighing less than 30 kg).

Plasma PK parameters for SAGE-547 will be calculated where appropriate (e.g.,  $C_{max}$ ,  $C_{min}$ ,  $t_{max}$ ,  $AUC_{last}$ ,  $AUC_{\infty}$ ,  $CL_s$ ). In addition, similar PK parameters will be calculated for Captisol®. PK parameters for important metabolites of SAGE-547 may be calculated. An evaluation will be made of the feasibility of adopting a population-PK approach to assess drug-drug-interactions with SAGE-547 as victim of AEDs.

In addition, the Visit 9 sample may be analyzed for plasma concentrations of third-line agents.

#### Other Analysis

If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR and closest relatives will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations. The minimum volume of cerebrospinal fluid for analysis is 100 microlitres.

Full details of all pharmacokinetic analyses will be described in the Pharmacokinetic Analysis Plan.

#### **11.2.8.2. Correlation of QT/QTc Changes and Plasma Concentrations of SAGE-547**

An analysis will be performed to determine whether there is any correlation between changes in QT/QTc interval and plasma concentrations of SAGE-547, in order to investigate any effect that SAGE-547 may have on QT/QTc interval.

#### **11.2.8.3. Pharmacoeconomic Data**

At Visit 12 or Visit 12R, the following information will be collected: number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital. If the subject dies before Visit 12 or Visit 12R, data will be collected up to the date of death. The definition of “hospital” is the institution that the subject was initially treated in. If the subject is transferred to another hospital, that hospital would be the “discharge destination from the hospital” and the “number of days in hospital” would be the number of days in the initial treating hospital.

For those subjects discharged from hospital before Visit 12/12R, the following questions will be asked:

- On what study day was the subject discharged from hospital?
- What type of facility was the subject discharged to (another hospital, a rehabilitation center, a supported care facility, home, other)?
- How many days did the subject stay in this facility?

The following questions will be answered regarding the stay in the ICU and hospital:

- Was the subject still in the ICU at the end of Visit 10/10R?
- If the FOUR Score was  $\geq 12$  at Visit 10/10R and the subject was in the ICU at Visit 10/10R, what was the reason for the subject not being discharged from the ICU (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, other)?
- Was the subject still an in-patient in the hospital at the end of Visit 12/12R?

- If the FOUR Score was  $\geq 15$  at Visit 12/12R and the subject was in the hospital at Visit 12/12R, what was the reason for the subject not being discharged from the hospital (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, unsuitable home circumstances, other)?

#### 11.2.8.4. STESS

The STESS will be assessed during Visit 1 in order to assess the severity of the status epilepticus.

#### 11.2.8.5. FOUR Score

The Full Outline of UnResponsiveness or FOUR Score is designed to assess conscious level and unlike other scores, is suitable for subjects who are intubated. It assesses four domains of neurological function (eye responses, motor responses, brainstem reflexes, and breathing pattern).

The FOUR Score will be collected at the following time points relative to each infusion of study drug (the initial blinded infusion and the second open-label infusion if this is administered):

- baseline, +24, +48, +72, +96, +120, +144, +168, and +192 hours (all +/- 2 hours) after the start of the infusion, and at Visit 11/11R and Visit 12/12R.

#### 11.2.8.6. Glasgow Outcome Scale (GOS)

The GOS is a relatively common assessment scale used to standardize descriptions of the objective degree of recovery from brain injury such as cerebral trauma, or in this case SRSE. It was first used in 1975 ([Jennett and Bond 1975](#)) and allows a prediction of the long-term course of rehabilitation to return to work and everyday life. The scale classifies subjects into 5 groups:

- Death
- Persistent vegetative state
- Severe disability
- Moderate disability
- Good recovery

The GOS will be assessed at Visit 12 or Visit 12R.

#### 11.2.8.7. Supervision Rating Scale (SRS)

The Supervision Rating (SRS) measures the level of supervision that a patient/subject receives from caregivers. The SRS rates level of supervision on a 13-point ordinal scale that can optionally be grouped into five ranked categories (Independent, Overnight Supervision, Part-Time Supervision, Full-Time Indirect Supervision, and Full-Time Direct Supervision). The SRS was designed to be rated by a clinician based on interviews with the subject and an informant who has observed at first hand the level of supervision received by the subject ([Boake 2000](#)). Scoring is a one-step procedure in which the clinician assigns the rating that is closest to the subject's level. Ratings are based on the level of supervision received, not on how much supervision a subject is judged or predicted to need.

The SRS will be assessed at Visit 1 and Visit 12 or Visit 12R. The Visit 1 assessment will be a retrospective assessment of the supervision required by the subject immediately prior to the admission that included the index episode of status epilepticus.

**11.2.8.8. Modified Rankin Scale – 9Q (mRS-9Q)**

The Modified Rankin Scale (mRS) is a commonly used scale to determine disability and functional dependence due to neurological insult such as stroke in adults. The 7-point scale (0 – 6) denotes functional capacity from no symptoms (0) to severe disability (5) and death (6). The Modified Rankin Scale – 9Q is a shortened version consisting of 9 questions that reliably determines the mRS score and was developed to both simplify the assessment and expand the rater base to non- medically trained personnel ([Patel, Rao et al. 2012](#)). The assessment is a web-based tool in the public domain with automatic score calculation and error checking found at [www.modifiedrankin.com](http://www.modifiedrankin.com).

The mRS will be assessed at Visit 1 and at Visit 12 or Visit 12R. The baseline assessment will be a retrospective assessment of the disability and dependence of the subject immediately prior to the admission that included the index episode of status epilepticus.

## 12. STUDY PROCEDURES

The study procedures listed below by study day reflect the required data collection times for this protocol. When a time window is necessary, this is specified below. If no time window is specified, the test may be performed at any time within the specified 24-hour period.

### 12.1. Visit 1 (V2-≤30h)

The baseline period will be up to approximately 84 hours prior to starting blinded study treatment and should include the assessments/procedures listed below and summarized in [Table 1 and Table 2 \(for retreatment\)](#), the Schedules of Events.

- Informed consent
- Eligibility checklist
- Verification of inclusion/exclusion criteria.
- Demographic information and medical history obtained by proxy and confirmed by the subject when possible.
- SE and wean history
- Blood will be collected from female subjects 18 years to 55 years for a serum pregnancy test unless they are known to be pre-menstrual or post-menopausal or to have had a hysterectomy.
- Blood and urine samples collected for clinical laboratory testing.
- Pharmacogenetic sample will be collected from consenting/eligible subjects.
- Vital signs
- Height
- Weight
- An ECG reading taken.
- Administration of the STESS.
- Administration of the FOUR Score.
- Administration of SRS.
- Administration of the mRS-9Q assessment.
- Assessment of the CGI scale.
- Evaluation of epilepsy status.
- Administration of continuous IV third-line agents.
- Perform EEG.
- Recording of adverse events.
- Recording of previous and concomitant anti-epileptic drugs.
- Recording of previous and concomitant third-line agents.
- Recording of concomitant pressors.

- Recording of other concomitant medications, procedures, and treatments.

## **12.2. Visit 2 (V3-≤54h)**

- Recording of adverse events.
- Recording of concomitant anti-epileptic drugs.
- Recording of concomitant third-line agents.
- Recording of concomitant pressors.
- Recording of other concomitant medications, procedures, and treatments.
- Wean of continuous third-line agent:
  - If wean is successful, subject is followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (these subjects are Qualifying Wean Success subjects or QWS subjects);
  - If wean is not successful, there is ongoing intravenous administration of at least one continuous IV third-line agent and EEG is performed and the subject is randomized.

## **12.3. SAGE-547 Treatment Period**

### **12.3.1. Visit 3/3R (0-24 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs will be recorded at:
  - 0, +30, +60 minutes (+/-15 minutes) and +2, +4, +8 (+/- 30 minutes) and +24 hours (+/- 2 hours) after the start of the infusion
- ECG readings will be recorded immediately after PK sampling at:
  - 0 (pre-dose) and at +0.5, +1, +3, +6, +12, and +24 hours after the start of the blinded study drug infusion.
- A blood sample for PK analysis should be collected at the following time points (all +/- 15 minutes except where otherwise stated):
  - 0 (pre-dose, within two hours of the start of the infusion) and at +0.5, +1 (+/- 5 minutes), +3, +6, +12, and +24 hours after the start of the blinded study drug infusion.
- Completion of the FOUR Score
  - +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the end of the 24 hour observation period following the QW)
- Ongoing intravenous administration of a continuous IV third-line agent.

- Study drug administration in loading (Hour 0-1) and maintenance infusions (at completion of Hour 1).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.3.2. Visit 4/4R (25-48 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +48 hours (+/- 2 hours) after the start of the infusion
- An ECG reading taken immediately after PK sampling:
  - +48 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +48 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +48 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent.
- Ongoing study drug maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.3.3. Visit 5/5R (49-72 hours)**

- Weight
- Vital signs should be recorded at:
  - +72 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +72 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +72 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +72 hours (+/- 2 hours) after the start of the infusion

- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.4. Visit 6/6R (73-96 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +96 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +96 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +96 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +96 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Perform EEG.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.5. Visit 7/7R (97-120 hours)**

- Weight
- Vital signs should be recorded at:
  - +120 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +120 hours after the start of the study drug infusion

- A blood sample for PK analysis should be collected:
  - +120 hours (+/- 15 minutes) after the start of study drug infusion, immediately prior to the end of the maintenance infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +120 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled. Complete wean by 120 hours if at all possible.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## **12.4. SAGE-547 Taper Period**

### **12.4.1. Visit 8/8R (121-144 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +144 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after each PK sampling:
  - +128, +136 hours and +144 hours after the start of the study drug infusion
  - During the open-label retreatment phase of the study ECG readings at: +126, +132, +138 hours and +144 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected (+/- 15 minutes unless otherwise stated):
  - +128 (immediately prior to the end of the first taper step), +136 hours (+/- 5 minutes, immediately prior to the end of the second taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of study drug infusion.
  - During the open-label retreatment phase of the study PK blood draws at: +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 hours (+/- 5 minutes, immediately prior to the end of the third taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of the study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +144 hours (+/- 2 hours) after the start of the infusion



- Complete wean of third line agents by H144 if not completed by H120.
- Perform EEG.
- Taper of SAGE-547 infusion begins at hour 121.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## **12.5. Follow-up Period**

### **12.5.1. Visit 9/9R (145-168 hours)**

- Vital signs should be recorded at:
  - +168 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +152, +160 hours (+/- 2 hours) after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +152 and +160 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +168 hours (+/- 2 hours) after the start of the infusion
- Perform EEG.
- Assessment of the presence of physiologic brain activity using EEG.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.5.2. Visit 10/10R (169-192 hours)**

- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +192 hours (+/- 2 hours) after the start of the infusion
- At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine eligibility for retreatment with the higher dose of study drug. This determination may occur at any point

during Visit 10: the retreatment infusion must begin within the Visit 10 window. All patients for retreatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.

- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.3. Visit 11/11R (Visit 3/3R + 14d (±2))**

- Blood samples collected for clinical laboratory testing (renal panel only).
- Completion of the FOUR Score (QWS subjects also).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.4. Visit 12/12R (Visit 3/3R + 21d (±2))**

All assessments also performed for QWS subjects.

- Completion of the FOUR Score.
- Administration of the GOS.
- Administration of the SRS.
- Administration of the mRS-9Q assessment.
- Evaluation of epilepsy status (see [Section 11.1.2.2](#) for details).
- Assessment of the CGI Scale.
- Recording of adverse events.
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications.
- Collection of pharmacoeconomic data.
- Mortality will be assessed throughout the study period.

## **13. STATISTICS**

### **13.1. Statistical Plan**

Complete details for the analysis and reporting of data from this study will be contained in the Statistical Analysis Plan (SAP).

#### **13.1.1. Interim Analysis**

When approximately 50% of subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment

will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### 13.1.2. Study Populations

The **Safety Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to actual treatment. This analysis population will be used for all safety analyses.

The **Intent to Treat Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to randomized treatment. This analysis population will be used for all efficacy analyses.

The **Modified Intent to Treat Population** is defined as all subjects who:

1. complete their initial course of blinded SAGE-547 or placebo treatment unless the non-completion was due a drug-related adverse event; and
2. have at least one attempt to wean from third-line agents prior to the end of blinded study treatment infusion unless the failure to wean was because seizures were not controlled.

Subjects will be classified according to randomized treatment. This analysis population will be used for sensitivity analyses of the primary endpoint and select secondary efficacy endpoints.

Narratives will be prepared for all subjects who do not complete the infusion of blinded study medication or were not subjected to any wean attempts. Narratives will include details of the cause of SE, the comorbid conditions, the adverse event(s), and reasons for non-completion of the infusion or failure to attempt weaning. This blinded narrative will be reviewed by the medical monitors and the patient adjudicated as MITT eligible or ineligible. Acceptable reasons for defining a subject as MITT ineligible include death or withdrawal of consent due to progression of the underlying cause of SE or comorbid conditions, unless the cause of death or progression of disease were thought by the investigator, sponsor, or DSMB to be related to study drug.

The **Per-Protocol (PP) Population** is defined as a subset of the MITT population but will exclude data from all subjects with significant protocol violations or deviations. Subjects will be classified according to actual treatment received. This data set will be used for sensitivity analyses to examine the robustness of results for the primary and key secondary efficacy endpoints.

The **Pharmacokinetics Population** is defined as all subjects who at least had an infusion of blinded SAGE-547 initiated and have at least one pharmacokinetic sample collected.

The **Pharmacogenetic Population** is defined all subjects who consent to being included in the pharmacogenetic assessment and provide a pharmacogenetic sample.

Summary statistics of all data collected will be presented for subjects who were QW successes.

### 13.1.3. General Aspects

Tabular displays of descriptive statistics will be provided for all variables. Summary tables will include n, mean, mean, standard deviation, minimum and maximum for continuous variable and frequency and percentage for categorical variables.

### **13.1.4. Analysis of Primary Endpoint**

The analysis of response to treatment (see Section 11.1.1 for definition of primary endpoint) between SAGE-547 treated subjects and placebo treated subjects will be performed on the ITT population using a Cochran-Mantel-Haenszel (CMH) test with variables for treatment, concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). The CMH general association statistic and its associated p-value will be presented. The comparison of treatment response rates will be conducted at the 5% level of significance. To confirm the CMH results, a permutation test will also be conducted.

An additional analysis of the primary endpoint will also be performed on the MITT population. In addition sensitivity analyses of the primary endpoint will be performed using the ITT population based on:

- the number of third-line agents (one, two, or three) subjects were administered post-randomization; and
- which third line agent was the subject of the first TW.

### **13.1.5. Analysis of Secondary Efficacy Endpoints**

Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section (Section 6). Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. The analysis of the secondary endpoints will also be performed on the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

### **13.1.6. Analysis of Other Endpoints**

Safety and “Other” endpoints will only be summarized by treatment group.

Summaries of safety endpoints will be based on the overall Safety Population.

### **13.1.7. Epilepsy and SRSE Status**

Diagnosis of epilepsy and recurrence of RSE or SRSE will be documented as the percentage of subjects by time point and overall. Kaplan-Meier curves may be plotted if sufficient data are available.

Utilization of AEDs during follow-up and during recurrence will be summarized.

### **13.1.8. Questionnaires**

The data collected from each questionnaire will be interpreted according to the standard methodology for that questionnaire. There will be no adjustment for missing values.

### **13.1.9. Pharmacokinetic Data Analysis**

Details of the pharmacokinetic data analysis will be described in detail in a separate Pharmacokinetic Analysis Plan.

### **13.1.10. Pharmacogenetic Data Analysis**

Any genotype data generated in this study will be stored within a secured database within Sage Therapeutics and / or a third party contracted to work with Sage Therapeutics to analyze the samples. Because the number of subjects agreeing to participate in the genetic research component of the study is unknown, it is not possible to establish, a priori, whether sufficient samples will be obtained to support formal statistical evaluation of data. As a consequence a Pharmacogenetic Analysis Plan will only be prepared where appropriate and the results obtained from any genetic research will be reported in a report separate from the main study CSR.

### **13.1.11. Retreated Subjects**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are retreated with SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo.

### **13.1.12. EEG-Responders**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who are classified as EEG-responders/non-responders based on the independent assessment of the PAEEG. Summaries will be derived for the two randomized treatment groups.

### **13.1.13. QT/QTc Assessment**

An analysis of the correlation between changes in QT/QTc intervals and SAGE-547 plasma levels will be performed to investigate if there is a potential effect that SAGE-547 may have on QT/QTc interval. A detailed description of the QT/QTc assessment will be included in the SAP.

### **13.1.14. Quantitative EEG**

The six EEG records for each subject may be subjected to exploratory quantitative EEG analysis, the details of which will be included in the EEG Analysis Plan. In summary the following comparisons may be made, SAGE-547 versus placebo: the QWEEG versus the TWEEG (main analysis); the CEEG versus PAEEG (subsidiary analysis); and TAEEG versus PAEEG (exploratory analysis).

## **13.2. Determination of Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between treatment groups at a 5% level of significance. Randomization will be stratified by concomitant

pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

### **13.3. Statistical Analysis Plan**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

## **14. ADVERSE EVENTS**

The safety procedures in this study will be detailed in a Safety Management Plan, which will be agreed and signed before the first subject is randomized in the study. [Section 14.1](#) summarizes Investigator responsibilities regarding the identification and documentation of AEs, the classification of AEs for relationship to study drug and severity, and the reporting of AE information to the Sponsor and the IRB.

[Section 14.2](#) summarizes Sponsor/Medical Monitor Responsibilities regarding monitoring of AE data and reporting relevant safety information to FDA.

[Section 14.3](#) lists important AE definitions.

### **14.1. Investigator Responsibilities**

#### **14.1.1. Identification and Documentation of Adverse Events by Investigator**

Subjects will be evaluated and questioned generally (if possible) to identify AEs during the course of the study. AEs will be collected from the signature of the consent form through Visit 12/12R. Adverse events that occur prior to completion of screening will be captured on the Medical History eCRF. Adverse events that occur after completion of screening will be recorded on the Adverse Event eCRF.

All AEs revealed by observation, other diagnostic procedures, or spontaneously reported by the subject and/or in response to an open question from study personnel will be recorded on the Adverse Event Form. Any clinically significant deterioration in laboratory assessments or other clinical findings are considered an AE and must be recorded on the Adverse Event Form, unless otherwise stated. AE information recorded will be entered into the database on an ongoing basis.

AEs with a relationship considered related to study drug (probable, possible) should be followed until the event is resolved or the Investigator determines the event is stable or no longer clinically significant. AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

For SAEs, an electronic Serious Adverse Event eCRF must be completed with as much information as possible and submitted in the time frame described below in [Section 14.1.3](#). When new significant information is obtained as well as when the outcome of an event is known, the electronic SAE eCRF should be updated within 24 hours. If the subject was an outpatient at the time of the SAE and was re-hospitalized due to the SAE, a copy of relevant hospital records (e.g., admission report, laboratory test results, discharge summary, etc.) may be requested to be included as part of the subject medical file.

All SAEs will be followed until resolved or until a stable status has been achieved.

**14.1.2. Adverse Event Classification****14.1.2.1. Relationship to Investigational Drug**

None:	No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state.
Possible:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject, but this is not known for sure.
Probable:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

**14.1.2.2. Severity**

Mild	Discomfort noticed, but no disruption to daily activity.  For subjects that are unconscious, this may be a slight or minor change in a lab result or clinical sign or symptom that does not require immediate corrective action.
Moderate	Discomfort sufficient to reduce or affect normal daily activity, but is not hazardous to health; prescription drug therapy may be employed to treat the AE.  For subjects that are unconscious, this may be a clinically meaningful change that may require immediate corrective action.
Severe	Inability to work or perform normal daily activity and represented a definite hazard to health; prescription drug therapy and/or hospitalization may be employed to treat the AE.  For unconscious subjects, this may be a significant clinical change that requires immediate corrective action.

**14.1.2.3. Action Taken with Investigational Drug**

None	Study medication was continued without change.
Discontinued	Study medication was terminated.
Dose adjusted	Study medication dose/infusion rate was changed and then continued per protocol.
Interrupted	Study medication was interrupted and then continued per protocol.
Unknown	The action taken with regard to study medication is unknown.
Not applicable	Administration of study medication was not ongoing.



**14.1.2.4. Assessment of Outcome**

Ongoing	At the end of the study, the event has not resolved or stabilized.
Ongoing and stable	The event is ongoing but has stabilized and is unlikely to change
Resolved	The event has resolved or the subject recovered without sequelae.
Resolved with sequelae	The event has at least one secondary outcome that may result in permanent disability and/or functional limitation.
Unknown	The status of the event is unknown.
Death	The subject has expired.

**14.1.3. Investigator Reporting to Sponsor and Sponsor Emergency Contact**

All new SAEs that come to the Investigator and/or Sponsor's notice during the course of the study (up to and including the last study visit) must be reported by the Investigator on the designated electronic report form within 24 hours of the point in time when the Investigator becomes aware of the SAE. As additional information becomes available, the designated electronic report form must be updated within 24 hours.

Investigators must report any SAE, whether or not considered drug related. The report must include an assessment of whether there is a reasonable possibility that the drug caused the event.

In a medical emergency (ie, an event that requires immediate attention regarding the treatment of a subject, operation of the clinical study, and/or the use of investigational drug), study site staff will apply appropriate medical intervention according to current standards of care, and contact the Medical Monitor.

**14.1.4. Medical Monitor and Emergency Contact Information**

[REDACTED], MD  
[REDACTED]

**14.1.5. SAE Reporting Contact Information**

Contact information and reporting instructions are provided in the Safety Management Plan.

**14.1.6. Reporting to Institutional Review Boards (IRBs)**

It is the responsibility of the Investigator to promptly notify the institution's IRB of all serious and unexpected suspected adverse reactions (see [Section 14.3](#) for definitions).

## **14.2. Sponsor/Medical Monitor Responsibilities**

### **14.2.1. Monitoring of Adverse Event Data**

The Medical Monitor will review any newly reported adverse events in an ongoing basis. If the aggregate assessment indicates that an event is occurring more frequently than would normally be expected in this population, or as previously observed, and the sponsor believes that the events are causally related to the administration of SAGE-547, the Sponsor will then report that information in an IND safety report.

### **14.2.2. Data Safety Monitoring Board**

An independent DSMB will monitor the clinical, PK and PD data for safety signals throughout the study and will be asked to assess the placebo response rate at the time of the interim analysis to determine final sample size. In order to perform their monitoring function the DSMB will have access to un-blinded safety data as necessary.

The composition and procedures for the board will be described in a separate DSMB Charter.

### **14.2.3. Reporting to FDA**

The Sponsor must report in an IND safety report any suspected adverse reaction to study treatment that is both serious and unexpected (21 CFR 312.32(c)(1)(i)). Before submitting an IND safety report, the Sponsor will ensure the event meets all three of the definitions: (1) suspected adverse reaction, (2) serious, (3) unexpected. If the AE does not meet all three of the definitions, it should not be submitted as an IND safety report. The Sponsor should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the adverse event and, therefore, that the event meets the definition of a suspected adverse reaction.

If there is a serious and unexpected suspected adverse reaction, the Sponsor will notify the appropriate regulatory agency(ies) and all appropriate parties on an expedited basis. In addition, Sponsors must submit expedited reports of an increased rate of occurrence or severity of serious suspected adverse reactions over that listed in the protocol or Investigational Brochure.

SUSARs will be unblinded prior to reporting to FDA. Unless it is necessary to unblind for the safety of the patient, the investigator will not be informed of the unblinding of the subject.

Under 21 CFR 312.32, Sponsors should identify in the protocol SAEs that it does not plan to report individually in an expedited manner, because they are known consequences of the disease or otherwise common in the study population. Given the grave condition and prognosis of SRSE being studied, individual occurrences of seizures or seizure activity will not be reported expeditiously in this study. Regardless of which events are reported in an expedited manner, all adverse events will be closely monitored throughout the study.

## **14.3. Adverse Event Definitions**

### **14.3.1. Adverse Event**

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

### **14.3.2. Suspected Adverse Reaction**

Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

### **14.3.3. Life-Threatening**

An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

### **14.3.4. Serious**

An AE or suspected adverse reaction is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE – see definition above
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disability
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

### **14.3.5. Unexpected**

An AE or suspected adverse reaction is considered “unexpected”:

- If it is not listed in the Investigational Brochure or is not listed at the specificity or severity that has been observed, or
- If an Investigational Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigational Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigational Brochure listed only cerebral vascular accidents.

“Unexpected,” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigational Brochure as occurring with a class of drugs or as anticipated from

the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

#### **14.4. Emergency Identification of Study Medication**

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject's treatment in the study via the IVRS; this normally requires prior approval by the medical monitor. However, if the subject is at immediate risk and the Investigator believes that immediate knowledge of the study treatment will alter medical management, discussion with the medical monitor may take place after unblinding. The Investigator will not unblind the medical monitor during that discussion. The process of unblinding will ensure that only the investigator is unblinded; the medical monitor, study management team, and data management team will not be made aware of the treatment allocation of an individual subject. All cases of emergency unblinding will be fully documented in a way that does not unblind the medical monitor, study management team, and data management team.

### **15. STUDY ADMINISTRATIVE CONSIDERATIONS**

#### **15.1. Quality Control and Quality Assurance**

The Investigators and institutions will permit trial related monitoring, audits, IRB review, and regulatory inspections as requested by FDA, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed informed consent forms, etc.) in addition to case report forms.

Quality assurance and quality control systems with written standard operating procedures (SOPs) will be followed to ensure this trial will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The site's dedicated study monitor will arrange to visit the Investigator at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be identified and resolved. The study monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality assurance officers named by Sage Therapeutics or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements, made by the Sponsor with the Investigator/institution and any other parties involved with the clinical trial, will be in writing in a separate agreement.

## **15.2. Data Handling and Recordkeeping**

### **15.2.1. Data Handling**

Procedures for data handling (including electronic data) used in this protocol will be documented in a Data Management Plan.

### **15.2.2. Case Report Form Completion**

eCRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of demographics, study drug administration, study procedures, AEs, questionnaire completion, efficacy assessments and subject status, including survival.

The Investigator will maintain copies of the eCRFs at the study site. For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate eCRF.

### **15.2.3. Retention of Study Records**

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval and until there are no pending or contemplated marketing applications or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to an appropriate person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

## **15.3. Confidentiality**

To maintain subject privacy, all eCRFs, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available trial registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by Sage Therapeutics to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

#### **15.4. Publication Policy**

All information concerning SAGE-547 is considered confidential and shall remain the sole property of Sage Therapeutics. The Investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval from Sage Therapeutics. No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between Sage Therapeutics and the Investigator.

#### **15.5. Protocol Amendments**

Changes to the conduct of the study should be prepared as a protocol amendment by the Sponsor. Protocol amendments should receive written IRB/IEC approval prior to implementation at the investigative site, except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the trial (eg, change of monitor, telephone numbers). In this case, Sage Therapeutics will amend and implement the protocol change and subsequently notify the regulatory authorities and the Investigative sites who will notify the respective IRB, as appropriate.

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**APPENDIX 1. APPENDIX 1: FOUR SCORE****FOUR score****Full Outline of UnResponsiveness****Eye response**

- E4: eyelids open or opened, tracking, or blinking to command
- E3: eyelids open but not tracking
- E2: eyelids closed but open to loud voice
- E1: eyelids closed but open to pain
- E0: eyelids remain closed with pain

**Motor response**

- M4: thumbs-up, fist or peace sign
- M3: localizing to pain
- M2: flexion response to pain
- M1: extension response to pain
- M0: no response to pain or generalized myoclonus status

**Brainstem reflexes**

- B4: pupil and corneal reflexes present
- B3: one pupil wide and fixed
- B2: pupil or corneal reflexes absent
- B1: pupil and corneal reflexes absent
- B0: absent pupil, corneal and cough reflex

**Respiration pattern**

- R4: not intubated, regular breathing pattern
- R3: not intubated, Cheyne-Stokes breathing pattern
- R2: not intubated, irregular breathing
- R1: breathes above ventilatory rate
- R0: breathes at ventilator rate or apnea

Reference ([Iyer, Hoel et al. 2009](#)).

**APPENDIX 2. GLASGOW OUTCOME SCALE (GOS)****GLASGOW  
OUTCOME  
SCALE**

Patient Name: \_\_\_\_\_  
 Rater Name: \_\_\_\_\_  
 Date: \_\_\_\_\_

*Note:* The scale presented here is based on the original article by Jennett and Bond. It has become common practice in clinical trial administration, however, to use a modified version that places the scores in reverse order (i.e., "good recovery" = 1, "moderate disability" =2, etc.).

Score	Description
1	DEATH
2	PERSISTENT VEGETATIVE STATE Patient exhibits no <i>obvious cortical</i> function.
3	SEVERE DISABILITY (Conscious but disabled). Patient depends upon others for daily support due to mental or physical disability or both.
4	MODERATE DISABILITY (Disabled but independent). Patient is independent as far as daily life is concerned. The disabilities found include varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes.
5	GOOD RECOVERY Resumption of normal activities even though there may be minor neurological or psychological deficits.

**TOTAL (1-5):** \_\_\_\_\_

Reference ([Jennett and Bond 1975](#)).

## APPENDIX 3. SUPERVISION RATING SCALE (SRS)

### SUPERVISION RATING SCALE (SRS)

**Instructions:** Circle the rating that is closest to the amount of supervision that the patient *actually receives*. "Supervision" means that someone is responsible for being with the patient.

<u>Rating</u>	<u>Description</u>
<b>Level 1: INDEPENDENT</b>	
1	The patient lives alone or independently. Other persons can live with the patient, but they cannot take responsibility for supervision (for example, a child or elderly person).
2	The patient is unsupervised overnight. The patient lives with one or more persons who <i>could</i> be responsible for supervision (for example, a spouse or roommate), but they are <i>all</i> sometimes absent overnight.
<b>Level 2: OVERNIGHT SUPERVISION</b>	
3	The patient is only supervised overnight. One or more supervising persons are always present overnight but they are <i>all</i> sometimes absent for the rest of the day.
<b>Level 3: PART-TIME SUPERVISION</b>	
4	The patient is supervised overnight and part-time during waking hours, but is allowed on independent outings. One or more supervising persons are always present overnight and are also present during part of waking hours every day. However, the patient is sometimes allowed to leave the residence without being accompanied by someone who is responsible for supervision.
5	The patient is supervised overnight and part-time during waking hours, but is unsupervised during working hours. Supervising persons are <i>all</i> sometimes absent for enough time for them to work full-time outside the home.
6	The patient is supervised overnight and during most waking hours. Supervising persons are <i>all</i> sometimes absent for periods longer than one hour, but less than the time needed to hold a full-time job away from home.
7	The patient is supervised overnight and during almost all waking hours. Supervising persons are <i>all</i> sometimes absent for periods shorter than one hour.
<b>Level 4: FULL-TIME INDIRECT SUPERVISION</b>	
8	The patient is under full-time indirect supervision. At least one supervising person is <i>always</i> present, but the supervising person does not check on the patient more than once every 30 minutes.
9	Same as #8 plus requires overnight safety precautions (for example, a deadbolt on outside door).
<b>Level 5: FULL-TIME DIRECT SUPERVISION</b>	
10	The patient is under full-time direct supervision. At least one supervising person is always present and the supervising person checks on the patient more than once every thirty minutes.
11	The patient lives in a setting in which the exits are physically controlled by others (for example, a locked ward).
12	Same as #11 plus a supervising person is designated to provide full-time line-of-sight supervision (for example, an escape watch or suicide watch).
13	The patient is in physical restraints.

3/12/93

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## APPENDIX 4. MODIFIED RANKIN SCALE – LEVEL OF FUNCTION SURVEY (mRS-9Q)

1. Do you have any symptoms that are bothering you? (For example, trouble with reading or writing, trouble speaking, problems with vision, numbness, weakness, balance trouble, or problems with swallowing?)	YES <input type="radio"/>	NO <input type="radio"/>
2. Are you able to do the same work as before?	YES <input type="radio"/>	NO <input type="radio"/>
3. Are you able to keep up with your hobbies?	YES <input type="radio"/>	NO <input type="radio"/>
4. Have you maintained your ties to friends and family?	YES <input type="radio"/>	NO <input type="radio"/>
5. Do you need help making a simple meal, doing household chores, or balancing a checkbook?	YES <input type="radio"/>	NO <input type="radio"/>
6. Do you need help with shopping or traveling close to home?	YES <input type="radio"/>	NO <input type="radio"/>
7. Do you need another person to help you walk?	YES <input type="radio"/>	NO <input type="radio"/>
8. Do you need help with eating, going to the toilet, or bathing?	YES <input type="radio"/>	NO <input type="radio"/>
9. Do you stay in bed most of the day and need constant nursing care?	YES <input type="radio"/>	NO <input type="radio"/>

## APPENDIX 5. CLINICAL GLOBAL IMPRESSION (CGI)

### Clinical Global Impression (CGI)

#### 1. Severity of illness

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- |                             |   |
|-----------------------------|---|
| 0 = Not assessed            | 4 = Moderately ill                        |
| 1 = Normal, not at all ill  | 5 = Markedly ill                          |
| 2 = Borderline mentally ill | 6 = Severely ill                          |
| 3 = Mildly ill              | 7 = Among the most extremely ill patients |

#### 2. Global improvement: Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.

Compared to his condition at admission to the project, how much has he changed?

- |                        |                     |
|------------------------|---------------------|
| 0 = Not assessed       | 4 = No change       |
| 1 = Very much improved | 5 = Minimally worse |
| 2 = Much improved      | 6 = Much worse      |
| 3 = Minimally improved | 7 = Very much worse |

#### 3. Efficacy index: Rate this item on the basis of drug effect only.

Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.

EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect		Side effects			
		None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
<b>Marked</b>	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
<b>Moderate</b>	Decided improvement. Partial remission of symptoms	05	06	07	08
<b>Minimal</b>	Slight improvement which doesn't alter status of care of patient	09	10	11	12
<b>Unchanged or worse</b>		13	14	15	16
Not assessed = 00					

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

**APPENDIX 6. STATUS EPILEPTICUS SEVERITY SCORE (STESS)**

Outcome Predictor	Feature	Score
Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type (prior to first treatment)	Simple-partial, complex-parial, absence, myoclonic (complicating idiopathic generalized epilepsy)	0
	Generalized-convulsive	1
	Nonconvulsive status epilepticus in coma	2
Age	< 65 years	0
	≥ 65 years	2
History of previous seizures	Yes	0
	No or unknown	1
Summed Total		

## CYPs

## INHIBITORS

- A **Weak inhibitor** is one that causes a  $> 1.25$ -fold but  $< 2$ -fold increase in the plasma AUC values or 20-50% decrease in clearance.

FDA preferred<sup>1</sup> and acceptable<sup>2</sup> inhibitors for in vitro experiments.\*

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4,5,7
■ fluvoxamine	clopidogrel	■ gemfibrozil <sup>2</sup>	■ fluconazole <sup>2</sup>	PPIs:	■ bupropion	diethyl- dithiocarbamate <sup>2</sup>	HIV Antivirals:
■ ciprofloxacin	thiotepa			esomeprazole	■ cinacalcet	disulfiram	■ indinavir
	ticlopidine <sup>2</sup>	■	■ amiodarone	lansoprazole	■ fluoxetine		■ nelfinavir
■ cimetidine	voriconazole	trimethoprim <sup>2</sup>		omeprazole <sup>2</sup>	■ paroxetine		■ ritonavir
			efavirenz	pantoprazole	■ quinidine <sup>1</sup>		
amiodarone		glitazones	fenofibrate	Other:	■ duloxetine		■ clarithromycin
efavirenz		montelukast <sup>1</sup>	fluconazole	chloramphenicol	■ sertraline		■ itraconazole <sup>1</sup>
fluoroquinolones		quercetin <sup>1</sup>	fluvastatin	cimetidine	■ terbinafine		■ ketoconazole
fluvoxamine			fluvoxamine <sup>2</sup>	felbamate			■ nefazodone
furafylline <sup>1</sup>			isoniazid	fluoxetine	■ amiodarone		■ saquinavir
interferon			lovastatin	fluvoxamine	■ cimetidine		■ suboxone
methoxsalen			metronidazole	indomethacin			■ telithromycin
mibefradil			paroxetine	ketocoazole			
ticlopidine			phenylbutazone	modafinil			
			probenicid	oral			
			sertraline	contraceptives			
			sulfamethoxazole	oxcarbazepine			
			sulfaphenazole <sup>1</sup>	probenicid			
			teniposide	ticlopidine <sup>2</sup>			
			voriconazole	topiramate			
			zafirlukast	voriconazole			
					celecoxib		■ aprepitant
					chlorpheniramine		■ erythromycin
					chlorpromazine		■ fluconazole
					citalopram		■ grapefruit juice
					clemastine		■ verapamil <sup>2</sup>
					clomipramine		■ diltiazem
					cocaine		
					diphenhydramine		■ cimetidine
					doxepin		
					doxorubicin		amiodarone
					escitalopram		NOT azithromycin
					halofantrine		chloramphenicol
					haloperidol		boceprevir
					histamine H1		ciprofloxacin
					receptor antagonists		delaviridine
					hydroxyzine		diethyl- dithiocarbamate
					levomepromazine		fluvoxamine
					methadone		gestodene
					metoclopramide		imatinib
					mibefradil		mibefradil
					midodrine		mifepristone
					moclobemide		norfloxacin
					perphenazine		norfluoxetine
					promethazine		starfruit
					ranitidine		telaprevir
					reduced-haloperidol		voriconazole
					ritonavir		
					ticlopidine		
					tripelennamine		

## INDUCERS

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4,5,7
broccoli	artemisinin	rifampin <sup>1</sup>	carbamazepine	carbamazepine	dexamethasone	ethanol	HIV Antivirals:
brussel sprouts	carbamazepine		enzalutamide	efavirenz	rifampin	isoniazid	efavirenz
carbamazepine	efavirenz		nevirapine	enzalutamide			nevirapine
char-grilled meat	nevirapine		phenobarbital	norethindrone			
insulin	phenobarbital		rifampin	NOT			barbiturates
methylcholanthrene <sup>1</sup>	phenytoin		secobarbital	pentobarbital			carbamazepine
modafinil	rifampin		St. John's Wort	prednisone			enzalutamide
nafcillin				rifampicin <sup>1</sup>			glucocorticoids
beta-naphthoflavone <sup>1</sup>				ritonavir			modafinil
omeprazole <sup>1</sup>				St. John's Wort			oxcarbazepine
rifampin							phenobarbital <sup>2</sup>
tobacco							phenytoin <sup>2</sup>
							pioglitazone
							rifabutin
							rifampin <sup>1</sup>
							St. John's Wort
							troglitazone <sup>1</sup>

Indiana University Table of P450 Drug Interactions: <http://medicine.iupui.edu/CLINPHARM/ddis/main-table>

## UGTs

Enzyme	Overall Effect	Inhibitor/Inducer	Therapeutic Class
UGT2B17	In Vitro Inhibition	(R)-warfarin	Anticoagulants and Antiplatelets
UGT2B17	In Vitro Inhibition	(S)-flurbiprofen	NSAIDS
UGT2B17	In Vitro Inhibition	(S)-warfarin	Anticoagulants and Antiplatelets
UGT2B17	In Vitro Inhibition	4-ethylphenol	None
UGT2B17	In Vitro Inhibition	caffeic acid	Food Products
UGT2B17	In Vitro Inhibition	desloratadine (descarboethoxyloratadine)	H-1 Receptor Antagonists
UGT2B17	In Vitro Inhibition	diclofenac	NSAIDS
UGT2B17	In Vitro Inhibition	diethylstilbestrol	Estrogens
UGT2B17	In Vitro Inhibition	epigallocatechin gallate	Food Products
UGT2B17	In Vitro Inhibition	epitestosterone	Androgens
UGT2B17	In Vitro Inhibition	hexamethoxyflavone (HMF)	None
UGT2B17	In Vitro Inhibition	ibuprofen	NSAIDS
UGT2B17	In Vitro Inhibition	quercetin	Food Products
UGT2B17	In Vitro Inhibition	red wine	Food Products
UGT2B17	In Vitro Inhibition	silibinin (silybin; milk thistle derivative)	Herbal Medications
UGT2B17	In Vitro Inhibition	warfarin	Anticoagulants and Antiplatelets
UGT2B17	In Vitro Inhibition	zafirlukast	Antiasthmatics



Enzyme	Overall Effect	Inhibitor/Inducer	Therapeutic Class
UGT2B7	In Vitro Inhibition	(R)-bicalutamide	Antiandrogens
UGT2B7	In Vitro Inhibition	(R)-carvedilol	Alpha/Beta Adrenergic Antagonists
UGT2B7	In Vitro Inhibition	(R)-ibuprofen	NSAIDS
UGT2B7	In Vitro Inhibition	(R)-warfarin	Anticoagulants and Antiplatelets
UGT2B7	In Vitro Inhibition	(S)-carvedilol	Alpha/Beta Adrenergic Antagonists
UGT2B7	In Vitro Inhibition	(S)-flurbiprofen	NSAIDS
UGT2B7	In Vitro Inhibition	(S)-ibuprofen	NSAIDS
UGT2B7	In Vitro Inhibition	(S)-warfarin	Anticoagulants and Antiplatelets
UGT2B7	In Vitro Inhibition	10-hydroxywarfarin	Anticoagulants and Antiplatelets
UGT2B7	In Vitro Inhibition	1-naphthol	None
UGT2B7	In Vitro Inhibition	20(S)-ginsenoside Rg3	Herbal Medications
UGT2B7	In Vitro Inhibition	20(S)-protopanaxadiol	Herbal Medications
UGT2B7	In Vitro Inhibition	20(S)-protopanaxatriol	Herbal Medications
UGT2B7	In Vitro Inhibition	3-oxo-dehydroandrographolide	Herbal Medications
UGT2B7	In Vitro Inhibition	3-oxo-deoxyandrographolide	Herbal Medications
UGT2B7	In Vitro Inhibition	4-hydroxyestradiol	Estrogens
UGT2B7	In Vitro Inhibition	4-hydroxywarfarin	Anticoagulants and Antiplatelets
UGT2B7	In Vitro Inhibition	4-methylumbelliferone	None
UGT2B7	In Vitro Inhibition	7-hydroxywarfarin	Anticoagulants and Antiplatelets
UGT2B7	In Vitro Inhibition	alclofenac	NSAIDS
UGT2B7	In Vitro Inhibition	alpha-naphthoflavone	None
UGT2B7	In Vitro Inhibition	amitriptyline	Tricyclics and Tetracyclics
UGT2B7	In Vitro Inhibition	andrographis paniculata ethanol extract	Herbal Medications
UGT2B7	In Vitro Inhibition	andrographolide	Herbal Medications
UGT2B7	In Vitro Inhibition	androstenediol	Androgens
UGT2B7	In Vitro Inhibition	androsterone	Androgens
UGT2B7	In Vitro Inhibition	aprepitant	Neurokinin-1 Receptor Antagonist
UGT2B7	In Vitro Inhibition	arbidol	Antivirals
UGT2B7	In Vitro Inhibition	baicalein	Herbal Medications
UGT2B7	In Vitro Inhibition	baicalin	Food Products
UGT2B7	In Vitro Inhibition	bakuchiol	Herbal Medications
UGT2B7	In Vitro Inhibition	bicalutamide	Antiandrogens
UGT2B7	In Vitro Inhibition	bilirubin	None
UGT2B7	In Vitro Inhibition	blueberry extract	Food Products
UGT2B7	In Vitro Inhibition	borneol	Herbal Medications
UGT2B7	In Vitro Inhibition	canagliflozin	Sodium-dependent Glucose Cotransporter 2 (SGLT2) Inhibitors
UGT2B7	In Vitro Inhibition	cannabidiol	Cannabinoids
UGT2B7	In Vitro Inhibition	canrenoic acid	Diuretics
UGT2B7	In Vitro Inhibition	canrenone	Diuretics
UGT2B7	In Vitro Inhibition	carbamazepine	Anticonvulsants
UGT2B7	In Vitro Inhibition	chenodeoxycholic acid sodium	Endogenous Compounds
UGT2B7	In Vitro Inhibition	chlormadinone acetate	Progestins
UGT2B7	In Vitro Inhibition	chrysin	Herbal Medications
UGT2B7	In Vitro Inhibition	cicloprofen	NSAIDS
UGT2B7	In Vitro Inhibition	cinnamaldehyde	Herbal Medications
UGT2B7	In Vitro Inhibition	clomipramine	Tricyclics and Tetracyclics
UGT2B7	In Vitro Inhibition	codeine	Opioids
UGT2B7	In Vitro Inhibition	cyproheptadine	H-1 Receptor Antagonists
UGT2B7	In Vitro Inhibition	daio aqueous extract	Herbal Medications
UGT2B7	In Vitro Inhibition	dapagliflozin	Sodium-dependent Glucose Cotransporter 2 (SGLT2) Inhibitors
UGT2B7	In Vitro Inhibition	dehydroandrographolide	Herbal Medications
UGT2B7	In Vitro Inhibition	demethylzeylasteral	Herbal Medications
UGT2B7	In Vitro Inhibition	deoxyandrographolide	Herbal Medications
UGT2B7	In Vitro Inhibition	desipramine	Tricyclics and Tetracyclics
UGT2B7	In Vitro Inhibition	diazepam	Benzodiazepines
UGT2B7	In Vitro Inhibition	diclofenac	NSAIDS
UGT2B7	In Vitro Inhibition	diflunisal	NSAIDS
UGT2B7	In Vitro Inhibition	domperidone	Other Antiemetics
UGT2B7	In Vitro Inhibition	efavirenz	NonNucleoside Reverse Transcriptase Inhibitors (NNRTIs)

UGT2B7	In Vitro Inhibition	erlotinib	Kinase Inhibitors
UGT2B7	In Vitro Inhibition	estradiol (17-beta-)	Estrogens
UGT2B7	In Vitro Inhibition	etonitazenyl	Drug Addiction Treatments
UGT2B7	In Vitro Inhibition	fatty acids	Endogenous Compounds
UGT2B7	In Vitro Inhibition	fenoprofen	NSAIDS
UGT2B7	In Vitro Inhibition	fluconazole	Antifungals
UGT2B7	In Vitro Inhibition	flunitrazepam	Benzodiazepines
UGT2B7	In Vitro Inhibition	flurbiprofen	NSAIDS
UGT2B7	In Vitro Inhibition	gefitinib	Kinase Inhibitors
UGT2B7	In Vitro Inhibition	gemfibrozil	Fibric Acid Derivatives
UGT2B7	In Vitro Inhibition	ginseng dry extract BST204	Herbal Medications
UGT2B7	In Vitro Inhibition	glycocholic acid hydrate	Endogenous Compounds
UGT2B7	In Vitro Inhibition	glycyrrhetic acid	Herbal Medications
UGT2B7	In Vitro Inhibition	glycyrrhizin	Herbal Medications
UGT2B7	In Vitro Inhibition	gossypol	Herbal Medications
UGT2B7	In Vitro Inhibition	haloperidol	Antipsychotics
UGT2B7	In Vitro Inhibition	hippuric acid	None
UGT2B7	In Vitro Inhibition	honokiol	Herbal Medications
UGT2B7	In Vitro Inhibition	hyodeoxycholic acid	Other
UGT2B7	In Vitro Inhibition	ibuprofen	NSAIDS
UGT2B7	In Vitro Inhibition	icaraside II	Herbal Medications
UGT2B7	In Vitro Inhibition	imipramine	Tricyclics and Tetracyclics
UGT2B7	In Vitro Inhibition	indomethacin	NSAIDS
UGT2B7	In Vitro Inhibition	indoxyl sulfate	None
UGT2B7	In Vitro Inhibition	irinotecan	Topoisomerase Inhibitors
UGT2B7	In Vitro Inhibition	irosustat	Other Antineoplastics
UGT2B7	In Vitro Inhibition	irosustat metabolite 667-coumarin	Other Antineoplastics
UGT2B7	In Vitro Inhibition	isoborneol	Herbal Medications
UGT2B7	In Vitro Inhibition	isomenthol	Food Products
UGT2B7	In Vitro Inhibition	Jumi-haidoku-to aqueous extract	Herbal Medications
UGT2B7	In Vitro Inhibition	kaempferol	Food Products
UGT2B7	In Vitro Inhibition	kanzo aqueous extract	Herbal Medications
UGT2B7	In Vitro Inhibition	ketamine	Anesthetics
UGT2B7	In Vitro Inhibition	ketoconazole	Antifungals
UGT2B7	In Vitro Inhibition	ketoprofen	NSAIDS
UGT2B7	In Vitro Inhibition	liquiritigenin	Herbal Medications
UGT2B7	In Vitro Inhibition	liquiritin (licorice derivative)	Herbal Medications
UGT2B7	In Vitro Inhibition	lithocholic acid	Other
UGT2B7	In Vitro Inhibition	lorazepam	Benzodiazepines
UGT2B7	In Vitro Inhibition	manidipine	Calcium Channel Blockers
UGT2B7	In Vitro Inhibition	meclofenamic acid	NSAIDS
UGT2B7	In Vitro Inhibition	medroxyprogesterone acetate	Antineoplastic Hormonal
UGT2B7	In Vitro Inhibition	mefenamic acid	NSAIDS
UGT2B7	In Vitro Inhibition	midazolam	Benzodiazepines
UGT2B7	In Vitro Inhibition	morphine	Opioids
UGT2B7	In Vitro Inhibition	mycophenolic acid	Immunosuppressants
UGT2B7	In Vitro Inhibition	naloxone	Antidotes
UGT2B7	In Vitro Inhibition	naltriben	Drug Addiction Treatments
UGT2B7	In Vitro Inhibition	naproxen (S-naproxen)	NSAIDS
UGT2B7	In Vitro Inhibition	nifedipine	Calcium Channel Blockers
UGT2B7	In Vitro Inhibition	niflumic acid	NSAIDS
UGT2B7	In Vitro Inhibition	nilotinib	Kinase Inhibitors
UGT2B7	In Vitro Inhibition	nintedanib	Respiratory Agents
UGT2B7	In Vitro Inhibition	nisoldipine	Calcium Channel Blockers
UGT2B7	In Vitro Inhibition	nitrendipine	Calcium Channel Blockers
UGT2B7	In Vitro Inhibition	olanzapine	Antipsychotics
UGT2B7	In Vitro Inhibition	oleandomycin	Antibiotics
UGT2B7	In Vitro Inhibition	otsuji-to aqueous extract	Herbal Medications
UGT2B7	In Vitro Inhibition	oxazepam (3-hydroxy-N-desmethyldiazepam)	Benzodiazepines
UGT2B7	In Vitro Inhibition	p-cresol	None

UGT2B7	In Vitro Inhibition	phenylbutazone	NSAIDS
UGT2B7	In Vitro Inhibition	pirprofen	NSAIDS
UGT2B7	In Vitro Inhibition	propofol	Anesthetics
UGT2B7	In Vitro Inhibition	quercetin	Food Products
UGT2B7	In Vitro Inhibition	quinidine	Antiarrhythmics
UGT2B7	In Vitro Inhibition	quinine	Antimalarials
UGT2B7	In Vitro Inhibition	raspberry ketones	Food Products
UGT2B7	In Vitro Inhibition	ritonavir	Protease Inhibitors
UGT2B7	In Vitro Inhibition	ryo-kei-jutsu-kan-to aqueous extract	Herbal Medications
UGT2B7	In Vitro Inhibition	scutellarein	Herbal Medications
UGT2B7	In Vitro Inhibition	scutellarin	Herbal Medications
UGT2B7	In Vitro Inhibition	sennidin A	Herbal Medications
UGT2B7	In Vitro Inhibition	sesamin monocatechol metabolite	Food Products
UGT2B7	In Vitro Inhibition	shakuyaku-kanzo-to aqueous extract	Herbal Medications
UGT2B7	In Vitro Inhibition	silibinin (silybin; milk thistle derivative)	Herbal Medications
UGT2B7	In Vitro Inhibition	sodium deoxycholate	Endogenous Compounds
UGT2B7	In Vitro Inhibition	sodium taurodeoxycholate hydrate	Endogenous Compounds
UGT2B7	In Vitro Inhibition	spironolactone	Diuretics
UGT2B7	In Vitro Inhibition	steviol	None
UGT2B7	In Vitro Inhibition	sulfinpyrazone	Antigout and Uricosuric Agents
UGT2B7	In Vitro Inhibition	tacrolimus	Immunosuppressants
UGT2B7	In Vitro Inhibition	tamoxifen	Antineoplastic Hormonal
UGT2B7	In Vitro Inhibition	tangeretin	Food Products
UGT2B7	In Vitro Inhibition	taurochenodeoxycholate	None
UGT2B7	In Vitro Inhibition	taurocholic acid sodium salt hydrate	Endogenous Compounds
UGT2B7	In Vitro Inhibition	taurolithocholic acid	Endogenous Compounds
UGT2B7	In Vitro Inhibition	tauroursodeoxycholate sodium	Endogenous Compounds
UGT2B7	In Vitro Inhibition	temazepam (3-hydroxydiazepam)	Benzodiazepines
UGT2B7	In Vitro Inhibition	testosterone	Androgens
UGT2B7	In Vitro Inhibition	thienorphine	Opioids
UGT2B7	In Vitro Inhibition	tiaprofenic acid	NSAIDS
UGT2B7	In Vitro Inhibition	tokaku-joki-to aqueous extract	Herbal Medications
UGT2B7	In Vitro Inhibition	trifluoperazine	Antipsychotics
UGT2B7	In Vitro Inhibition	tripterine (celastrol)	Herbal Medications
UGT2B7	In Vitro Inhibition	ursodeoxycholic acid	Other
UGT2B7	In Vitro Inhibition	valerenic acid (valerian derivative)	Herbal Medications
UGT2B7	In Vitro Inhibition	valproic acid	Anticonvulsants
UGT2B7	In Vitro Inhibition	verapamil	Calcium Channel Blockers
UGT2B7	In Vitro Inhibition	warfarin	Anticoagulants and Antiplatelets
UGT2B7	In Vitro Inhibition	zafirlukast	Antiasthmatics
UGT2B7	In Vitro Inhibition	zidovudine	Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

School of Pharmacy, University of Washington, Drug Interaction Database Program: <https://www.druginteractioninfo.org/>

**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY  
TO EVALUATE THE EFFICACY AND SAFETY OF SAGE-547 INJECTION  
IN THE TREATMENT OF SUBJECTS WITH SUPER-REFRACTORY  
STATUS EPILEPTICUS**

**PROTOCOL NUMBER: 547-SSE-301**

**IND NUMBER: 117901**

**EudraCT Number: 2015-002142-31**

Product: SAGE-547 Injection (allopregnanolone)

Sponsor Contact: [REDACTED], MD

[REDACTED]  
Sage Therapeutics  
215 First Street  
Cambridge, MA 02142

Medical Monitor: [REDACTED], MD

Date of Protocol: 09 March 2015  
Date of Amendment One 27 May 2015  
Date of Amendment Two 17 November 2015  
(Adults Only)  
Date of Amendment Two 21 March 2016  
(Adults Only, Germany  
Specific)

**Confidentiality Statement**

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

**PROTOCOL NUMBER: 547-SSE-301**

Sponsor [REDACTED]:

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]

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[REDACTED]

Sponsor [REDACTED]:

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

CRO [REDACTED]:

[REDACTED]

## 1. SIGNATURE PAGE

Title of Protocol:

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus

Protocol No: 547-SSE-301

### Sponsor Approval

[Redacted Signature]

21 March 2016

[Redacted Name], MD

Date (dd/mmm/yyyy)

Sage Therapeutics

### Investigator Agreement

By signing this page I attest that I have read and understand the contents of Clinical Protocol 547-SSE-301 and any current amendments. I agree to adhere to the design, conduct, and reporting requirements of the study as stated in the clinical protocol and to my obligations to the Sponsor as described in the protocol and executed contracts between myself, my Institution, and the Sponsor. I also agree to adhere to any subsequent amendments to the clinical protocol.

Investigator's Signature: \_\_\_\_\_

Investigator's Name: \_\_\_\_\_

Institution: \_\_\_\_\_

Date: \_\_\_\_\_

## 2. SYNOPSIS

<b>Name of Sponsor:</b> Sage Therapeutics 215 First Street Cambridge, MA 02142																							
<b>Protocol No.</b> 547-SSE-301	<b>Phase:</b> 3																						
<b>Name of Investigational Product:</b> SAGE-547 Injection																							
<b>Name of Active Ingredient:</b> Allopregnanolone																							
<b>Title of the Protocol:</b> A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus																							
<b>Dosing Regimen: SAGE-547 or Placebo Dosing Schedule</b> <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 10px;"> <thead> <tr> <th style="width: 20%;">Hour</th> <th style="width: 40%;">Type and Duration of SAGE-547 Infusions</th> <th style="width: 40%;">Dose</th> </tr> </thead> <tbody> <tr> <td>H1</td> <td>One hour loading Infusion</td> <td>300 µg/kg/h</td> </tr> <tr> <td>H2 – H120</td> <td>119 hour maintenance infusion</td> <td>90 µg/kg/h</td> </tr> <tr> <td>H121 – H128</td> <td>8 hour taper</td> <td>65 µg/kg/h</td> </tr> <tr> <td>H129 – H136</td> <td>8 hour taper</td> <td>45 µg/kg/h</td> </tr> <tr> <td>H137 – H144</td> <td>8 hour taper</td> <td>25 µg/kg/h</td> </tr> </tbody> </table>			Hour	Type and Duration of SAGE-547 Infusions	Dose	H1	One hour loading Infusion	300 µg/kg/h	H2 – H120	119 hour maintenance infusion	90 µg/kg/h	H121 – H128	8 hour taper	65 µg/kg/h	H129 – H136	8 hour taper	45 µg/kg/h	H137 – H144	8 hour taper	25 µg/kg/h			
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<b>Study Sites</b> Up to 180 sites in the USA, Europe, and Canada.																							

**Number of Subjects**

The study will randomize 140 subjects at up to 180 sites.

**Study Population**

Subjects will be aged 18 years or more, in SRSE<sup>1</sup> (as defined in the Inclusion Criteria [Section 8.1](#)), and being managed in an intensive care setting.

**Duration of Subject Involvement**

Individual subject participation will be up to 30 days.

**Study Design**

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

Patients will follow one of three paths to entry to the study. The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst suppression with a third-line agent. These subjects will be consented for the study after admission to the intensive care unit, but before any third-line agents are administered for burst suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their legally authorized representative (LAR). Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours. Once burst suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The second path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst suppression pattern on the EEG. These subjects may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

<sup>1</sup> In this study, the term Super-Refractory Status Epilepticus or SRSE is equivalent to “Refractory Status Epilepticus (RSE) that has failed standard treatment” and the two terms are used interchangeably.



The third path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These subjects may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 treatment or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within six hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo).

The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that subjects, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as both the ability to wean the subject off all third-line agents before the end of the infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication infusion, and concurrent signs of physiologic brain activity as determined by EEG. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#) and [Table 2](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo will all subsequently be eligible to be administered SAGE-547 at the higher dose.

### Visit Schedule

The visit schedule and an overview of events at each visit is provided in [Table 1](#), [Table 2](#) and [Table 3](#) Schedule of Assessments.

**Study Objectives*****Primary objective:***

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult subjects with SRSE, and for the response to endure at least 24 hours after the end of the SAGE-547 or placebo infusion (primary response).

***Secondary objectives:***

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in the Clinical Global Impression scale (CGI) between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

***Safety objectives:***

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

***Other objectives:***

1. To evaluate the impact of retreatment with a higher dose SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;

3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;
6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS).

## Endpoints

### *Primary endpoint:*

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### *Secondary endpoints:*

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### *Safety endpoints:*

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.

**Other endpoints:**

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who fail to respond to their randomized double blind treatment and are retreated with a higher dose of SAGE-547.
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS).

**Inclusion Criteria**

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects 18 years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst suppression pattern; or who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst suppression pattern.

**Exclusion Criteria**

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone or any excipients in SAGE-547.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy.
4. Subjects who have any of the following:

- a. a GFR low enough to warrant dialysis for whatever reason, but dialysis is not planned or non-continuous dialysis is planned (that would not adequately remove Captisol<sup>®</sup>);
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the opinion of the investigator, of less than 30 days;
  - e. a do not resuscitate (DNR) order.
5. Subjects who are being administered more than three third-line agents concomitantly or in whom the qualifying wean cannot be completed within 24 hours, or who are being administered a third-line agent for other indications such as management of raised intra-cranial pressure that would preclude weaning according to this protocol.
  6. Subjects with a living will that does not allow heroic measures.
  7. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
  8. Subjects who have been enrolled in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not withdraw or complete and then re-enroll).

### Pharmacogenetic Research

In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### Statistical Analysis

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

### Interim Analysis

When approximately 50% of the subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### Analysis of Primary Endpoint

The analysis of response to treatment between SAGE-547 treated subjects and placebo treated subjects will be performed using a Cochran-Mantel-Haenszel test with variables for treatment, concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). In this analysis, a treatment responder is a subject who is successfully

weaned off all third-line agents and blinded study medication prior to the end of study treatment infusion and remains off third-line agents for at least 24 hours following cessation of the blinded study medication, and who has concurrent signs of physiologic brain activity as determined by EEG. The analysis will be based on the ITT Population. The comparison of treatment response rates will be conducted at the 5% level of significance.

### **Analysis of Secondary Efficacy Endpoints**

The primary analysis will be repeated for the MITT population. Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section. Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. Secondary analyses will be repeated for the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from Baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third-line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

Summaries of safety endpoints will be based on the overall Safety Population which is defined as all subjects who at least initiated the infusion with blinded study treatment.

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are retreated with SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo. Summary statistics will be presented for subjects who were QW successes.

### **Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

**Table 1: Schedule of Assessments for Protocol 547-SSE-301: One Infusion of Study Drug (blinded)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical/SE/Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X		X	X	X	X	X	X				
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X		X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X		X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X		X	X		X		X		X		
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X			
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>n</sup>											X
Modified Rankin Score (mRS)	X <sup>n</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV 3rd-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>o</sup>				
EEG	X	X				X		X	X			
Randomization		X										
Study Drug Administration <sup>p</sup>			X	X	X	X	X	X				
TW Outcome & Retreat Decision										X <sup>q</sup>		
Physiologic Brain Activity									X			
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

**Table 2: Schedule of Assessments for Protocol 547-SSE-301: Two Infusions of Study Drug (one blinded, one open-label)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V3R
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	0-24h
Eligibility Checklist	X										S
Informed Consent <sup>a</sup>	X										E
Inclusion/Exclusion Criteria	X										E
Demography <sup>b</sup>	X										
Medical and SE and Wean History <sup>c</sup>	X										T
Height	X										A
Weight <sup>d</sup>	X		X	X	X	X	X	X			B
Serum Pregnancy Test <sup>e</sup>	X										L
Hematology <sup>f</sup>	X		X	X		X		X		X	E
Serum Chemistry and GFR <sup>g</sup>	X		X	X		X		X		X	
Urinalysis <sup>h</sup>	X		X	X		X		X		X	E
Pharmacogenetic sample	X										X
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X	T
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X	E
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X		N
STESS	X										I
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	O
Glasgow Outcome Score (GOS)											N
Supervision Rating Scale (SRS)	X <sup>n</sup>										
Modified Rankin Score (mRS)	X <sup>n</sup>										
Epilepsy Status	X										N
Clinical Global Impression (CGI)	X										E
Continuous IV Third-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>o</sup>			X
EEG	X	X				X		X	X		T
Randomization		X									
Study Drug Administration <sup>p</sup>			X	X	X	X	X	X			
TW Outcome and Retreat Decision										X <sup>q</sup>	P
Physiologic Brain Activity									X		
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X	A
Concomitant Anti-Epileptic Drugs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	G
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	E
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X	
Pharmacoeconomic Data											
Mortality											



Table 2 continued

	V3R	V4R	V5R	V6R	V7R	V8R	V9R	V10R	V11R	V12R
	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3R+14d (±2d)	V3R+21d (±2d)
Weight <sup>d</sup>	X	X	X	X	X	X				
Serum Pregnancy Test <sup>e</sup>										
Hematology <sup>f</sup>	X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X	X		X		X		X		
Vital Signs <sup>i</sup>	X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>	X	X	X	X	X	X	X			
STESS										
FOUR Score <sup>m</sup>	X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)										X
Supervision Rating Scale (SRS)										X
Modified Rankin Score (mRS)										X
Epilepsy Status										X
Clinical Global Impression Scale (CGI)										X
Continuous IV Third-Line Agent(s)	X	X	Wean	Wean	Wean	Wean <sup>o</sup>				
EEG			X			X	X			
Randomization										
Study Drug Administration <sup>p</sup>	X	X	X	X	X	X				
TW Success and Physiologic Brain Activity							X			
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data										X
Mortality										X

**Table 3: Schedule of Assessments for Protocol 547-SSE-301: Qualifying Wean Successes**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical and SE and Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X											
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X											
Serum Chemistry and GFR <sup>f</sup>	X											
Urinalysis <sup>h</sup>	X											
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X											
ECG <sup>j</sup>	X											
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>n</sup>											X
Modified Rankin Score (mRS)	X <sup>n</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV Third-Line Agent(s)	X	Wean										
EEG	X	X										
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

<sup>a</sup> Written informed consent by proxy (LAR) will be obtained prior to starting any study-related procedures not considered standard of care.

<sup>b</sup> Demographic information will be obtained by proxy and confirmed by the subject when possible.

<sup>c</sup> Medical history will be obtained by proxy and confirmed by the subject when possible. All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Dosing changes with the third-line agent(s) that constitute a wean attempt will be marked as such on the CRF, and the start/stop dates and times of all wean attempts prior to V3 will be recorded, as well as the outcome of the wean attempt.

- <sup>d</sup> Weight will be collected at Screening (V1) and once during each 24 hour period of the initial study drug infusion period (V3-V8) and second infusion period (V3R-V8R, if applicable). Daily weight will be used to determine the appropriate infusion rate of each dose.
- <sup>e</sup> Serum pregnancy test for females aged 18 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy.
- <sup>f</sup> Blood samples will be taken for hematology and serum chemistry and GFR calculation at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will document whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.
- <sup>g</sup> Blood samples will be taken at V11 or V11R for serum chemistry (renal panel only).
- <sup>h</sup> Urine samples will be taken for urinalysis and NAG at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will add a comment about whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.
- <sup>i</sup> Vital signs will be recorded at the following time points relative to the start of each infusion of study drug: Screening (V1), at 0, 30, 60 minutes ( $\pm 15$  minutes), at 2, 4, and 8 hours ( $\pm 30$  minutes), and at 24, 48, 72, 96, 120, 144, 168, and 192 hours ( $\pm 2$  hours).
- <sup>j</sup> ECG (12-lead) should be performed at Screening (V1) and at the following times relative to the start of study drug infusion. For the blinded (first) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 128, 136, 144, 152, 160, and 192 hours ( $\pm 2$  hours). For the open label SAGE-547 (second) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 126, 132, 138, 144, 152, 160, and 192 hours ( $\pm 2$  hours). Heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours.
- <sup>k</sup> Plasma will be collected to assay for study drug concentrations at the following time points relative to the start of each infusion of study drug: For the blinded (first) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion. For the open label SAGE-547 (second) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open label SAGE-547 study drug infusion. Pre-dose samples may be taken within two hours before starting the infusion of study drug; timepoints up to and including 1h will have a time window of  $\pm 5$  minutes; all other timepoints will have a window of  $\pm 15$  minutes.
- <sup>m</sup> FOUR Score assessments will be performed at Screening (V1), 24, 48, 72, 96, 120, 144, 168, and 192 hours (all  $\pm 2$  hours) relative to the start of each infusion of study drug, and at V11 or V11R, and at V12 or V12R.
- <sup>n</sup> SRS at V1 will be a retrospective assessment of the supervision required by the subject immediately prior to admission that includes the index episode of the SE, and mRS at V1 will be a retrospective assessment of the disability and dependence of the subject immediately prior to admission that includes the index episode of the SE.
- <sup>o</sup> Target for complete wean of all continuous IV third-line agents by 144 hours at V8/V8R if not completed by 120 hours at V7/V7R.
- <sup>p</sup> Study drug infusion is intended for IV administration only with a dedicated peripheral IV line using Sage-approved IV administration bags and lines.
- <sup>q</sup> At V10 only a decision to re-treat at a higher dose of SAGE-547 will be made by the Investigator if the continuous IV third-line agent wean has failed or the third-line agent requires re-introduction during V9. Subjects who become eligible for re-treatment at a higher dose of SAGE-547 will discontinue the planned visit schedule at V10, then repeat V3 (V3R) and all applicable subsequent visits.
- <sup>r</sup> AEs will be collected from the time Informed Consent is obtained and prior to the start of study-specific screening procedures not considered standard of care. Collection of AEs will continue throughout the study from V1 through V12 or V12R.
- <sup>s</sup> Subjects may enter the study on AEDs and be administered AEDs during the study. All Concomitant AEDs must be recorded on the CRF with details including date and time of starting/stopping each AED, the route of administration, changes in doses, and frequency of administration. Details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the CRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.
- <sup>t</sup> All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Details will include the name of the drug, the start/stop dates and times, and, after consent, the doses with start/stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

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**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
AE	adverse event
AED	anti-epileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the time-concentration curve
AW	additional weans
BDZ	benzodiazepine
BIEEG	blinded infusion electroencephalogram
BUN	blood urea nitrogen
CBC	complete blood count
CEEG	consent electroencephalogram
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
C <sub>max</sub>	maximum plasma concentration
C <sub>min</sub>	minimum plasma concentration
CNS	central nervous system
CRF	case report form
CSR	clinical study report
CYP2C9	cytochrome P450 enzyme involved in drug metabolism
DNR	do not resuscitate
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EEG	electroencephalogram
EIND	Emergency Use Investigational New Drug Application
EP	European Pharmacopeia
ESETT	Established Status Epilepticus Treatment Trial
FDA	Food and Drug Administration
FOUR	Full Outline of UnResponsiveness
GABA	$\gamma$ -aminobutyric acid
GABA <sub>A</sub>	$\gamma$ -aminobutyric acid-gated chloride channel

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GOS	Glasgow Outcome Scale
H	hour
HPLC	high performance liquid chromatography
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent to Treat
IV	intravenous
IVRS	Interactive Voice Randomization System
LAR	legally authorized representative
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent to Treat
mRS-9Q	Modified Rankin Score - 9Q
MS/MS	tandem mass spectrometry
nM	nanomolar
NMDA	n-methyl-D-aspartic acid
OW	other weans
PAEEG	primary endpoint electroencephalogram
PD	pharmacodynamics
PK	pharmacokinetic
QOL	quality of life
QW	qualifying wean
QWEEG	qualifying wean electroencephalogram
RBC	red blood cell

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
RSE	refractory status epilepticus
SAE	serious adverse event
SAP	Statistical Analysis Plan
SE	status epilepticus
SOP	standard operating procedure
SRS	Severity Rating Scale
SRSE	Super-refractory status epilepticus
SSRI	Selective serotonin re-uptake inhibitors
STESS	Status Epilepticus Severity Score
SUSAR	Suspected Unexpected Serious Adverse Reactions
SWFI	Sterile Water for Injection
TAEEG	taper electroencephalogram
T <sub>max</sub>	time at maximum plasma concentration
TW	terminal wean
TWEEG	terminal wean electroencephalogram
US	United States
USP	United States Pharmacopeia

### 3. INTRODUCTION AND RATIONALE

#### 3.1. Status Epilepticus

Status epilepticus (SE) is a life-threatening seizure condition in which the brain is in a state of persistent seizure triggered by neuronal hyperexcitability. The Neurocritical Care Society defines SE as one continuous unremitting seizure lasting longer than five minutes or recurrent seizures without regaining consciousness between seizures for greater than five minutes (Brophy, Bell et al. 2012). Common causes of SE include preexisting epilepsy, cerebrovascular disease (in adults), electrolyte and metabolic disturbances, anoxia, encephalopathies, head trauma, high fever (in children, especially in the first year of life) and drug or substance intoxication. SE is associated with substantial morbidity and mortality.

##### 3.1.1. Epidemiology of SE

Geography, sex, age, and race influence the epidemiology of SE, whose incidence has a bimodal distribution, peaking in infants/young children and the elderly (Hauser 1990; DeLorenzo, Pellock et al. 1995; Wu, Shek et al. 2002). The incidence of SE in the elderly population is at least twice that in the general population. Concurrent medical conditions often exist in the elderly population, which can complicate therapy and worsen the prognosis of SE (Chapman, Smith et al. 2001).

The annual incidence of SE in the US is generally quoted to be within the range of 18/100,000 to 61/100,000, based on a 19-year retrospective study in Rochester, Minnesota (Hesdorffer, Logroscino et al. 1998) and a 2-year prospective study in Richmond, Virginia (DeLorenzo, Pellock et al. 1995), respectively. Two studies from Europe give annual incidences of a similar magnitude, ranging between 9.9/100,000 and 15.8/100,000 (Coeytaux, Jallon et al. 2000; Knake, Rosenow et al. 2001). It is thus estimated that in the United States each year there are as many as 150,000 cases of SE (DeLorenzo, Pellock et al. 1995).

#### 3.2. Refractory SE

When a patient begins to seize, the emergency medical technician will administer a first-line intravenous (IV) benzodiazepine (BDZ), such as diazepam, lorazepam or midazolam (Silbergleit, Durkalski et al. 2012), which is done either at the scene of the seizure or in the ambulance. If this is unsuccessful at abating the seizure, additional doses of the first-line therapy will be administered in the emergency room. Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line therapy, which is an IV anti-epileptic drug (AED) such as phenytoin or valproic acid (Novy, Logroscino et al. 2010; Shorvon 2011; Hocker, Britton et al. 2013).

Approximately 20-30% of patients refractory to first-line treatment will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to approximately 70-80% of patients who receive second-line therapy refractory to that therapy.

If a patient's SE continues after administration of BDZs and AEDs, the subject is diagnosed as having refractory status epilepticus (RSE), which must be treated quickly to terminate the seizure activity, maintain the patient's airway, and prevent cerebral damage. RSE patients are immediately admitted to the Intensive Care Unit (ICU) and placed in a medically-induced coma to stop all seizure-related activity. The drugs used to induce coma are continuously-infused IV agents,

commonly propofol, midazolam, or pentobarbital/thiopental, referred to as third-line agents (Brophy, Bell et al. 2012).

The RSE patient is continually monitored using electroencephalography (EEG) to ensure burst suppression is achieved. Burst suppression is a pattern of brain waves seen on an EEG, characterized by periods of activity alternating with periods of little or no activity in the brain, informing medical personnel of the effectiveness of the medically-induced coma. The goal of burst suppression is to allow the brain and corresponding neuronal tissue to restore function and reset to normal pre-seizure levels.

### **3.2.1. Epidemiology of RSE**

Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line AED therapy. In turn, approximately 20 – 30% of these patients treated with AEDs will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to 28% of the total estimated SE patient population refractory to second-line therapy. Based on the previously-cited estimated incidence in the US, this means that there are up to 42,000 incident cases of RSE in the USA, annually (DeLorenzo, Pellock et al. 1995).

### **3.3. Super-refractory SE**

After 24 hours of burst suppression, the patient is weaned off of the third-line therapy. If the weaning is unsuccessful (neuronal activity has not returned to normal), the third-line agent is re-administered or a different third-line agent is started, and the patient is considered to be in super-refractory status epilepticus (SRSE) (Chapman, Smith et al. 2001; Shorvon 2011; Brophy, Bell et al. 2012). SAGE-547 is being developed as an adjunct to third-line therapy in patients in RSE who have failed standard treatment. In this protocol, the term “RSE that has failed standard treatment” is deemed to be equivalent to the term “SRSE” and the two may be used interchangeably.

#### **3.3.1. Epidemiology of SRSE**

The incidence of SRSE is very poorly understood, mainly because the diagnostic codes used for SE do not generally differentiate its nature as responding or refractory to treatment. Based on the variable reporting of outcomes data, the incident cases of SRSE could represent between one and two-thirds of the RSE patients (Novy, Logroscino et al. 2010; Ferlisi and Shorvon 2012; Hocker, Britton et al. 2013; Sutter, Marsch et al. 2013). More detailed epidemiology studies are needed to better elucidate the proportion of RSE patients whose condition becomes super-refractory. A recent review of ICU discharge data in the USA suggests an annual incidence of approximately 35,000, based on patients who required at least three days in the ICU for SE [Sage data on file].

#### **3.3.2. Outcomes of SRSE**

SE has varying degrees of mortality depending on the underlying etiologies. Table 4 outlines the acute mortality in patients with SE by etiology (Neligan and Shorvon 2010). The mortality rate of SRSE is estimated to be 30% to 50% using current standard of care.

The causes of death from SE (and therefore SRSE) are heterogeneous, resulting from neuronal cell death, complications of underlying medical conditions, or adverse effects of the current standard treatments. Prognosis worsens and mortality increases with longer duration of SE, i.e. with SE that develops into RSE or SRSE (Neligan and Shorvon 2010), and with longer duration of

medically-induced coma ([Ferlisi and Shorvon 2012](#)). There is an obvious unmet medical need to improve upon the current standard of care treatment regimens.

Morbidity is high and survivors have outcomes ranging from poor function to vegetative state ([Shorvon 2011](#)). Approximately one third of patients with RSE and SRSE will recover, but with chronic neurologic or other deficits ([Neligan and Shorvon 2010](#); [Hocker, Britton et al. 2013](#)). In all, it is estimated that less than 25-30% of all SRSE patients have a favorable functional outcome.

**Table 4: Approximate Mortality of Status Epilepticus in Different Etiologies**

Underlying Etiology	Associated Acute Mortality in Patients with SE (%)
Drug reduction/withdrawal, poor AED compliance, or low AED levels	0-10
Cerebrovascular Disease	20-60
Metabolic Disorders	10-35
Acute CNS Infection	0-30
Anoxia	60-100
Alcohol Abuse	0-10
Head Trauma	0-25
Drug Overdose/Toxicity	10-25
Brain Tumors	0-20
Cryptogenic/Idiopathic	5-20

### 3.3.3. Unmet Medical Need in Super-refractory Status Epilepticus

Treatment approaches for SRSE consist of diagnosis and treatment of underlying medical conditions, adding and changing anti-seizure drugs, and repeated attempts at weaning from IV anesthetic agents. Treatment of SRSE has three aims:

- to prevent excitotoxicity, which begins within 24 hours of SE onset;
- to prevent cerebral damage by initiating neuroprotective burst suppression;
- to prevent the complications of extended periods of anesthesia or unconsciousness ([Shorvon 2011](#)).

Currently, there are no therapies that have been specifically approved for RSE or SRSE. The primary drugs used to induce coma are continuously infused IV anesthetics such as propofol, midazolam, or pentobarbital/thiopental, known as third-line agents. Use of these drugs to control SRSE has only been studied in small retrospective reviews or small prospective studies without controls ([Hocker, Britton et al. 2013](#)) therefore there is no agreement on which drug is optimal nor on an optimal dosing regimen for the treatments that are used.

The most common adverse effect of the third-line agents is hemodynamic instability; in addition, they are not universally effective, with breakthrough seizures and withdrawal seizures requiring dose adjustments and changes in third-line agent(s). The drug thought to be most effective in SRSE, pentobarbital, is also associated with the most toxic adverse effect profile, comprising



decreased blood pressure and cardiorespiratory collapse (Claassen, Hirsch et al. 2002). The ability to wean patients successfully off the third-line agents as quickly as possible is therefore paramount, and an adjunct to SRSE treatment that enhances the success of the third-line agents and supports their successful weaning in a short timeframe would be an important addition to the therapeutic armamentarium. Preliminary clinical data show that SAGE-547 has been a successful adjunct to third-line therapy in this regard.

### 3.4. SAGE-547 Injection

Allopregnanolone is an endogenous, naturally occurring neuroactive steroid formed in the corpus luteum of the ovary, adrenal cortex and central nervous system (CNS) (Holzbauer, Birmingham et al. 1985; Paul and Purdy 1992; Ottander, Poromaa et al. 2005). It is a metabolite of progesterone created by the actions of 5- $\alpha$  reductase and 3- $\alpha$  hydroxy-steroid dehydrogenase. Allopregnanolone is a potent positive allosteric modulator of both synaptic and extra-synaptic GABA<sub>A</sub> receptors.

SAGE-547 Injection (allopregnanolone aqueous formulation in Captisol<sup>®</sup>) is being developed for the treatment of patients in RSE who have not responded to standard treatment. SAGE-547 Injection is a solution of 5 mg/mL allopregnanolone in Sterile Water for Injection (SWFI), USP and 250 mg/mL betadex sulfobutyl-ether sodium, NF. It is further diluted with Sterile Water for Injection, USP (SWFI) in IV bags to achieve an allopregnanolone concentration of approximately 1.67 mg/mL in an approximately isotonic solution and will be administered intravenously.

#### 3.4.1. Scientific Rationale for SAGE-547 in SRSE

Ineffective recruitment of inhibitory neurotransmission, together with excessive neuronal excitation, likely plays a role in the initiation and propagation of the electrical disturbance occurring in SE. GABA ( $\gamma$ -aminobutyric acid), the major inhibitory neurotransmitter in the central nervous system (CNS), is released from GABAergic neurons and binds to several types of GABA receptors (GABA<sub>A</sub>, GABA<sub>B</sub>, and GABA<sub>C</sub>) on target neurons. GABA<sub>A</sub> receptors are macromolecular proteins that form a chloride ion channel complex and contain specific binding sites for GABA and a number of allosteric regulators, including barbiturates, benzodiazepines, and some anesthetic agents. GABA receptor-mediated inhibition contributes significantly to the normal termination of a seizure (Kapur and Macdonald 1997). SAGE-547 is a positive allosteric modulator of the GABA<sub>A</sub> receptor.

The importance of terminating seizure activity as soon as possible is underpinned by a growing body of evidence from research and clinical observation that SE becomes more difficult to control as its duration increases. It has been postulated that this occurs due to a mechanistic shift from inadequate GABAergic inhibitory receptor-mediated transmission to excessive N-methyl-D-aspartic acid (NMDA) excitatory receptor-mediated transmission (Kapur and Macdonald 1997). As prolonged epileptiform bursting results in a reduction of GABA<sub>A</sub>-mediated synaptic inhibition, antiepileptic treatments which rely on enhancing intrasynaptic GABA<sub>A</sub> neurotransmission become less effective the longer SE continues.

Furthermore, the constitutive process of synaptic GABA<sub>A</sub> receptor internalization is accelerated by the increased neuronal activity associated with seizures. These findings suggest that the rate of GABA<sub>A</sub> receptor internalization is regulated by neuronal activity, and its acceleration contributes to the reduction of inhibitory transmission observed during prolonged seizures (Kapur and Macdonald 1997). Of note is that SAGE-547 binds to extrasynaptic as well as intrasynaptic GABA<sub>A</sub> receptors;

extrasynaptic receptors remain active with ongoing seizure activity, resulting in a putative mode of action for SAGE-547 in SRSE.

Status epilepticus induces cerebral damage that includes neuronal cell necrosis, gliosis, and network reorganization. The major cause of cell death in cerebral damage is excitotoxicity, which is initiated by glutaminergic receptor over-activation, causing calcium to flood the cell, thereby leading to apoptosis and necrosis. This process is initiated within a few hours of the start of seizure activity, and provides the medical imperative to terminate SE as quickly as possible. To prevent the consequences of the excitotoxicity cascade, it is recommended that anesthesia be initiated within 1-2 hours of onset of seizures at doses designed to induce EEG burst suppression ([Shorvon and Ferlisi 2011](#)).

### **3.4.2. SAGE-547 Clinical Program in the Treatment of SRSE**

The current SAGE-547 development program includes:

- an ongoing Phase 2 open-label trial, Study 547-SSE-201;
- this proposed Phase 3 randomized, double-blind, placebo-controlled trial, Study 547-SSE-301;
- a planned open-label, expanded access protocol, Study 547-SSE-302;
- a number of EINDs for SAGE-547 in patients with SRSE.

The designs of these studies are all similar, with a five to six day infusion of SAGE-547 (or placebo), during which time attempts are made to wean the subject off all third-line agents. In the Phase 3 studies, those subjects who cannot be weaned off third-line agents while being administered SAGE-547 (or placebo) will be eligible for a second open-label infusion of SAGE-547 at a higher dose, which is also being employed for the latter patients being enrolled in the Phase 2 study. Follow up of subjects is for 21 – 30 days after the first infusion of study medication.

### **3.4.3. Data from the SAGE-547 Development Program**

The data from 30 subjects included in the on-going clinical evaluation of SAGE-547 for the treatment of adults and children with SRSE clearly offers preliminary evidence that SAGE-547 could provide substantial and clinically significant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate. These subjects comprise 20 from the ongoing Phase 2 trial (71% success rate in 12/17 evaluable subjects) and 10 subjects who received EIND treatments (78% success rate in 7/9 evaluable subjects).

Successful therapy of SRSE has been defined as “the SE is completely controlled by the therapy, without breakthrough of withdrawal seizures, or discontinuation due to side effects or death during therapy,” ([Ferlisi and Shorvon 2012](#)). By this definition, which is in accord with the efficacy assessments used in the overall clinical evaluation of SAGE-547, 19 of the 26 (73%) subjects with SRSE who completed the SAGE-547 infusion were treatment successes. As data collection is ongoing, this information is preliminary and subject to change upon further monitoring.

Published reports on RSE and SRSE have stated mortality rate ranges from 35% to 65%. The underlying etiologies of SE in the 547-SAGE-201 study and EINDs are heterogeneous, and each one conveys a different risk of mortality and longer term morbidity. However, the death rate in subjects who have received SAGE-547, 6 out of 30 (20%) subjects, appears to be lower than the published

rates. None of the deaths were considered related to SAGE-547: brain tumor, organophosphate toxicity, respiratory failure, respiratory arrest due to ventilator support withdrawal, and breast cancer.

In the Phase 2 study, 20 SAEs (15 non-fatal) have been reported in 13 (65%) subjects, and of these 3 events in 2 subjects (10%) were considered by the investigator to be related to SAGE-547: pulmonary emboli and tracheostomy dehiscence/infection. The Sponsor did not consider these events to be related to SAGE-547, rather to the underlying disease states. Four of the 20 subjects (20%) experienced AEs considered possibly related to SAGE-547 by the investigator, namely moderate myopathy and severe pulmonary emboli in 1 subject, moderate tracheostomy dehiscence and tracheostomy infection in 1 subject, moderate thrombocytosis in 1 subject and moderate BUN, ALT and AST elevation in 1 subject.

Review of the most current safety data from 547-SAGE-201 reveals that there were changes in serum chemistry, hematology, and urinalysis during the study, but that none of those changes were assessed as related to SAGE-547. There were also no SAGE-547-related changes to vital signs.

Despite the heterogeneity in the underlying causes of SE, the ages of the subject, comorbidities, which normally complicate the treatment of SE, and the fact that all subjects had failed current standard of care treatment, a large majority of subjects had a successful therapy outcome, with discontinuation of all third-line agents and resolution of SE.

Refer to the Investigational Brochure for further information on the pre-clinical and clinical data supporting the use of SAGE-547 in SRSE.

### **3.5. Study Rationale - SAGE-547 in SRSE**

#### **3.5.1. Justification for the Control Group**

Although SAGE-547 has demonstrated extremely promising activity in subjects with SRSE, both in the Phase 2 study and during the EINDs, these have been open-label investigations with no control data for comparison. Generally in the literature there are few data describing the success rates of wean attempts of third-line agents, and few comparative data on the effectiveness of the three main third-line agents, propofol, pentobarbital/thiopental, and midazolam.

Several options for a control group in Study 547-SSE-301 were considered:

- No control group was thought to be unacceptable since there are no reliable published data on success rates in this population that could be used for broad comparisons;
- An active control was considered but found to be impractical since none of the third-line agents are approved for their use in SRSE, no standardized dosing regimens or treatment guidelines have been adopted for the management of SRSE, and clinicians were unlikely to agree which of the available third-line agents would be reserved for the active control arm;
- Historical controls were considered but abandoned because of the practical difficulties of obtaining high quality data, the lack of ability to prospectively match cases, and a suspicion that clinical practice in the standard of care of SRSE is evolving, mandating the use of prospective, concurrent control data;
- Comparison to standard of care alone was considered as a feasible design. However, in a field where no widely adopted treatment guidelines exist, there was a concern that knowledge of the treatment group (SAGE-547 plus standard of care versus standard of care

alone) would alter the behavior of the investigators such that they could be more aggressive with weaning in the SAGE-547 group;

- Placebo control is not without its challenges since the preliminary efficacy data for SAGE-547 show that the compound exerts central pharmacological effects and is associated with positive outcomes in around 70% of patients. There is therefore a potential ethical concern about administering placebo to desperately ill patients who have often exhausted all treatment options for SRSE. This concern has been addressed in two ways: firstly all patients receive current standard of care; secondly, all subjects who fail to be weaned from their third-line agents at the end of the blinded infusion of study drug will be administered open-label SAGE-547 without un-blinding their initial treatment allocation, so treatment with the investigational product is not denied, but delayed about a week in the setting of ongoing receipt of full current standard of care.

It was therefore decided that a blinded, placebo-controlled design was appropriate for Study 547-SSE-301.

### **3.5.2. Justification for the Dose Regimen**

The standard dose regimen has been studied in 19 subjects in the 547-SSE-201 Phase 2 trial; the average peak plasma concentration of SAGE-547 at the end of the loading dose was approximately 144 ng/ml. The average plasma concentration during the maintenance infusion was approximately 70 ng/ml. At these concentrations, there were no clear safety signals although two-thirds of subjects experienced an SAE and there were four deaths, all related to the underlying comorbid conditions. The standard dosing regimen was associated with an approximate 70% successful treatment outcome. For these reasons, the standard dosing regimen has been adopted for the initial SAGE-547 infusion to be compared in a blinded fashion to placebo.

In the 547-SSE-201 trial, three subjects have thus far received the higher dose regimen. This dose regimen has also been well tolerated. The average peak plasma concentrations at the end of the loading dose for both dosing regimens will be in the same range, as the loading dose is the same for both regimens. The average plasma concentrations observed during the higher maintenance dose are 102 ng/ml (n=2). The rationale for adopting the higher dose regimen as the open-label infusion of SAGE-547 for subjects who are retreated in this 547-SSE-301 trial is that those who fail on the standard SAGE-547 dose regimen are afforded the opportunity to have access to a higher dose. The justification to also administer the higher dose regimen to failures on placebo is that the regimen has thus far been well tolerated, and this methodology preserves the blind for the initial infusion.

A five-day dosing regimen with SAGE-547 was investigated in the Phase 2 study, 547-SSE-201. There were some cases when weaning off all third-line agents was not possible within 48 hours, but weaning was completed after the end of the infusion of SAGE-547. For this reason, the duration of dosing with SAGE-547 has been increased from 120 hours (five days) in Phase 2 to 144 hours (six days) in this Phase 3 study.

### **3.5.3. Rationale for Genetic Testing Sub-study**

Sage Therapeutics intends to perform genetic research in the SAGE-547 development program in order to explore how genetic variations may affect the metabolism and activity of SAGE-547. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials, and, possibly, to genetically-guided

treatment strategies for optimizing decision making with respect to individual benefit:risk. Participation of subjects in genetic research as part of the overall clinical study is optional.

### **3.6. Benefit-Risk Evaluation of the Present Study**

Previous reports of human administration of exogenous allopregnanolone indicate that for exposures in men and women up to 150 nM, the most commonly reported AEs were sedation (recorded as sleepiness or tiredness), feelings of intoxication (like alcohol), flushing, and mild headache (Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007). No SAEs were reported (Navarro, Kaddouz et al. 2003; Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007; Kask, Backstrom et al. 2008; Kask, Backstrom et al. 2009; Timby, Hedstrom et al. 2011a). In view of the reduced consciousness and sedation of study subjects at entry into this protocol, none of these previously-reported events are likely to impact subjects in this study.

To date, in the SAGE-547 Phase 2 study and the EIND subjects, a majority of subjects demonstrated a successful therapy outcome (>70%). The majority in the clinical trial (65%) have also experienced SAEs, but none has been considered related to SAGE-547 by the Sponsor (SAEs in 2 subjects (10%) were considered possibly related by Investigator). Five deaths have been reported in 30 subjects (20%), all related to the underlying cause of SRSE and not related to SAGE-547 – this is in the context of published mortality rates between 35% and 65%. These preliminary data suggest that SAGE-547 has the potential to provide clinically relevant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate.

The underlying etiologies of SE are heterogeneous, and each one conveys a different risk of mortality. Subjects who survive SRSE still have a high risk of severe morbidity (Neligan and Shorvon 2010). The subjects treated with SAGE-547 in Study 547-SSE-201, are heterogeneous in factors such as age and etiology of SE, factors that usually complicate treatment and can increase morbidity and mortality. Even with this heterogeneity, the preliminary efficacy and safety data for SAGE-547 are very encouraging, and the mortality rate suggests that the risk to benefit assessment of this treatment rests on the side of benefit.

## **4. ETHICS**

### **4.1. Institutional Review Board or Independent Ethics Committee**

This protocol will be reviewed and approved by the Institutional Review Board (IRB) where the study is conducted. The IRB will meet all FDA requirements governing IRBs (CFR, Title 21, Part 56).

### **4.2. Ethical Conduct of the Study**

The Sponsor, the Medical Monitor, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable ICH and GCP guidelines, and must also conduct the study in accordance with local regulations.

### **4.3. Subject Information and Informed Consent**

Subjects prospectively enrolled in this study will be unable to give consent. Therefore, consent will be given by proxy by a legally authorized representative (LAR). Written informed consent is required for each subject prior to any testing under this protocol not considered standard of care,

including screening tests and evaluations. Should a subject gain the ability to sufficiently comprehend the situation and consent during the course of the study, written informed consent or verbal assent will be documented as required or recommended by the institution's IRB.

The form of consent to be obtained will depend on the condition of the subject as determined by the Principal Investigator. The informed consent form (ICF), as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50.

It is the responsibility of the Investigator to obtain consent and to provide the subject's LAR with a copy of the signed and dated informed consent form. The informed consent form for subject participation must also be available as part of the subject file for review by the site's dedicated study monitor or any authorized auditor of the Sponsor or regulatory authorities.

All ICFs used in this study must be approved by the appropriate IRB and by the Sponsor. The ICF must not be altered without the prior agreement of the relevant IRB and the Sponsor.

#### **4.4. Ethical and Regulatory Considerations for Pharmacogenetic Sub-study**

##### **4.4.1. Informed Consent for Pharmacogenetics**

The genetic component of this study is optional and subjects may participate in other components of the main study without having to agree to participate in the genetic component. If subject chooses to participate in the genetic component of the study, the subject or LAR must sign and date a specific consent form for the genetic component of the study in addition to the main study consent form. The principal investigator(s) is responsible for ensuring that consent is freely given and that the subject understands that they may discontinue from the genetic aspect of the study independent of their decision to remain within or withdrawal from the main study.

##### **4.4.2. Subject Data Protection Relative to Pharmacogenomics**

Sage Therapeutics will not provide individual genotype results to subjects, their family members, their general physician, their employer or any insurance company unless required to do so by law. While extra precautions will be taken to preserve confidentiality and to prevent genetic data from being linked to an individual's identity outside of a restricted access site, in certain exceptional situations (e.g. in case of a medical emergency or as a consequence of a specific regulatory need), certain individuals may see both genetic data and the personal identifiers of a subject; however in all cases a subject's medical information and genetic files will remain physically separated.

## **5. STUDY OBJECTIVES**

### **5.1. Primary Objective**

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult subjects with SRSE, and for the response to endure at least 24 hours after cessation of the SAGE-547 or placebo infusion (primary response).

## 5.2. Secondary Objectives

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in Clinical Global Impression Scale between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

## 5.3. Safety Objectives

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

## 5.4. Other Objectives

1. To evaluate the impact of retreatment with a higher dose of SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol<sup>®</sup> and identified SAGE-547 metabolite plasma concentrations;
3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;

6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS).

## **6. ENDPOINTS**

### **6.1. Primary Endpoint**

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### **6.2. Secondary Endpoints**

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) and to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### **6.3. Safety Endpoints**

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.



## 6.4. Other Endpoints

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who fail to respond to their randomized double blind treatment and are retreated with a higher dose of SAGE-547;
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS).

## 7. INVESTIGATIONAL PLAN

### 7.1. Overview of Study Design

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

Figure 1 provides an overview of the study design and Figure 2 gives the details of treatment and follow-up on the active treatment arm. Patients will follow one of three paths to entry to the study. The first path is for patients who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst suppression with a third-line agent. These patients will be consented for the study after admission to the intensive care unit, but before any third-line agents are administered for burst suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their LAR. Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours. Once burst suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see Table 3). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The second path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst suppression pattern on the EEG. These patients may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at

least 24 hours of continuous burst suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The third path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These patients may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within six hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third line agent wean attempts prior to randomization (one vs two or more).

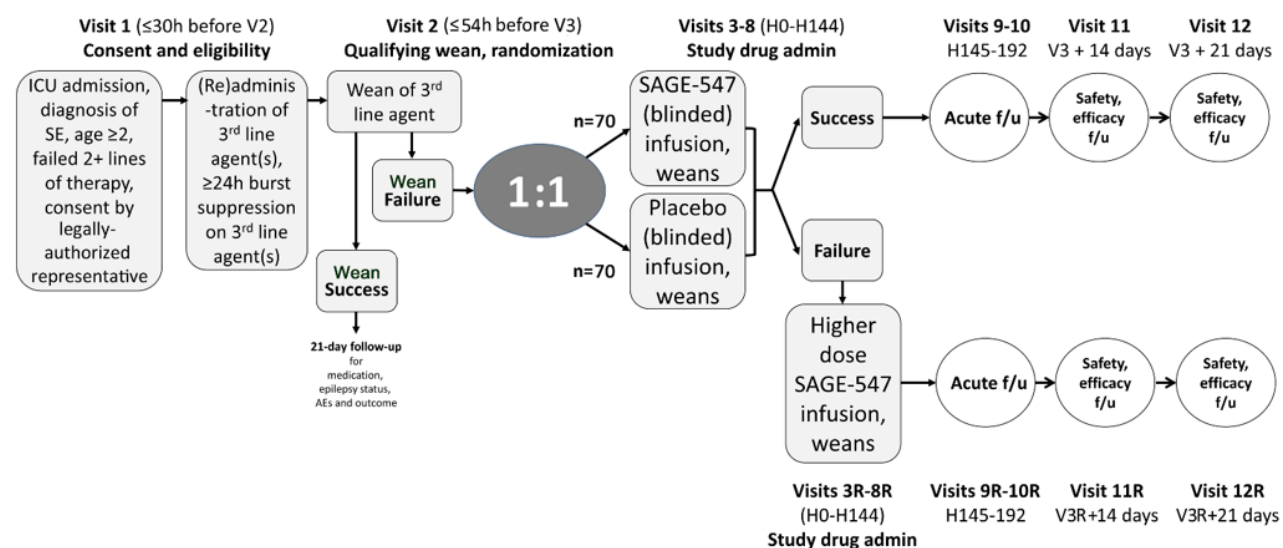
The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as the ability to wean the subject off all third-line agents before the end of the first infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication. Subjects must also have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) at the end of the primary endpoint assessment period as determined by EEG in order to be deemed a success. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#), [Table 2](#) and [Table 3](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. Eligibility for retreatment must be confirmed in writing by the medical monitor prior to the open-label infusion starting. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo will all subsequently be eligible to be administered SAGE-547 at the higher dose.

**Figure 1: Study Design**



## 7.2. Trial Conduct

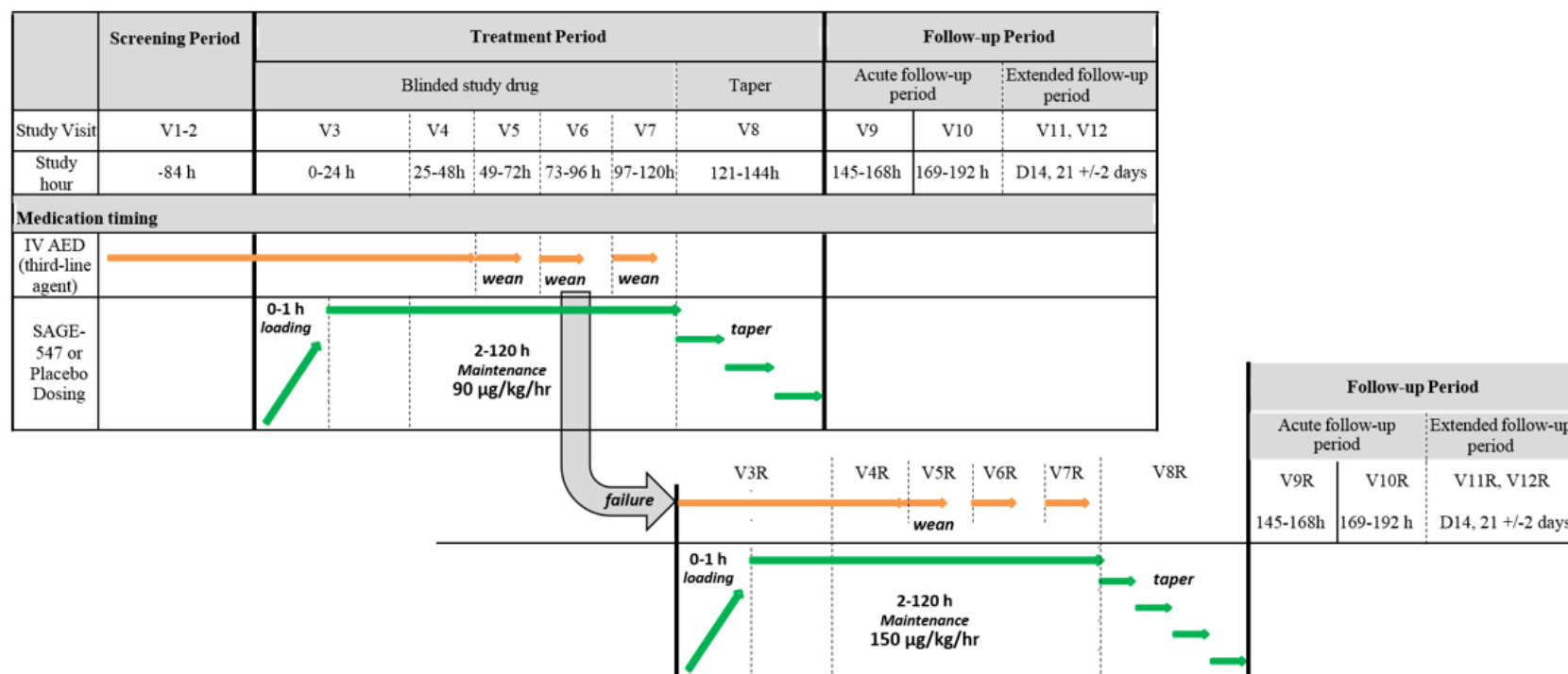
This study will be conducted according to the principles of the World Medical Association Declaration of Helsinki and most recent amendment, and in compliance with the protocol approved by the IRBs/Independent Ethics Committees (IECs), and in accordance with ICH Guidelines on GCP standards.

## 7.3. Blinding and Randomization

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo). Details of the dynamic randomization process will be included in the SAP.

The randomized portion of the study will be blinded, with the two treatment products (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

The second infusion of SAGE-547 will be administered on an open label basis to subjects who failed the primary endpoint wean.

**Figure 2: Details of Treatment Administration and Follow-up**

## 8. SELECTION AND WITHDRAWAL OF SUBJECTS

The study will randomize 140 patients at up to 180 sites. All subjects deemed eligible to enroll must have written Medical Monitor approval on a case-by-case basis prior to undertaking the qualifying wean.

### 8.1. Inclusion Criteria

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects 18 years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; *or* who have previously failed one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst suppression pattern; *or* who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst suppression pattern.

### 8.2. Exclusion Criteria

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy.
4. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis but for whatever reason, dialysis is not planned or non-continuous dialysis planned (that would not adequately remove Captisol®);
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the experience of the investigator, is less than 30 days;
  - e. a do not resuscitate (DNR) order.
5. Subjects who are being administered more than three third-line agents concomitantly or for whom the qualifying wean cannot be completed within 24 hours or who are being

administered a third-line agent for indications such as raised intra-cranial pressure that would preclude weaning according to this protocol.

6. Subjects with a living will that does not allow heroic measure.
7. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
8. Subjects who have been enrolled in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not withdraw or complete and then re-enroll).

### **8.3. Selection and Consent of Subjects for Pharmacogenetic Substudy**

All subjects will be asked to participate in pharmacogenetic research; however, participation in research is voluntary and a subject can decide to decline his/her participation without penalty or loss of benefit. Participation or lack thereof will not be a cause for exclusion from any aspect of the main study. In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **8.4. Subject Withdrawal / Study Termination**

#### **8.4.1. Withdrawal/Discontinuation of Individual Subjects**

The reasons for study drug discontinuation and/or subject withdrawal from the study must be recorded in the subject's electronic case report form (eCRF). The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject has been discontinued/withdrawn due to an AE.

##### **8.4.1.1. Withdrawal from the Study**

Subjects or their LAR may withdraw subjects from the study at any time for any reason without compromising the subject's medical care. The Investigator will also withdraw subjects upon the request of Sage Therapeutics or upon termination of the study.

Subjects who withdraw from the study prior to Visit 10 (or 10R) should complete the procedures scheduled for the day of study drug taper (hour 121-144; Visit8/8R) on the day of their withdrawal, including the SAGE-547 taper schedule, with the addition of the mortality assessment from Visit 12/12R. Subjects who withdraw from the study after Visit 10/10R should undergo study procedures as outlined for Visit 12/12R on the day of their withdrawal. In all cases, the reason for subject withdrawal will be recorded in the eCRF.

Withdrawal of subjects for any reason should be discussed with the Medical Monitor.

##### **8.4.1.2. Discontinuation of Study Drug**

If it is necessary to discontinue the study drug earlier than planned, subjects should continue to be followed per protocol to capture safety and efficacy assessments for the duration of the study period.

The investigator may withdraw the subject from the study drug for the following reasons:

- Upon subject's or LAR's request

- The subject or LAR is unwilling or unable to adhere to the protocol-specified visits
- The subject experiences an intolerable adverse event
- During the course of the study, the subject develops symptoms or conditions listed in the exclusion criteria.
- Other medical reason, at the discretion of the Investigator and/or the Medical Monitor

Subjects who discontinue the study due to an AE considered related to study drug should be followed until the event is resolved, considered stable, or the Investigator determines the event is no longer clinically significant. Study drug discontinuation due to AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

#### **8.4.2. Study Termination**

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of AEs or other findings suggesting unacceptable risk to subjects, administrative or operational reasons. In the event of study termination, Sage Therapeutics will provide written notification to the Investigator. Investigational sites must promptly notify their IRB and initiate withdrawal procedures for participating subjects.

## **9. INVESTIGATIONAL PRODUCT**

### **9.1. Identity of Investigational Product**

SAGE-547 Injection (allopregnanolone)

### **9.2. Clinical Supplies**

#### **9.2.1. SAGE-547**

Adequate supplies of SAGE-547 Injection and materials for intravenous administration will be provided to each site.

SAGE-547 Injection is a clear, colorless sterile solution of allopregnanolone intended for intravenous injection. SAGE-547 Injection is an aqueous solution of 5 mg/mL allopregnanolone in 250 mg/mL Captisol® (betadex sulfobutyl-ether sodium, NF). It is presented either un-buffered or buffered with 10 mM citrate at a pH of 6.0 in either 20 mL or 50 mL vials. SAGE-547 is further diluted according to the Pharmacy Manual to achieve an approximately isotonic solution and will be administered intravenously.

No preservatives are included in the drug product, which is intended to be used as a single-use vial. All inactive components (excipients) used in the formulation are compendial grade and conform to current USP/EP, and include sodium citrate, citric acid and betadex sulfobutyl-ether sodium (Captisol®).

#### **9.2.2. Placebo**

Placebo will be identical to SAGE-547 and presented in identical vials. Placebo will be manufactured in a similar way to SAGE-547 and comprises all excipients but no SAGE-547.

### **9.2.3. Blinding**

The vials of SAGE-547 and placebo will be identical in every way so that they are indistinguishable by the pharmacist, investigator, anyone treating or managing the patient, the monitors, and the sponsor. In this way the first infusion of study drug administered to each patient will be double-blind.

For the blinded study drug infusions, subject-specific dosing kits will be provided. These dosing kits will be pre-labelled with kit number for the first blinded infusion. For the second-infusion, open-label kits will be provided, which will require subject assignment by the pharmacy for reconciliation purposes. The study kits must be stored under refrigerated conditions (2-8 °C). IV administration bags and lines may be provided for the blinded and open-label infusions. Refer to the Pharmacy Manual for additional details.

The label for the SAGE-547 Injection vials will include standard product identification information according to the Code of Federal Regulations, 21CFR 312.6. All study labels will also contain the following statement:

Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use.

### **9.3. Preparation of SAGE-547 or Placebo Injection for Dosing**

The Pharmacy will be responsible for preparing the blinded and open-label study drug for subject dosing. The prepared admixture will be assigned a room temperature (20-25 °C) storage shelf life of 24 hours from time of compounding.

SAGE-547, which is hypertonic, will require dilution with SWFI to achieve an approximately isotonic solution according to the instructions provided in the Pharmacy Manual. Exactly the same procedures will be used to prepare the placebo admixture, so that all site staff remain blinded as to treatment allocation for the first infusion of study drug. SAGE-547 Injection is not intended to be administered to patients undiluted.

Refer to the Pharmacy Manual for specific instructions regarding infusion preparation.

### **9.4. Administration and Accountability**

The Pharmacy will maintain accurate records of all investigational product supplies. Accurate records will be kept regarding the volume of SAGE-547 Injection or placebo used for each IV preparation, as well as the required infusion rate or rates, and the date and time of preparation. Reasons for departure from the expected dosing regimen must also be recorded. To satisfy regulatory requirements regarding drug accountability, all study medication will be reconciled in full. Refer to the Pharmacy Manual for additional details.

## **10. TREATMENT OF SUBJECTS**

### **10.1. Dosing Schedule (Blinded Infusions)**

SAGE-547 Injection or placebo will be administered according to the dosing schedules in Table 5. The infusion rates to accomplish these µg/kg/h doses will be calculated according to the weight of the subject. The infusion rates will be applied to blinded study drug for the first infusion of study medication.



**Table 5: SAGE-547 or Placebo Dosing Schedule**

Hour	Type and Duration of Study Drug Infusion	Description
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	90 µg/kg/h
H121 – H128	8 hour taper	65 µg/kg/h
H129 – H136	8 hour taper	45 µg/kg/h
H137 – H144	8 hour taper	25 µg/kg/h

## 10.2. Dosing Schedule (Open-Label Infusions)

If a subject fails wean from third-line agent(s) or requires re-instatement of third-line therapy within 24 hours of discontinuing the initial infusion of study drug, SAGE-547 Injection will be re-administered according to the dosing schedule in Table 6. The infusion rates to accomplish these µg/kg/h doses will be calculated according to the weight of the subject. These infusion rates will be applied to SAGE-547 re-treatment for the open-label second infusions of study medication.

**Table 6: SAGE-547 Open Label Dosing Schedule**

Hour	Type and Duration of SAGE-547 Infusion	Description
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	150 µg/kg/h
H121 – H126	6 hour taper	125 µg/kg/h
H127 – H132	6 hour taper	95 µg/kg/h
H133 – H138	6 hour taper	65 µg/kg/h
H139 – H144	6 hour taper	35 µg/kg/h

## 10.3. Route of Administration

SAGE-547 Injection is intended for IV administration only. The compatibility of SAGE-547 with other drugs is unknown, and the product should be administered via a dedicated peripheral IV line using any Sage-supplied study-specific IV administration bags and lines. In order to preserve blinding, these instructions also apply to the blinded placebo infusions.

## 10.4. Treatment Period

The treatment period with double-blind SAGE-547 or placebo is six 24-hour periods (144 hours), which may encompass 6-7 calendar days. The retreatment period is of identical duration.

## 10.5. Concomitant Medications, Procedures and Treatments

Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. All concomitant medications, procedures, and treatments should be documented throughout the study from Screening through Visit 12/12R and recorded on the eCRF.

SAGE-547 has demonstrated inhibitory effects on cytochrome P450 isoenzyme 2C9 (CYP2C9).

Therefore, AEDs such as phenytoin and phenobarbital that are primarily metabolized by CYP2C9 should be closely monitored during SAGE-547 administration to ensure target exposures are maintained.

#### **10.5.1. Concomitant AEDs**

Subjects may enter the study on AEDs, and be administered AEDs during the study. All of these must be recorded on the eCRF with details including date and time of starting and stopping each AED, the route of administration, changes in doses, and frequency of administration. In addition, details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the eCRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.

#### **10.5.2. Concomitant Third-Line Agents**

All third-line agents (as defined in [Section 8](#)) administered since the diagnosis of SE will be recorded on the eCRF, whatever path the patient took for entry into the study. Details will include the name of the drug, the start and stop dates and times, and, after consent, the doses with start and stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

In addition, those changes in dose that constitute a wean attempt will be marked as such on the eCRF. In this way the start and stop dates and times of all wean attempts (see [Section 11](#) for definitions) will be recorded, as will the type of wean (QW, OW, or TW) and the outcome of the wean attempt (successful, failed and dose of this third-line agent increased or failed and this third-line agent stopped and another third-line agent started). Those wean attempts that occur after the TW up to and including Visit 12/12R will be marked “AW”.

Some third-line agents (such as propofol) are also used to induce sedation to facilitate a subject’s ability to tolerate the ventilator. For subjects requiring such sedation, propofol is the preferred agent unless there are contraindications. The eCRF will make clear from the indication for the third-line agent when it is being used for burst or seizure suppression and when it is being used as ventilator support or for another purpose. The investigator will add a note to the eCRF to justify that the doses used are appropriate for sedation and not for seizure or burst suppression. The doses used for ventilator support and other similar uses are usually much lower than those used for seizure or burst suppression, and use of these third-line agents for these other purposes does not constitute a wean failure under this protocol.

#### **10.5.3. Concomitant Pressors**

The start and stop dates and times of all pressors will be recorded as well as the start and stop dates and times of all dose changes.

#### **10.5.4. Other Concomitant Medications**

All other concomitant medications must be recorded on the eCRF with details including date and time of starting and stopping, the route of administration, dose, and frequency of administration.

## **11. STUDY ASSESSMENTS**

### **11.1. Efficacy Assessments**

#### **11.1.1. Primary Efficacy**

Success or failure will be determined, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo infusion and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the blinded (first) infusion of SAGE-547 or placebo. In addition, subjects must have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) to be deemed to be successes. All subjects who fail to complete their infusion of randomized treatment or do not have at least one attempt during study treatment to wean off all third-line agents will be considered as “failures” for the primary endpoint.

##### **11.1.1.1. Weaning**

Third-line agents are anesthetic agents that are administered in order to reach a seizure or burst suppression EEG pattern. For the purposes of this study, third-line agents are defined as continuous intravenous infusions of pentobarbital/thiopental, midazolam, propofol, and ketamine at maintenance doses alone or in combination sufficient to produce a burst suppression pattern on the EEG. The following are considered to be minimum maintenance doses of these agents that may be expected alone or in combination to achieve EEG burst suppression. If subjects are on lower doses than these and are not in EEG burst suppression for the 24 hours prior to the QW or the first 12 hours of the blinded study drug infusion, they will be considered to be screen failures/protocol violators and will exit the study.

- Pentobarbital: 1 mg/kg/hour
- Thiopental: 3 mg/kg/hour
- Midazolam: 0.1 mg/kg/hour
- Propofol: 3 mg/kg/hour
- Ketamine 1.2 mg/kg/hour

The timing and nature of the third-line agent weans will be guided by the Clinical Standardization Guidelines for the study, and the clinical judgment of the investigator, and will always be primarily done in the best medical interests of the subject. Advice about weaning may be sought from the Clinical Standardization Team, a group of fellow investigators with experience of performing clinical trials in subjects with SRSE. The Clinical Standardization Team will be able to discuss EEGs related to key study timepoints (qualifying wean, terminal wean, and the period after the end of the blinded study drug infusion if the terminal wean was successful) in a timely manner in order to provide advice about compliance with the Clinical Standardization Guidelines.

The following guidance for weaning applies to all weans of third-line agents undertaken during the study. These weans include the qualifying wean (QW); the terminal wean (TW), which is the wean of the third-line agent if the subject is on only one third-line agent or the wean of the last third-line agent if the subject is on more than one third-line agent; the other weans (OW), which are the weans of the third-line agents other than the TW if the subject is on more than one third-line agent. The guidance also applies to additional weans (AW), which are the weans from third line agents that take

place after the TW for the first blinded study drug infusion or the second open-label study drug infusion.

### **QW Guidance**

- Wean to be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace that third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Investigators should allow 24 hours to lapse after the end of a “successful” qualifying wean before finally declaring the QW a success. If a third-line agent needs to be re-instituted within that 24 hours, the QW is a failure, and the subject may then be randomized in the study.

### **OW Guidance**

- First OW should not begin before H49 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- If the subject is on two third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the TW. However the OW may be completed over a shorter or longer time period and may overlap if clinically indicated with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- If the subject is on three third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the wean of the second agent. The second agent should be weaned over 24 hours and that wean completed before starting the TW. However the OWs may be completed over a shorter or longer time period and may overlap if clinically indicated with each other and with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- All OWs should be completed before H96 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **TW Guidance**

- The TW is defined as the wean of the last third-line agent.
- If the subject is on one third-line agent, the TW should not begin before H49 and should begin no later than H97 after starting administration of study drug or starting the open-label infusion of SAGE-547. If the subject has had one or more OWs, the TW should ideally begin

as soon as the last OW is complete but in any case not later than H97 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

- The TW must be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace this third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Every effort must be made to complete the TW before H120 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547, but the TW must be complete before H144 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **AW Guidance**

- AWs will take place when medically indicated in the opinion of the investigator.
- Ideally the AW should take place over 24 hours, but completion may be over a shorter or longer time period than this. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.

#### **11.1.1.2. EEG**

Electroencephalographs (EEGs) that are representative of the intermittent or continuous EEG being used to support key investigator decisions will be collected at the following time points:

- A 24-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst suppression for the second path to eligibility, and a variable pattern for the third path to eligibility. This EEG will capture as much as possible of the burst suppression pattern that precedes the QW.
- EEG will be performed to cover the qualifying wean (QWEEG). EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for up to 24 hours after the end of the QW. The duration of the QWEEG will be up to 48.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s), the decision to re-institute a third-line agent(s) at doses intended to induce burst suppression, and the decision that the QW is a success.
- EEG will be performed from three hours prior to the start of the blinded infusion to 12 hours after the start of the blinded infusion. This will be called the BIEEG. The intent of this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG and to assess the depth of burst suppression in the first 12 hours of blinded study drug infusion.

- EEG will be performed to cover the final or terminal wean of third-line agent (TWEEG). The TW is the wean of the final third-line agent during the blinded administration of study drug or the open-label infusion of SAGE-547; if the subject was on one third-line agent, the TW is the wean of that agent. If the subject was on three third-line agents, the TW is the wean of the third and final agent. EEG recording will start 30 minutes prior to the start of the TW, continue for up to 24 hours during the TW, and then continue for the one hour after the end of the TW. The duration of the TWEEG will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the final third-line agent or the decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity could not be managed using intermittent bolus doses of AEDs.
- EEG will be performed during the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 (TAEED). The TAEED is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the start of the taper (at Hour 119.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours during the taper, and then continue for the one hour after the end of the taper (to Hour 145 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547). The duration of the TAEED will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity seen during the taper could not be managed using intermittent bolus doses of AEDs.
- EEG will be obtained to cover the end of the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 and the ensuing 24-hour period, during which the primary endpoint is assessed (PAEED). The PAEED is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the end of taper (at Hour 143.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours after the end of the blinded administration of study treatment or the open-label infusion of SAGE-547, and then continue for the one hour after the end of the 24-hour assessment period (to Hour 169 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547). The duration of the PAEED will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity seen in the 24 hours following the end of the blinded administration of study treatment or the open-label infusion of SAGE-547 that could not be managed using intermittent bolus doses of AEDs.

In practice, most subjects are on continuous EEG monitoring or long periods of intermittent EEG monitoring. However, this protocol does not mandate continuous EEG monitoring and breaks from EEG monitoring to provide relief to the scalp from the irritating effects of the electrodes are advised according to local practice. If a break in EEG monitoring is mandated by local practice guidelines at a time when one of the protocolled EEG segments is to be collected, the break in EEG monitoring will take precedence, with the reason for missing the EEG reading noted on the eCRF. The EEGs obtained for the study are therefore part of the existing EEG record rather than being obtained de-novo at each timepoint. For timepoints where there might be some ambiguity, such as the TWEEG,

the final EEG record is that of the final attempt to wean the last third-line agent, even if earlier attempts to wean that agent took place. In some cases (the TAEED and PAEEG, for instance), the EEG records will overlap, but different cuts are taken to service the different EEG record requirements.

The electronic EEG file will be de-identified, the date and time of the start and stop of the EEG and the subject number will be attached to the file, and the study time point will be indicated (CEEG, QWEEG, BIEEG, TWEEG, TAEED, and PAEEG). The PI will indicate on the eCRF what the EEG shows, as follows:

- For the CEEG, the PI will describe the EEG pattern that determined which path to eligibility the subject was on.
- For the QWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure or success on the qualifying wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the qualifying wean constitutes a failure); the QWEEG will extend to cover the 24 hours after the end of third line agents in order to confirm that the QW was a success.
- For the BIEEG, the PI will note the date and time of the start of the EEG and the pattern seen on the EEG.
- For the TWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure on the terminal wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the terminal wean).
- For the TAEED, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst suppression before the end of the SAGE-547 infusion).
- For the PAEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst suppression in the 24 hours following the end of the SAGE-547 infusion).

A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm the depth of burst suppression prior to the QW and during the first 12 hours of the blinded study drug infusion, the PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period (average EEG power at the end of Visit 9 of more than two microvolts):

- All subjects will have the CEEG and QWEEG collected and stored, and the CEEG and QWEEG read;
- Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;

- Those subjects randomized who are not retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the BIEEG, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read;
- Those subjects randomized who are retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion and the TWEEG, TAEED, and PAEEG related to the open-label study drug infusion collected and stored, and the BIEEG, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read.

All EEG records may be subject to quantitative EEG analysis.

### **11.1.2. Secondary Efficacy**

#### **11.1.2.1. Clinical Global Impression Scale (CGI)**

The clinical global impression scales are often utilized in clinical trials to allow clinicians to integrate several sources of information into a single rating of the subject's condition. Both the CGI-Severity (Question 1, CGI-S) and the CGI-Improvement (Question 2, CGI-I) employ a 7-point Likert scale measuring severity of the disease state in the subject and improvement, respectively. All severity assessments after initiation of SAGE-547 treatment should consider the general state of the subject over the preceding week. The third question on the scale will not be employed in this trial, and where the scale states "mental illness", this means "physical illness" in this trial.

The CGI-S will be evaluated at Visit 1 and at the last visit, Visit 12 or 12R. The CGI-I will be evaluated at Visit 12 or 12R.

#### **11.1.2.2. Epilepsy Status**

At Visit 1, the diagnosis of epilepsy will be documented as a no/yes question. If there was a previous diagnosis of epilepsy, further details will be documented, including:

- Date of diagnosis;
- Details of anti-epileptic drugs currently being taken;
- Type of epilepsy;
- Seizure frequency in the past month.

Information about the current (index) episode of status epilepticus will be obtained at Visit 1:

- Date of onset
- Date of failure to respond to first line agent(s) and the name(s) of the agent(s)
- Date of failure to respond to second line agent(s) and the name(s) of the agent(s)
- Any previous treatment with third line agents and the response to those agents (details of the third line agent drugs and previous wean attempts will be recorded on the Third Line Agent Medication CRF)
- The cause of the index episode of status epilepticus
- If the subject was transferred from another hospital or from within the hospital, the reason for the transfer will be recorded (such as for study enrollment, due to lack of medical options)



at original hospital or unit, due to lack of beds at the original hospital or unit, family request, other)

Previous (non-index) diagnosis of status epilepticus will be documented as a no/yes question. If SE did occur in the past, further information will be gathered, including:

- SE, RSE, or SRSE diagnosis, whichever was the most severe diagnosis for each episode;
- Cause;
- Treatment, including experimental treatments and need for intubation/ventilation;
- Dates of onset and duration if the episode of status epilepticus occurred in the past 12 months.

At Visit 12 or Visit 12R, the following information will be gathered:

- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of SE up to and including Visit 12 or Visit 12R;
- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of seizures (convulsive and non-convulsive) up to and including Visit 12 or Visit 12R;
- Number of separate episodes of SE after H144 at the end of Visit 8 or Visit 8R (no/yes); if yes,
  - SE, RSE, or SRSE diagnosis;
  - Cause;
  - Treatment, including experimental treatments and need for intubation/ventilation;
  - Dates of onset and duration.

Note that a separate episode of SE is defined as an episode of SE separated from other periods of status epilepticus by at least 24 hours.

- Diagnosis of epilepsy since Visit 11 or Visit 11R will be documented as a no/yes question. If a diagnosis of epilepsy has been made, further details will be documented, including:
  - Status as ongoing or new epilepsy since Visit 11 or Visit 11R after initiation of SAGE-547 treatment;
  - Details of anti-epileptic drugs currently being taken;
  - Type of epilepsy and seizure frequency in the past week.

## 11.2. Safety Assessments

The safety and tolerability of SAGE-547 will be assessed using adverse events, clinical laboratory measures, vital signs, ECG intervals and morphology, and mortality. All safety assessments should be performed per hospital standard of care and will be collected periodically throughout the study according to [Table 1](#), [Table 2](#), and [Table 3](#) (Schedules of Assessments).

### 11.2.1. Adverse Events

AEs will be collected after informed consent has been signed and prior to study-specific screening procedures not considered standard of care, during subject preparation for SAGE-547

administration and through Visit 12 or Visit 12R. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™) coding system (current version). See [Section 14](#) for additional details.

### **11.2.2. Clinical Laboratory Tests**

Blood samples will be taken for hematology, and serum chemistry and GFR will be calculated at:

- Visit 1 and then at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.
- Blood samples will be taken at Visit 11 or Visit 11R for serum chemistry (renal panel only).

Urine samples (20 ml) will be taken for urinalysis and urine NAG analysis at:

- Visit 1 and at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.

These samples will be analyzed at a central laboratory; hour-to-hour medical decisions will be based on sampling for laboratory testing done outside the protocol as part of normal standard of care. GFR will be calculated by the central laboratory.

Any out-of-range values will be flagged by the laboratory; the investigator will add a comment about whether the abnormality is clinically significant. Clinical significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

#### **11.2.2.1. Hematology and Serum Chemistry**

Hematology will include complete blood count (CBC) white blood cell count with differential, platelet count and red blood cell (RBC) count, hemoglobin and hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose. In addition triglycerides will be measured in serum chemistry samples (to aid assessment of lipemia in pharmacokinetic samples).

#### **11.2.2.2. Pregnancy Test**

Females of child-bearing potential will be tested for pregnancy by serum pregnancy test at Visit 1. In this study, since an accurate history of menstruation in girls and menopause in older women may not be available at Visit 1, “child-bearing potential” is taken to mean any female aged 18 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy. Female subjects with a positive pregnancy test will be ineligible for study participation.

#### **11.2.2.3. Urinalysis**

Urinalysis will include assessment of protein, blood, leukocytes, glucose, ketones, urobilinogen, pH, and specific gravity.

### 11.2.3. Vital Signs

Blood pressure, heart rate, and temperature will be recorded at the following time points relative to the first infusion of study drug, and to the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547:

- Visit 1;
- At 0, +30, +60 minutes (+/-15 minutes) and +2, +4 and +8 hours (+/- 30 minutes) after the start of the infusion;
- At +24, +48, +72, +96, +120, +144, +168, and +192 hours (+/- 2 hours) after the start of the infusion.

### 11.2.4. Weight and Height

Weight and height will be measured at Visit 1 and weight will also be measured once during each 24 hour period of the first infusion of study drug, and of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547. These daily weights will be used to modify the dose of SAGE-547 if required. If it is not possible to weigh the subject daily, an actual weight must be obtained prior to starting the blinded study drug, and that weight used to calculate the dose of study drug to be administered. If this is not possible, permission from the Monitor must be obtained to use another method to obtain the subject's weight (such as information from the LAR or estimating using an established local protocol).

### 11.2.5. ECG

12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours; at other times the allowed time window for ECGs is +/- 2 hours:

- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +128, +136, +144, +152, +160, and +192 hours after the start of the blinded (first) study drug infusion
- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +126, +132, +138, +144, +152, +160, and +192 hours after the start of the open-label (second) study drug

The heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm.

### 11.2.6. Mortality

Mortality will be recorded on the Visit 12 or Visit 12R case report form. If the subject has died, the following information will be collected:

- Date of death;
- Cause of death.

As accurate as possible cause of death will be collected, which will be further categorized as due to one of the following causes:

- SE;
- complications of long term intubation and third-line agent infusions;

- underlying cause of qualifying SE;
- co-morbidity existing at the time of the qualifying SE;
- new co-morbidity or trauma;
- study drug;
- other (specify).

### 11.2.7. Pharmacogenetic Samples

If a subject's LAR consents to pharmacogenetic sampling, a blood sample for genetic research will be collected at Visit 1 in order to avoid the possible introduction of bias through the exclusion of patients who may withdraw from study due to an AE (a subject population that may be of specific interest for subsequent genetic analysis). If for any reason a sample cannot be taken prior to treatment, a sample can be drawn at any point prior to completion with the restriction that no more than one genetic sample be taken per subject.

The objective of this research is to collect and store blood samples for possible DNA extraction and exploratory research into how genes or specific genetic variation may influence response (i.e. distribution, safety, tolerability, and efficacy) to SAGE-547. Specific genetic variations of interest include but are not limited to: classes of metabolizing enzymes (e.g. Cytochrome P450 supra-family genes), genes encoding enzymes involved in the production and metabolism of allopregnanolone (e.g. AKR1C4 (3 $\alpha$ -hydroxysteroid dehydrogenase)), genes associated with the GABA receptor (e.g. GABRA1-A6, GABRB1-B3, GABRD, GABRE, GABRG1-3) and genes associated with the production and degradation of GABA.

Future research may suggest other genes or gene categories as candidates for influencing not only response to SAGE-547 but also susceptibility to disorders for which SAGE-547 is being evaluated. Thus, the genetic research may involve study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.

#### 11.2.7.1. Biological Sampling and Coding Procedures (Pharmacogenetics)

To ensure patient confidentiality, utmost care will be taken in the coding and storage of pharmacogenetic samples.

*Extraction and coding:* DNA will be extracted from the blood sample and the DNA sample will be assigned a unique number replacing information from sampling tube. The assigned DNA number will be used to identify the sample and its corresponding information within Sage Therapeutics or at any designated contract laboratory for the purpose of sequencing of other DNA specific analysis. No personal details sufficient for individual identification will be available to any person (internal or external to Sage Therapeutics) working with the DNA.

*Genotype/Phenotype Analysis:* Samples and data from genetic analysis will be coded. The link between subject enrollment / randomization code and DNA number will be maintained and stored in a secure environment with restricted access. The established link will be used to identify relevant DNA samples for analysis, facilitated correlation of genotype results with clinical data, allow regulatory audit, and to trace samples for destruction in case of withdrawal of consent.

### 11.2.7.2. Retention of Biological Samples for Pharmacogenetic Analysis

Extracted DNA is a finite research that is destroyed in the process of being analyzed. Primary blood samples from which DNA can be extracted will be stored and used until no further analyses are possible, a maximum storage period of 25 years from time of last subject last visit has been reached, or an individual or LAR withdraws his/her or their consent.

### 11.2.8. Other Outcomes

#### 11.2.8.1. Pharmacokinetic Data

Formal plasma analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS)). In addition, all samples will be analyzed for important SAGE-547 metabolites (if and when these are identified) and Captisol® concentrations.

#### Plasma Analysis

Plasma will be collected to assay for SAGE-547 concentrations at the following time points relative to the start of each infusion of study drug:

- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion.
- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open label SAGE-547 study drug infusion.
- All samples will also be analyzed for plasma concentrations of important metabolites of SAGE-547 if and when these are identified.
- All samples will also be analyzed for plasma concentrations of Captisol®.

The plasma samples will be drawn from the arm contralateral to that used for drug administration. Drawing samples from peripheral arterial or venous lines or from a central line is permissible. PK collection times should be adhered to as strictly as possible. The allowed time window for all samples is: pre-dose in the two hours prior to starting the infusion of study drug; samples up to and including 1h, +/- 5 minutes; subsequent samples, +/- 15 minutes. Subject-specific PK kits for sampling including instructions on collection and processing methods, and storage and shipping conditions, will be provided separately. To maintain the blind, all subjects will have samples taken as outlined above: subjects receiving SAGE-547 will have all samples analyzed for all analytes. Subjects on placebo may have samples analyzed to investigate endogenous allopregnanolone and metabolite concentrations, as well as Captisol® concentrations; experience with the plasma concentration data will determine if and which placebo samples are analyzed.

Each blood sample will be 3 ml in volume for subjects weighing 30 kg or more, and 1 ml in volume for subjects weighing less than 30 kg. Separate aliquots will be obtained from each sample to service

the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum blood draw for PK analysis for a subject having two infusions of study drug will be 99 ml (33 ml for subjects weighing less than 30 kg).

Plasma PK parameters for SAGE-547 will be calculated where appropriate (e.g.,  $C_{max}$ ,  $C_{min}$ ,  $t_{max}$ ,  $AUC_{last}$ ,  $AUC_{\infty}$ ,  $CL_s$ ). In addition, similar PK parameters will be calculated for Captisol®. PK parameters for important metabolites of SAGE-547 may be calculated. An evaluation will be made of the feasibility of adopting a population-PK approach to assess drug-drug-interactions with SAGE-547 as victim of AEDs.

In addition, the Visit 9 sample may be analyzed for plasma concentrations of third-line agents.

#### Other Analysis

If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations. The minimum volume of cerebrospinal fluid for analysis is 100 microlitres.

Full details of all pharmacokinetic analyses will be described in the Pharmacokinetic Analysis Plan.

#### **11.2.8.2. Correlation of QT/QTc Changes and Plasma Concentrations of SAGE-547**

An analysis will be performed to determine whether there is any correlation between changes in QT/QTc interval and plasma concentrations of SAGE-547, in order to investigate any effect that SAGE-547 may have on QT/QTc interval.

#### **11.2.8.3. Pharmacoeconomic Data**

At Visit 12 or Visit 12R, the following information will be collected: number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital. If the subject dies before Visit 12 or Visit 12R, data will be collected up to the date of death. The definition of “hospital” is the institution that the subject was initially treated in. If the subject is transferred to another hospital, that hospital would be the “discharge destination from the hospital” and the “number of days in hospital” would be the number of days in the initial treating hospital.

For those subjects discharged from hospital before Visit 12/12R, the following questions will be asked:

- On what study day was the subject discharged from hospital?
- What type of facility was the subject discharged to (another hospital, a rehabilitation center, a supported care facility, home, other)?
- How many days did the subject stay in this facility?

The following questions will be answered regarding the stay in the ICU and hospital:

- Was the subject still in the ICU at the end of Visit 10/10R?
- If the FOUR Score was  $\geq 12$  at Visit 10/10R and the subject was in the ICU at Visit 10/10R, what was the reason for the subject not being discharged from the ICU (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, other)?
- Was the subject still an in-patient in the hospital at the end of Visit 12/12R?

- If the FOUR Score was  $\geq 15$  at Visit 12/12R and the subject was in the hospital at Visit 12/12R, what was the reason for the subject not being discharged from the hospital (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, unsuitable home circumstances, other)?

#### 11.2.8.4. STESS

The STESS will be assessed during Visit 1 in order to assess the severity of the status epilepticus.

#### 11.2.8.5. FOUR Score

The Full Outline of UnResponsiveness or FOUR Score is designed to assess conscious level and unlike other scores, is suitable for subjects who are intubated. It assesses four domains of neurological function (eye responses, motor responses, brainstem reflexes, and breathing pattern).

The FOUR Score will be collected at the following time points relative to each infusion of study drug (the initial blinded infusion and the second open-label infusion if this is administered):

- baseline, +24, +48, +72, +96, +120, +144, +168, and +192 hours (all +/- 2 hours) after the start of the infusion, and at Visit 11/11R and Visit 12/12R.

#### 11.2.8.6. Glasgow Outcome Scale (GOS)

The GOS is a relatively common assessment scale used to standardize descriptions of the objective degree of recovery from brain injury such as cerebral trauma, or in this case SRSE. It was first used in 1975 ([Jennett and Bond 1975](#)) and allows a prediction of the long-term course of rehabilitation to return to work and everyday life. The scale classifies subjects into 5 groups:

- Death
- Persistent vegetative state
- Severe disability
- Moderate disability
- Good recovery

The GOS will be assessed at Visit 12 or Visit 12R.

#### 11.2.8.7. Supervision Rating Scale (SRS)

The Supervision Rating (SRS) measures the level of supervision that a patient/subject receives from caregivers. The SRS rates level of supervision on a 13-point ordinal scale that can optionally be grouped into five ranked categories (Independent, Overnight Supervision, Part-Time Supervision, Full-Time Indirect Supervision, and Full-Time Direct Supervision). The SRS was designed to be rated by a clinician based on interviews with the subject and an informant who has observed at first hand the level of supervision received by the subject ([Boake 2000](#)). Scoring is a one-step procedure in which the clinician assigns the rating that is closest to the subject's level. Ratings are based on the level of supervision received, not on how much supervision a subject is judged or predicted to need.

The SRS will be assessed at Visit 1 and Visit 12 or Visit 12R. The Visit 1 assessment will be a retrospective assessment of the supervision required by the subject immediately prior to the admission that included the index episode of status epilepticus.

**11.2.8.8. Modified Rankin Scale – 9Q (mRS-9Q)**

The Modified Rankin Scale (mRS) is a commonly used scale to determine disability and functional dependence due to neurological insult such as stroke in adults. The 7-point scale (0 – 6) denotes functional capacity from no symptoms (0) to severe disability (5) and death (6). The Modified Rankin Scale – 9Q is a shortened version consisting of 9 questions that reliably determines the mRS score and was developed to both simplify the assessment and expand the rater base to non- medically trained personnel ([Patel, Rao et al. 2012](#)). The assessment is a web-based tool in the public domain with automatic score calculation and error checking found at [www.modifiedrankin.com](http://www.modifiedrankin.com).

The mRS will be assessed at Visit 1 and at Visit 12 or Visit 12R. The baseline assessment will be a retrospective assessment of the disability and dependence of the subject immediately prior to the admission that included the index episode of status epilepticus.



## 12. STUDY PROCEDURES

The study procedures listed below by study day reflect the required data collection times for this protocol. When a time window is necessary, this is specified below. If no time window is specified, the test may be performed at any time within the specified 24-hour period.

### 12.1. Visit 1 (V2-≤30h)

The baseline period will be up to approximately 84 hours prior to starting blinded study treatment and should include the assessments/procedures listed below and summarized in Table 1 and Table 2 (for retreatment), the Schedules of Events.

- Informed consent
- Eligibility checklist
- Verification of inclusion/exclusion criteria.
- Demographic information and medical history obtained by proxy and confirmed by the subject when possible.
- SE and wean history
- Blood will be collected from female subjects 18 years to 55 years for a serum pregnancy test unless they are known to be pre-menstrual or post-menopausal or to have had a hysterectomy.
- Blood and urine samples collected for clinical laboratory testing.
- Pharmacogenetic sample will be collected from consenting/eligible subjects.
- Vital signs
- Height
- Weight
- An ECG reading taken.
- Administration of the STESS.
- Administration of the FOUR Score.
- Administration of SRS.
- Administration of the mRS-9Q assessment.
- Assessment of the CGI scale.
- Evaluation of epilepsy status.
- Administration of continuous IV third-line agents.
- Perform EEG.
- Recording of adverse events.
- Recording of previous and concomitant anti-epileptic drugs.
- Recording of previous and concomitant third-line agents.
- Recording of concomitant pressors.

- Recording of other concomitant medications, procedures, and treatments.

## **12.2. Visit 2 (V3-≤54h)**

- Recording of adverse events.
- Recording of concomitant anti-epileptic drugs.
- Recording of concomitant third-line agents.
- Recording of concomitant pressors.
- Recording of other concomitant medications, procedures, and treatments.
- Wean of continuous third-line agent:
  - If wean is successful, subject is followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (these subjects are Qualifying Wean Success subjects or QWS subjects);
  - If wean is not successful, there is ongoing intravenous administration of at least one continuous IV third-line agent and EEG is performed and the subject is randomized.

## **12.3. SAGE-547 Treatment Period**

### **12.3.1. Visit 3/3R (0-24 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs will be recorded at:
  - 0, +30, +60 minutes (+/-15 minutes) and +2, +4, +8 (+/- 30 minutes) and +24 hours (+/- 2 hours) after the start of the infusion
- ECG readings will be recorded immediately after PK sampling at:
  - 0 (pre-dose) and at +0.5, +1, +3, +6, +12, and +24 hours after the start of the blinded study drug infusion.
- A blood sample for PK analysis should be collected at the following time points (all +/- 15 minutes except where otherwise stated):
  - 0 (pre-dose, within two hours of the start of the infusion) and at +0.5, +1 (+/- 5 minutes), +3, +6, +12, and +24 hours after the start of the blinded study drug infusion.
- Completion of the FOUR Score
  - +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the end of the 24 hour observation period following the QW)
- Ongoing intravenous administration of a continuous IV third-line agent.

- Study drug administration in loading (Hour 0-1) and maintenance infusions (at completion of Hour 1).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.3.2. Visit 4/4R (25-48 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +48 hours (+/- 2 hours) after the start of the infusion
- An ECG reading taken immediately after PK sampling:
  - +48 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +48 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +48 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent.
- Ongoing study drug maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.3.3. Visit 5/5R (49-72 hours)**

- Weight
- Vital signs should be recorded at:
  - +72 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +72 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +72 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +72 hours (+/- 2 hours) after the start of the infusion

- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.4. Visit 6/6R (73-96 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +96 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +96 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +96 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +96 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Perform EEG.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.5. Visit 7/7R (97-120 hours)**

- Weight
- Vital signs should be recorded at:
  - +120 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +120 hours after the start of the study drug infusion

- A blood sample for PK analysis should be collected:
  - +120 hours (+/- 15 minutes) after the start of study drug infusion, immediately prior to the end of the maintenance infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +120 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled. Complete wean by 120 hours if at all possible.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## **12.4. SAGE-547 Taper Period**

### **12.4.1. Visit 8/8R (121-144 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +144 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after each PK sampling:
  - +128, +136 hours and +144 hours after the start of the study drug infusion
  - During the open-label retreatment phase of the study ECG readings at: +126, +132, +138 hours and +144 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected (+/- 15 minutes unless otherwise stated):
  - +128 (immediately prior to the end of the first taper step), +136 hours (+/- 5 minutes, immediately prior to the end of the second taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of study drug infusion.
  - During the open-label retreatment phase of the study PK blood draws at: +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 hours (+/- 5 minutes, immediately prior to the end of the third taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of the study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +144 hours (+/- 2 hours) after the start of the infusion

- Complete wean of third line agents by H144 if not completed by H120.
- Perform EEG.
- Taper of SAGE-547 infusion begins at hour 121.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## **12.5. Follow-up Period**

### **12.5.1. Visit 9/9R (145-168 hours)**

- Vital signs should be recorded at:
  - +168 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +152, +160 hours (+/- 2 hours) after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +152 and +160 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +168 hours (+/- 2 hours) after the start of the infusion
- Perform EEG.
- Assessment of the presence of physiologic brain activity using EEG.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.5.2. Visit 10/10R (169-192 hours)**

- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +192 hours (+/- 2 hours) after the start of the infusion
- At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine eligibility for retreatment with the higher dose of study drug. This determination may occur at any point

during Visit 10: the retreatment infusion must begin within the Visit 10 window. All patients for retreatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.

- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.3. Visit 11/11R (Visit 3/3R + 14d (±2))**

- Blood samples collected for clinical laboratory testing (renal panel only).
- Completion of the FOUR Score (QWS subjects also).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.4. Visit 12/12R (Visit 3/3R + 21d (±2))**

All assessments also performed for QWS subjects.

- Completion of the FOUR Score.
- Administration of the GOS.
- Administration of the SRS.
- Administration of the mRS-9Q assessment.
- Evaluation of epilepsy status (see [Section 11.1.2.2](#) for details).
- Assessment of the CGI Scale.
- Recording of adverse events.
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications.
- Collection of pharmacoeconomic data.
- Mortality will be assessed throughout the study period.

## **13. STATISTICS**

### **13.1. Statistical Plan**

Complete details for the analysis and reporting of data from this study will be contained in the Statistical Analysis Plan (SAP).

#### **13.1.1. Interim Analysis**

When approximately 50% of subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment

will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### 13.1.2. Study Populations

The **Safety Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to actual treatment. This analysis population will be used for all safety analyses.

The **Intent to Treat Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to randomized treatment. This analysis population will be used for all efficacy analyses.

The **Modified Intent to Treat Population** is defined as all subjects who:

1. complete their initial course of blinded SAGE-547 or placebo treatment unless the non-completion was due a drug-related adverse event; and
2. have at least one attempt to wean from third-line agents prior to the end of blinded study treatment infusion unless the failure to wean was because seizures were not controlled.

Subjects will be classified according to randomized treatment. This analysis population will be used for sensitivity analyses of the primary endpoint and select secondary efficacy endpoints.

Narratives will be prepared for all subjects who do not complete the infusion of blinded study medication or were not subjected to any wean attempts. Narratives will include details of the cause of SE, the comorbid conditions, the adverse event(s), and reasons for non-completion of the infusion or failure to attempt weaning. This blinded narrative will be reviewed by the medical monitors and the patient adjudicated as MITT eligible or ineligible. Acceptable reasons for defining a subject as MITT ineligible include death or withdrawal of consent due to progression of the underlying cause of SE or comorbid conditions, unless the cause of death or progression of disease were thought by the investigator, sponsor, or DSMB to be related to study drug.

The **Per-Protocol (PP) Population** is defined as a subset of the MITT population but will exclude data from all subjects with significant protocol violations or deviations. Subjects will be classified according to actual treatment received. This data set will be used for sensitivity analyses to examine the robustness of results for the primary and key secondary efficacy endpoints.

The **Pharmacokinetics Population** is defined as all subjects who at least had an infusion of blinded SAGE-547 initiated and have at least one pharmacokinetic sample collected.

The **Pharmacogenetic Population** is defined all subjects who consent to being included in the pharmacogenetic assessment and provide a pharmacogenetic sample.

Summary statistics of all data collected will be presented for subjects who were QW successes.

### 13.1.3. General Aspects

Tabular displays of descriptive statistics will be provided for all variables. Summary tables will include n, mean, mean, standard deviation, minimum and maximum for continuous variable and frequency and percentage for categorical variables.



### **13.1.4. Analysis of Primary Endpoint**

The analysis of response to treatment (see Section 11.1.1 for definition of primary endpoint) between SAGE-547 treated subjects and placebo treated subjects will be performed on the ITT population using a Cochran-Mantel-Haenszel (CMH) test with variables for treatment, concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). The CMH general association statistic and its associated p-value will be presented. The comparison of treatment response rates will be conducted at the 5% level of significance. To confirm the CMH results, a permutation test will also be conducted.

An additional analysis of the primary endpoint will also be performed on the MITT population. In addition sensitivity analyses of the primary endpoint will be performed using the ITT population based on:

- the number of third-line agents (one, two, or three) subjects were administered post-randomization; and
- which third line agent was the subject of the first TW.

### **13.1.5. Analysis of Secondary Efficacy Endpoints**

Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section ([Section 6](#)). Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. The analysis of the secondary endpoints will also be performed on the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

### **13.1.6. Analysis of Other Endpoints**

Safety and “Other” endpoints will only be summarized by treatment group.

Summaries of safety endpoints will be based on the overall Safety Population.

### **13.1.7. Epilepsy and SRSE Status**

Diagnosis of epilepsy and recurrence of RSE or SRSE will be documented as the percentage of subjects by time point and overall. Kaplan-Meier curves may be plotted if sufficient data are available.

Utilization of AEDs during follow-up and during recurrence will be summarized.

### **13.1.8. Questionnaires**

The data collected from each questionnaire will be interpreted according to the standard methodology for that questionnaire. There will be no adjustment for missing values.

### **13.1.9. Pharmacokinetic Data Analysis**

Details of the pharmacokinetic data analysis will be described in detail in a separate Pharmacokinetic Analysis Plan.

### **13.1.10. Pharmacogenetic Data Analysis**

Any genotype data generated in this study will be stored within a secured database within Sage Therapeutics and / or a third party contracted to work with Sage Therapeutics to analyze the samples. Because the number of subjects agreeing to participate in the genetic research component of the study is unknown, it is not possible to establish, a priori, whether sufficient samples will be obtained to support formal statistical evaluation of data. As a consequence a Pharmacogenetic Analysis Plan will only be prepared where appropriate and the results obtained from any genetic research will be reported in a report separate from the main study CSR.

### **13.1.11. Retreated Subjects**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are retreated with SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo.

### **13.1.12. EEG-Responders**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who are classified as EEG-responders/non-responders based on the independent assessment of the PAEEG. Summaries will be derived for the two randomized treatment groups.

### **13.1.13. QT/QTc Assessment**

An analysis of the correlation between changes in QT/QTc intervals and SAGE-547 plasma levels will be performed to investigate if there is a potential effect that SAGE-547 may have on QT/QTc interval. A detailed description of the QT/QTc assessment will be included in the SAP.

### **13.1.14. Quantitative EEG**

The six EEG records for each subject may be subjected to exploratory quantitative EEG analysis, the details of which will be included in the EEG Analysis Plan. In summary the following comparisons may be made, SAGE-547 versus placebo: the QWEEG versus the TWEEG (main analysis); the CEEG versus PAEEG (subsidiary analysis); and TAEEG versus PAEEG (exploratory analysis).

## **13.2. Determination of Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between treatment groups at a 5% level of significance. Randomization will be stratified by concomitant

pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

### **13.3. Statistical Analysis Plan**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

## **14. ADVERSE EVENTS**

The safety procedures in this study will be detailed in a Safety Management Plan, which will be agreed and signed before the first subject is randomized in the study. [Section 14.1](#) summarizes Investigator responsibilities regarding the identification and documentation of AEs, the classification of AEs for relationship to study drug and severity, and the reporting of AE information to the Sponsor and the IRB.

[Section 14.2](#) summarizes Sponsor/Medical Monitor Responsibilities regarding monitoring of AE data and reporting relevant safety information to FDA.

[Section 14.3](#) lists important AE definitions.

### **14.1. Investigator Responsibilities**

#### **14.1.1. Identification and Documentation of Adverse Events by Investigator**

Subjects will be evaluated and questioned generally (if possible) to identify AEs during the course of the study. AEs will be collected from the signature of the consent form through Visit 12/12R. Adverse events that occur prior to completion of screening will be captured on the Medical History eCRF. Adverse events that occur after completion of screening will be recorded on the Adverse Event eCRF.

All AEs revealed by observation, other diagnostic procedures, or spontaneously reported by the subject and/or in response to an open question from study personnel will be recorded on the Adverse Event Form. Any clinically significant deterioration in laboratory assessments or other clinical findings are considered an AE and must be recorded on the Adverse Event Form, unless otherwise stated. AE information recorded will be entered into the database on an ongoing basis.

AEs with a relationship considered related to study drug (probable, possible) should be followed until the event is resolved or the Investigator determines the event is stable or no longer clinically significant. AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

For SAEs, an electronic Serious Adverse Event eCRF must be completed with as much information as possible and submitted in the time frame described below in [Section 14.1.3](#). When new significant information is obtained as well as when the outcome of an event is known, the electronic SAE eCRF should be updated within 24 hours. If the subject was an outpatient at the time of the SAE and was re-hospitalized due to the SAE, a copy of relevant hospital records (e.g., admission report, laboratory test results, discharge summary, etc.) may be requested to be included as part of the subject medical file.

All SAEs will be followed until resolved or until a stable status has been achieved.

**14.1.2. Adverse Event Classification****14.1.2.1. Relationship to Investigational Drug**

None:	No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state.
Possible:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject, but this is not known for sure.
Probable:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

**14.1.2.2. Severity**

Mild	Discomfort noticed, but no disruption to daily activity.  For subjects that are unconscious, this may be a slight or minor change in a lab result or clinical sign or symptom that does not require immediate corrective action.
Moderate	Discomfort sufficient to reduce or affect normal daily activity, but is not hazardous to health; prescription drug therapy may be employed to treat the AE.  For subjects that are unconscious, this may be a clinically meaningful change that may require immediate corrective action.
Severe	Inability to work or perform normal daily activity and represented a definite hazard to health; prescription drug therapy and/or hospitalization may be employed to treat the AE.  For unconscious subjects, this may be a significant clinical change that requires immediate corrective action.

**14.1.2.3. Action Taken with Investigational Drug**

None	Study medication was continued without change.
Discontinued	Study medication was terminated.
Dose adjusted	Study medication dose/infusion rate was changed and then continued per protocol.
Interrupted	Study medication was interrupted and then continued per protocol.
Unknown	The action taken with regard to study medication is unknown.
Not applicable	Administration of study medication was not ongoing.

**14.1.2.4. Assessment of Outcome**

Ongoing	At the end of the study, the event has not resolved or stabilized.
Ongoing and stable	The event is ongoing but has stabilized and is unlikely to change
Resolved	The event has resolved or the subject recovered without sequelae.
Resolved with sequelae	The event has at least one secondary outcome that may result in permanent disability and/or functional limitation.
Unknown	The status of the event is unknown.
Death	The subject has expired.

**14.1.3. Investigator Reporting to Sponsor and Sponsor Emergency Contact**

All new SAEs that come to the Investigator and/or Sponsor's notice during the course of the study (up to and including the last study visit) must be reported by the Investigator on the designated electronic report form within 24 hours of the point in time when the Investigator becomes aware of the SAE. As additional information becomes available, the designated electronic report form must be updated within 24 hours.

Investigators must report any SAE, whether or not considered drug related. The report must include an assessment of whether there is a reasonable possibility that the drug caused the event.

In a medical emergency (ie, an event that requires immediate attention regarding the treatment of a subject, operation of the clinical study, and/or the use of investigational drug), study site staff will apply appropriate medical intervention according to current standards of care, and contact the Medical Monitor.

**14.1.4. Medical Monitor and Emergency Contact Information**

[REDACTED], MD  
[REDACTED]

**14.1.5. SAE Reporting Contact Information**

Contact information and reporting instructions are provided in the Safety Management Plan.

**14.1.6. Reporting to Institutional Review Boards (IRBs)**

It is the responsibility of the Investigator to promptly notify the institution's IRB of all serious and unexpected suspected adverse reactions (see [Section 14.3](#) for definitions).

## **14.2. Sponsor/Medical Monitor Responsibilities**

### **14.2.1. Monitoring of Adverse Event Data**

The Medical Monitor will review any newly reported adverse events in an ongoing basis. If the aggregate assessment indicates that an event is occurring more frequently than would normally be expected in this population, or as previously observed, and the sponsor believes that the events are causally related to the administration of SAGE-547, the Sponsor will then report that information in an IND safety report.

### **14.2.2. Data Safety Monitoring Board**

An independent DSMB will monitor the clinical, PK and PD data for safety signals throughout the study and will be asked to assess the placebo response rate at the time of the interim analysis to determine final sample size. In order to perform their monitoring function the DSMB will have access to un-blinded safety data as necessary.

The composition and procedures for the board will be described in a separate DSMB Charter.

### **14.2.3. Reporting to FDA**

The Sponsor must report in an IND safety report any suspected adverse reaction to study treatment that is both serious and unexpected (21 CFR 312.32(c)(1)(i)). Before submitting an IND safety report, the Sponsor will ensure the event meets all three of the definitions: (1) suspected adverse reaction, (2) serious, (3) unexpected. If the AE does not meet all three of the definitions, it should not be submitted as an IND safety report. The Sponsor should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the adverse event and, therefore, that the event meets the definition of a suspected adverse reaction.

If there is a serious and unexpected suspected adverse reaction, the Sponsor will notify the appropriate regulatory agency(ies) and all appropriate parties on an expedited basis. In addition, Sponsors must submit expedited reports of an increased rate of occurrence or severity of serious suspected adverse reactions over that listed in the protocol or Investigational Brochure.

SUSARs will be unblinded prior to reporting to FDA. Unless it is necessary to unblind for the safety of the patient, the investigator will not be informed of the unblinding of the subject.

Under 21 CFR 312.32, Sponsors should identify in the protocol SAEs that it does not plan to report individually in an expedited manner, because they are known consequences of the disease or otherwise common in the study population. Given the grave condition and prognosis of SRSE being studied, individual occurrences of seizures or seizure activity will not be reported expeditiously in this study. Regardless of which events are reported in an expedited manner, all adverse events will be closely monitored throughout the study.

## **14.3. Adverse Event Definitions**

### **14.3.1. Adverse Event**

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

### **14.3.2. Suspected Adverse Reaction**

Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

### **14.3.3. Life-Threatening**

An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

### **14.3.4. Serious**

An AE or suspected adverse reaction is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE – see definition above
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disability
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

### **14.3.5. Unexpected**

An AE or suspected adverse reaction is considered “unexpected”:

- If it is not listed in the Investigational Brochure or is not listed at the specificity or severity that has been observed, or
- If an Investigational Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigational Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigational Brochure listed only cerebral vascular accidents.

“Unexpected,” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigational Brochure as occurring with a class of drugs or as anticipated from



the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

#### **14.4. Emergency Identification of Study Medication**

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject's treatment in the study via the IVRS; this normally requires prior approval by the medical monitor. However, if the subject is at immediate risk and the Investigator believes that immediate knowledge of the study treatment will alter medical management, discussion with the medical monitor may take place after unblinding. The Investigator will not unblind the medical monitor during that discussion. The process of unblinding will ensure that only the investigator is unblinded; the medical monitor, study management team, and data management team will not be made aware of the treatment allocation of an individual subject. All cases of emergency unblinding will be fully documented in a way that does not unblind the medical monitor, study management team, and data management team.

### **15. STUDY ADMINISTRATIVE CONSIDERATIONS**

#### **15.1. Quality Control and Quality Assurance**

The Investigators and institutions will permit trial related monitoring, audits, IRB review, and regulatory inspections as requested by FDA, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed informed consent forms, etc.) in addition to case report forms.

Quality assurance and quality control systems with written standard operating procedures (SOPs) will be followed to ensure this trial will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The site's dedicated study monitor will arrange to visit the Investigator at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be identified and resolved. The study monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality assurance officers named by Sage Therapeutics or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements, made by the Sponsor with the Investigator/institution and any other parties involved with the clinical trial, will be in writing in a separate agreement.

## **15.2. Data Handling and Recordkeeping**

### **15.2.1. Data Handling**

Procedures for data handling (including electronic data) used in this protocol will be documented in a Data Management Plan.

### **15.2.2. Case Report Form Completion**

eCRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of demographics, study drug administration, study procedures, AEs, questionnaire completion, efficacy assessments and subject status, including survival.

The Investigator will maintain copies of the eCRFs at the study site. For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate eCRF.

### **15.2.3. Retention of Study Records**

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval and until there are no pending or contemplated marketing applications or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to an appropriate person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

## **15.3. Confidentiality**

To maintain subject privacy, all eCRFs, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available trial registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by Sage Therapeutics to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

#### **15.4. Publication Policy**

All information concerning SAGE-547 is considered confidential and shall remain the sole property of Sage Therapeutics. The Investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval from Sage Therapeutics. No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between Sage Therapeutics and the Investigator.

#### **15.5. Protocol Amendments**

Changes to the conduct of the study should be prepared as a protocol amendment by the Sponsor. Protocol amendments should receive written IRB/IEC approval prior to implementation at the investigative site, except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the trial (eg, change of monitor, telephone numbers). In this case, Sage Therapeutics will amend and implement the protocol change and subsequently notify the regulatory authorities and the Investigative sites who will notify the respective IRB, as appropriate.

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## APPENDIX 1. FOUR SCORE

### FOUR score

#### Full Outline of UnResponsiveness

##### Eye response

- E4: eyelids open or opened, tracking, or blinking to command
- E3: eyelids open but not tracking
- E2: eyelids closed but open to loud voice
- E1: eyelids closed but open to pain
- E0: eyelids remain closed with pain

##### Motor response

- M4: thumbs-up, fist or peace sign
- M3: localizing to pain
- M2: flexion response to pain
- M1: extension response to pain
- M0: no response to pain or generalized myoclonus status

##### Brainstem reflexes

- B4: pupil and corneal reflexes present
- B3: one pupil wide and fixed
- B2: pupil or corneal reflexes absent
- B1: pupil and corneal reflexes absent
- B0: absent pupil, corneal and cough reflex

##### Respiration pattern

- R4: not intubated, regular breathing pattern
- R3: not intubated, Cheyne-Stokes breathing pattern
- R2: not intubated, irregular breathing
- R1: breathes above ventilatory rate
- R0: breathes at ventilator rate or apnea

Reference ([Iyer, Hoel et al. 2009](#)).

**APPENDIX 2. GLASGOW OUTCOME SCALE (GOS)****GLASGOW  
OUTCOME  
SCALE**

Patient Name: \_\_\_\_\_  
 Rater Name: \_\_\_\_\_  
 Date: \_\_\_\_\_

*Note:* The scale presented here is based on the original article by Jennett and Bond. It has become common practice in clinical trial administration, however, to use a modified version that places the scores in reverse order (i.e., "good recovery" = 1, "moderate disability" =2, etc.).

Score	Description
1	DEATH
2	PERSISTENT VEGETATIVE STATE Patient exhibits no <i>obvious cortical</i> function.
3	SEVERE DISABILITY (Conscious but disabled). Patient depends upon others for daily support due to mental or physical disability or both.
4	MODERATE DISABILITY (Disabled but independent). Patient is independent as far as daily life is concerned. The disabilities found include varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes.
5	GOOD RECOVERY Resumption of normal activities even though there may be minor neurological or psychological deficits.

**TOTAL (1-5):** \_\_\_\_\_

Reference ([Jennett and Bond 1975](#)).

## APPENDIX 3. SUPERVISION RATING SCALE (SRS)

### SUPERVISION RATING SCALE (SRS)

**Instructions:** Circle the rating that is closest to the amount of supervision that the patient *actually receives*. "Supervision" means that someone is responsible for being with the patient.

<u>Rating</u>	<u>Description</u>
<u>Level 1: INDEPENDENT</u>	
1	The patient lives alone or independently. Other persons can live with the patient, but they cannot take responsibility for supervision (for example, a child or elderly person).
2	The patient is unsupervised overnight. The patient lives with one or more persons who <i>could</i> be responsible for supervision (for example, a spouse or roommate), but they are <i>all</i> sometimes absent overnight.
<u>Level 2: OVERNIGHT SUPERVISION</u>	
3	The patient is only supervised overnight. One or more supervising persons are always present overnight but they are <i>all</i> sometimes absent for the rest of the day.
<u>Level 3: PART-TIME SUPERVISION</u>	
4	The patient is supervised overnight and part-time during waking hours, but is allowed on independent outings. One or more supervising persons are always present overnight and are also present during part of waking hours every day. However, the patient is sometimes allowed to leave the residence without being accompanied by someone who is responsible for supervision.
5	The patient is supervised overnight and part-time during waking hours, but is unsupervised during working hours. Supervising persons are <i>all</i> sometimes absent for enough time for them to work full-time outside the home.
6	The patient is supervised overnight and during most waking hours. Supervising persons are <i>all</i> sometimes absent for periods longer than one hour, but less than the time needed to hold a full-time job away from home.
7	The patient is supervised overnight and during almost all waking hours. Supervising persons are <i>all</i> sometimes absent for periods shorter than one hour.
<u>Level 4: FULL-TIME INDIRECT SUPERVISION</u>	
8	The patient is under full-time indirect supervision. At least one supervising person is <i>always</i> present, but the supervising person does not check on the patient more than once every 30 minutes.
9	Same as #8 plus requires overnight safety precautions (for example, a deadbolt on outside door).
<u>Level 5: FULL-TIME DIRECT SUPERVISION</u>	
10	The patient is under full-time direct supervision. At least one supervising person is always present and the supervising person checks on the patient more than once every thirty minutes.
11	The patient lives in a setting in which the exits are physically controlled by others (for example, a locked ward).
12	Same as #11 plus a supervising person is designated to provide full-time line-of-sight supervision (for example, an escape watch or suicide watch).
13	The patient is in physical restraints.

3/12/93

Corwin Boake, Ph.D., TIRR, 1333 Moursund, Houston, TX 77030-3405, 713/799-6990



## APPENDIX 4. MODIFIED RANKIN SCALE – LEVEL OF FUNCTION SURVEY (mRS-9Q)

1. Do you have any symptoms that are bothering you? (For example, trouble with reading or writing, trouble speaking, problems with vision, numbness, weakness, balance trouble, or problems with swallowing?)	YES <input type="radio"/>	NO <input type="radio"/>
2. Are you able to do the same work as before?	YES <input type="radio"/>	NO <input type="radio"/>
3. Are you able to keep up with your hobbies?	YES <input type="radio"/>	NO <input type="radio"/>
4. Have you maintained your ties to friends and family?	YES <input type="radio"/>	NO <input type="radio"/>
5. Do you need help making a simple meal, doing household chores, or balancing a checkbook?	YES <input type="radio"/>	NO <input type="radio"/>
6. Do you need help with shopping or traveling close to home?	YES <input type="radio"/>	NO <input type="radio"/>
7. Do you need another person to help you walk?	YES <input type="radio"/>	NO <input type="radio"/>
8. Do you need help with eating, going to the toilet, or bathing?	YES <input type="radio"/>	NO <input type="radio"/>
9. Do you stay in bed most of the day and need constant nursing care?	YES <input type="radio"/>	NO <input type="radio"/>

## APPENDIX 5. CLINICAL GLOBAL IMPRESSION (CGI)

### Clinical Global Impression (CGI)

#### 1. Severity of illness

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- |                             |   |
|-----------------------------|---|
| 0 = Not assessed            | 4 = Moderately ill                        |
| 1 = Normal, not at all ill  | 5 = Markedly ill                          |
| 2 = Borderline mentally ill | 6 = Severely ill                          |
| 3 = Mildly ill              | 7 = Among the most extremely ill patients |

#### 2. Global improvement: Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.

Compared to his condition at admission to the project, how much has he changed?

- |                        |                     |
|------------------------|---------------------|
| 0 = Not assessed       | 4 = No change       |
| 1 = Very much improved | 5 = Minimally worse |
| 2 = Much improved      | 6 = Much worse      |
| 3 = Minimally improved | 7 = Very much worse |

#### 3. Efficacy index: Rate this item on the basis of drug effect only.

Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.

EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect		Side effects			
		None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
<b>Marked</b>	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
<b>Moderate</b>	Decided improvement. Partial remission of symptoms	05	06	07	08
<b>Minimal</b>	Slight improvement which doesn't alter status of care of patient	09	10	11	12
<b>Unchanged or worse</b>		13	14	15	16
Not assessed = 00					

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

**APPENDIX 6. STATUS EPILEPTICUS SEVERITY SCORE (STESS)**

Outcome Predictor	Feature	Score
Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type (prior to first treatment)	Simple-partial, complex-parial, absence, myoclonic (complicating idiopathic generalized epilepsy)	0
	Generalized-convulsive	1
	Nonconvulsive status epilepticus in coma	2
Age	< 65 years	0
	≥ 65 years	2
History of previous seizures	Yes	0
	No or unknown	1
Summed Total		

**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY  
TO EVALUATE THE EFFICACY AND SAFETY OF SAGE-547 INJECTION  
IN THE TREATMENT OF SUBJECTS WITH SUPER-REFRACTORY  
STATUS EPILEPTICUS**

**PROTOCOL NUMBER: 547-SSE-301**

**IND NUMBER: 117901**

**EudraCT Number: 2015-002142-31**

Product: SAGE-547 Injection (allopregnanolone)

Sponsor Contact: [REDACTED], MD

[REDACTED]  
Sage Therapeutics  
215 First Street  
Cambridge, MA 02142

Medical Monitor: [REDACTED], MD

Date of Protocol: 09 March 2015  
Date of Amendment One 27 May 2015  
Date of Amendment Two 17 November 2015  
(Adults Only)

**Confidentiality Statement**

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

**PROTOCOL NUMBER: 547-SSE-301**

Sponsor [REDACTED]:

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]:

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

CRO [REDACTED]:

[REDACTED]

## 1. SIGNATURE PAGE

Title of Protocol:

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus

Protocol No: 547-SSE-301

### Sponsor Approval

[Redacted Signature]

18 November 2015

[Redacted Name] MD  
[Redacted Title]

Date (dd/mmm/yyyy)

Sage Therapeutics

### Investigator Agreement

By signing this page I attest that I have read and understand the contents of Clinical Protocol 547-SSE-301 and any current amendments. I agree to adhere to the design, conduct, and reporting requirements of the study as stated in the clinical protocol and to my obligations to the Sponsor as described in the protocol and executed contracts between myself, my Institution, and the Sponsor. I also agree to adhere to any subsequent amendments to the clinical protocol.

Investigator's Signature: \_\_\_\_\_

Investigator's Name: \_\_\_\_\_

Institution: \_\_\_\_\_

Date: \_\_\_\_\_

## 2. SYNOPSIS

<b>Name of Sponsor:</b> Sage Therapeutics 215 First Street Cambridge, MA 02142																							
<b>Protocol No.</b> 547-SSE-301		<b>Phase:</b> 3																					
<b>Name of Investigational Product:</b> SAGE-547 Injection																							
<b>Name of Active Ingredient:</b> Allopregnanolone																							
<b>Title of the Protocol:</b> A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus																							
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H1	One hour loading infusion	300 µg/kg/h																					
H2 –H120	119 hour maintenance infusion	150 µg/kg/h																					
H121 – H126	6 hour taper	125 µg/kg/h																					
H127 – H132	6 hour taper	95 µg/kg/h																					
H133 – H138	6 hour taper	65 µg/kg/h																					
H139 – H144	6 hour taper	35 µg/kg/h																					
<b>Study Sites</b> Up to 180 sites in the USA, Europe, and Canada.																							

**Number of Subjects**

The study will randomize 140 subjects at up to 180 sites.

**Study Population**

Subjects will be aged 18 years or more, in SRSE<sup>1</sup> (as defined in the Inclusion Criteria [Section 8.1](#)), and being managed in an intensive care setting.

**Duration of Subject Involvement**

Individual subject participation will be up to 30 days.

**Study Design**

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

Patients will follow one of three paths to entry to the study. The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst suppression with a third-line agent. These subjects will be consented for the study after admission to the intensive care unit, but before any third-line agents are administered for burst suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their legally authorized representative (LAR). Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours. Once burst suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The second path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst suppression pattern on the EEG. These subjects may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

<sup>1</sup> In this study, the term Super-Refractory Status Epilepticus or SRSE is equivalent to “Refractory Status Epilepticus (RSE) that has failed standard treatment” and the two terms are used interchangeably.



The third path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These subjects may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 treatment or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within six hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo).

The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that subjects, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as both the ability to wean the subject off all third-line agents before the end of the infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication infusion, and concurrent signs of physiologic brain activity as determined by EEG. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#) and [Table 2](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo will all subsequently be eligible to be administered SAGE-547 at the higher dose.

### Visit Schedule

The visit schedule and an overview of events at each visit is provided in [Table 1](#), [Table 2](#) and [Table 3](#) Schedule of Assessments.

**Study Objectives*****Primary objective:***

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult subjects with SRSE, and for the response to endure at least 24 hours after the end of the SAGE-547 or placebo infusion (primary response).

***Secondary objectives:***

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in the Clinical Global Impression scale (CGI) between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

***Safety objectives:***

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

***Other objectives:***

1. To evaluate the impact of retreatment with a higher dose SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;

3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;
6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS).

**Endpoints*****Primary endpoint:***

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

***Secondary endpoints:***

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

***Safety endpoints:***

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.

**Other endpoints:**

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who fail to respond to their randomized double blind treatment and are retreated with a higher dose of SAGE-547.
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS).

**Inclusion Criteria**

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects 18 years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst suppression pattern; or who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst suppression pattern.

**Exclusion Criteria**

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone or any excipients in SAGE-547.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy.
4. Subjects who have any of the following:

- a. a GFR low enough to warrant dialysis for whatever reason, but dialysis is not planned or non-continuous dialysis is planned (that would not adequately remove Captisol<sup>®</sup>);
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the opinion of the investigator, of less than 30 days;
  - e. a do not resuscitate (DNR) order.
5. Subjects who are being administered more than three third-line agents concomitantly or in whom the qualifying wean cannot be completed within 24 hours, or who are being administered a third-line agent for other indications such as management of raised intra-cranial pressure that would preclude weaning according to this protocol.
  6. Subjects with a living will that does not allow heroic measures.
  7. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
  8. Subjects who have been enrolled in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not withdraw or complete and then re-enroll).

### Pharmacogenetic Research

In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### Statistical Analysis

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

### Interim Analysis

When approximately 50% of the subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### Analysis of Primary Endpoint

The analysis of response to treatment between SAGE-547 treated subjects and placebo treated subjects will be performed using a Cochran-Mantel-Haenszel test with variables for treatment, concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). In this analysis, a treatment responder is a subject who is successfully

weaned off all third-line agents and blinded study medication prior to the end of study treatment infusion and remains off third-line agents for at least 24 hours following cessation of the blinded study medication, and who has concurrent signs of physiologic brain activity as determined by EEG. The analysis will be based on the ITT Population. The comparison of treatment response rates will be conducted at the 5% level of significance.

### **Analysis of Secondary Efficacy Endpoints**

The primary analysis will be repeated for the MITT population. Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section. Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. Secondary analyses will be repeated for the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from Baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third-line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

Summaries of safety endpoints will be based on the overall Safety Population which is defined as all subjects who at least initiated the infusion with blinded study treatment.

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are retreated with SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo. Summary statistics will be presented for subjects who were QW successes.

### **Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

**Table 1: Schedule of Assessments for Protocol 547-SSE-301: One Infusion of Study Drug (blinded)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical/SE/Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X		X	X	X	X	X	X				
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X		X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X		X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X		X	X		X		X		X		
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X			
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>n</sup>											X
Modified Rankin Score (mRS)	X <sup>n</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV 3rd-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>o</sup>				
EEG	X	X				X		X	X			
Randomization		X										
Study Drug Administration <sup>p</sup>			X	X	X	X	X	X				
TW Outcome & Retreat Decision										X <sup>q</sup>		
Physiologic Brain Activity									X			
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

**Table 2: Schedule of Assessments for Protocol 547-SSE-301: Two Infusions of Study Drug (one blinded, one open-label)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V3R
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	0-24h
Eligibility Checklist	X										S
Informed Consent <sup>a</sup>	X										E
Inclusion/Exclusion Criteria	X										E
Demography <sup>b</sup>	X										
Medical and SE and Wean History <sup>c</sup>	X										T
Height	X										A
Weight <sup>d</sup>	X		X	X	X	X	X	X			B
Serum Pregnancy Test <sup>e</sup>	X										L
Hematology <sup>f</sup>	X		X	X		X		X		X	E
Serum Chemistry and GFR <sup>g</sup>	X		X	X		X		X		X	
Urinalysis <sup>h</sup>	X		X	X		X		X		X	E
Pharmacogenetic sample	X										X
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X	T
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X	E
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X		N
STESS	X										I
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	O
Glasgow Outcome Score (GOS)											N
Supervision Rating Scale (SRS)	X <sup>n</sup>										
Modified Rankin Score (mRS)	X <sup>n</sup>										
Epilepsy Status	X										N
Clinical Global Impression (CGI)	X										E
Continuous IV Third-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>o</sup>			X
EEG	X	X				X		X	X		T
Randomization		X									
Study Drug Administration <sup>p</sup>			X	X	X	X	X	X			
TW Outcome and Retreat Decision										X <sup>q</sup>	P
Physiologic Brain Activity									X		
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X	A
Concomitant Anti-Epileptic Drugs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	G
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	E
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X	
Pharmacoeconomic Data											
Mortality											



Table 2 continued

	V3R	V4R	V5R	V6R	V7R	V8R	V9R	V10R	V11R	V12R
	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3R+14d (±2d)	V3R+21d (±2d)
Weight <sup>d</sup>	X	X	X	X	X	X				
Serum Pregnancy Test <sup>e</sup>										
Hematology <sup>f</sup>	X	X		X		X		X		
Serum Chemistry and GFR <sup>g</sup>	X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X	X		X		X		X		
Vital Signs <sup>i</sup>	X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>	X	X	X	X	X	X	X			
STESS										
FOUR Score <sup>m</sup>	X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)										X
Supervision Rating Scale (SRS)										X
Modified Rankin Score (mRS)										X
Epilepsy Status										X
Clinical Global Impression Scale (CGI)										X
Continuous IV Third-Line Agent(s)	X	X	Wean	Wean	Wean	Wean <sup>o</sup>				
EEG			X			X	X			
Randomization										
Study Drug Administration <sup>p</sup>	X	X	X	X	X	X				
TW Success and Physiologic Brain Activity							X			
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data										X
Mortality										X

**Table 3: Schedule of Assessments for Protocol 547-SSE-301: Qualifying Wean Successes**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical and SE and Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X											
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X											
Serum Chemistry and GFR <sup>f</sup>	X											
Urinalysis <sup>h</sup>	X											
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X											
ECG <sup>j</sup>	X											
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>n</sup>											X
Modified Rankin Score (mRS)	X <sup>n</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV Third-Line Agent(s)	X	Wean										
EEG	X	X										
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

<sup>a</sup> Written informed consent by proxy (LAR) will be obtained prior to starting any study-related procedures not considered standard of care.

<sup>b</sup> Demographic information will be obtained by proxy and confirmed by the subject when possible.

<sup>c</sup> Medical history will be obtained by proxy and confirmed by the subject when possible. All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Dosing changes with the third-line agent(s) that constitute a wean attempt will be marked as such on the CRF, and the start/stop dates and times of all wean attempts prior to V3 will be recorded, as well as the outcome of the wean attempt.

- <sup>d</sup> Weight will be collected at Screening (V1) and once during each 24 hour period of the initial study drug infusion period (V3-V8) and second infusion period (V3R-V8R, if applicable). Daily weight will be used to determine the appropriate infusion rate of each dose.
- <sup>e</sup> Serum pregnancy test for females aged 18 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy.
- <sup>f</sup> Blood samples will be taken for hematology and serum chemistry and GFR calculation at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will document whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.
- <sup>g</sup> Blood samples will be taken at V11 or V11R for serum chemistry (renal panel only).
- <sup>h</sup> Urine samples will be taken for urinalysis and NAG at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will add a comment about whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.
- <sup>i</sup> Vital signs will be recorded at the following time points relative to the start of each infusion of study drug: Screening (V1), at 0, 30, 60 minutes ( $\pm 15$  minutes), at 2, 4, and 8 hours ( $\pm 30$  minutes), and at 24, 48, 72, 96, 120, 144, 168, and 192 hours ( $\pm 2$  hours).
- <sup>j</sup> ECG (12-lead) should be performed at Screening (V1) and at the following times relative to the start of study drug infusion. For the blinded (first) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 128, 136, 144, 152, 160, and 192 hours ( $\pm 2$  hours). For the open label SAGE-547 (second) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 126, 132, 138, 144, 152, 160, and 192 hours ( $\pm 2$  hours). Heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours.
- <sup>k</sup> Plasma will be collected to assay for study drug concentrations at the following time points relative to the start of each infusion of study drug: For the blinded (first) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion. For the open label SAGE-547 (second) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open label SAGE-547 study drug infusion. Pre-dose samples may be taken within two hours before starting the infusion of study drug; timepoints up to and including 1h will have a time window of  $\pm 5$  minutes; all other timepoints will have a window of  $\pm 15$  minutes.
- <sup>m</sup> FOUR Score assessments will be performed at Screening (V1), 24, 48, 72, 96, 120, 144, 168, and 192 hours (all  $\pm 2$  hours) relative to the start of each infusion of study drug, and at V11 or V11R, and at V12 or V12R.
- <sup>n</sup> SRS at V1 will be a retrospective assessment of the supervision required by the subject immediately prior to admission that includes the index episode of the SE, and mRS at V1 will be a retrospective assessment of the disability and dependence of the subject immediately prior to admission that includes the index episode of the SE.
- <sup>o</sup> Target for complete wean of all continuous IV third-line agents by 144 hours at V8/V8R if not completed by 120 hours at V7/V7R.
- <sup>p</sup> Study drug infusion is intended for IV administration only with a dedicated peripheral IV line using Sage-approved IV administration bags and lines.
- <sup>q</sup> At V10 only a decision to re-treat at a higher dose of SAGE-547 will be made by the Investigator if the continuous IV third-line agent wean has failed or the third-line agent requires re-introduction during V9. Subjects who become eligible for re-treatment at a higher dose of SAGE-547 will discontinue the planned visit schedule at V10, then repeat V3 (V3R) and all applicable subsequent visits.
- <sup>r</sup> AEs will be collected from the time Informed Consent is obtained and prior to the start of study-specific screening procedures not considered standard of care. Collection of AEs will continue throughout the study from V1 through V12 or V12R.
- <sup>s</sup> Subjects may enter the study on AEDs and be administered AEDs during the study. All Concomitant AEDs must be recorded on the CRF with details including date and time of starting/stopping each AED, the route of administration, changes in doses, and frequency of administration. Details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the CRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.
- <sup>t</sup> All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Details will include the name of the drug, the start/stop dates and times, and, after consent, the doses with start/stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

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**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
AE	adverse event
AED	anti-epileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the time-concentration curve
AW	additional weans
BDZ	benzodiazepine
BIEEG	blinded infusion electroencephalogram
BUN	blood urea nitrogen
CBC	complete blood count
CEEG	consent electroencephalogram
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
C <sub>max</sub>	maximum plasma concentration
C <sub>min</sub>	minimum plasma concentration
CNS	central nervous system
CRF	case report form
CSR	clinical study report
CYP2C9	cytochrome P450 enzyme involved in drug metabolism
DNR	do not resuscitate
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EEG	electroencephalogram
EIND	Emergency Use Investigational New Drug Application
EP	European Pharmacopeia
ESETT	Established Status Epilepticus Treatment Trial
FDA	Food and Drug Administration
FOUR	Full Outline of UnResponsiveness
GABA	$\gamma$ -aminobutyric acid
GABA <sub>A</sub>	$\gamma$ -aminobutyric acid-gated chloride channel

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GOS	Glasgow Outcome Scale
H	hour
HPLC	high performance liquid chromatography
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent to Treat
IV	intravenous
IVRS	Interactive Voice Randomization System
LAR	legally authorized representative
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent to Treat
mRS-9Q	Modified Rankin Score - 9Q
MS/MS	tandem mass spectrometry
nM	nanomolar
NMDA	n-methyl-D-aspartic acid
OW	other weans
PAEEG	primary endpoint electroencephalogram
PD	pharmacodynamics
PK	pharmacokinetic
QOL	quality of life
QW	qualifying wean
QWEEG	qualifying wean electroencephalogram
RBC	red blood cell

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
RSE	refractory status epilepticus
SAE	serious adverse event
SAP	Statistical Analysis Plan
SE	status epilepticus
SOP	standard operating procedure
SRS	Severity Rating Scale
SRSE	Super-refractory status epilepticus
SSRI	Selective serotonin re-uptake inhibitors
STESS	Status Epilepticus Severity Score
SUSAR	Suspected Unexpected Serious Adverse Reactions
SWFI	Sterile Water for Injection
TAEEG	taper electroencephalogram
T <sub>max</sub>	time at maximum plasma concentration
TW	terminal wean
TWEEG	terminal wean electroencephalogram
US	United States
USP	United States Pharmacopeia

### 3. INTRODUCTION AND RATIONALE

#### 3.1. Status Epilepticus

Status epilepticus (SE) is a life-threatening seizure condition in which the brain is in a state of persistent seizure triggered by neuronal hyperexcitability. The Neurocritical Care Society defines SE as one continuous unremitting seizure lasting longer than five minutes or recurrent seizures without regaining consciousness between seizures for greater than five minutes (Brophy, Bell et al. 2012). Common causes of SE include preexisting epilepsy, cerebrovascular disease (in adults), electrolyte and metabolic disturbances, anoxia, encephalopathies, head trauma, high fever (in children, especially in the first year of life) and drug or substance intoxication. SE is associated with substantial morbidity and mortality.

##### 3.1.1. Epidemiology of SE

Geography, sex, age, and race influence the epidemiology of SE, whose incidence has a bimodal distribution, peaking in infants/young children and the elderly (Hauser 1990; DeLorenzo, Pellock et al. 1995; Wu, Shek et al. 2002). The incidence of SE in the elderly population is at least twice that in the general population. Concurrent medical conditions often exist in the elderly population, which can complicate therapy and worsen the prognosis of SE (Chapman, Smith et al. 2001).

The annual incidence of SE in the US is generally quoted to be within the range of 18/100,000 to 61/100,000, based on a 19-year retrospective study in Rochester, Minnesota (Hesdorffer, Logroscino et al. 1998) and a 2-year prospective study in Richmond, Virginia (DeLorenzo, Pellock et al. 1995), respectively. Two studies from Europe give annual incidences of a similar magnitude, ranging between 9.9/100,000 and 15.8/100,000 (Coeytaux, Jallon et al. 2000; Knake, Rosenow et al. 2001). It is thus estimated that in the United States each year there are as many as 150,000 cases of SE (DeLorenzo, Pellock et al. 1995).

#### 3.2. Refractory SE

When a patient begins to seize, the emergency medical technician will administer a first-line intravenous (IV) benzodiazepine (BDZ), such as diazepam, lorazepam or midazolam (Silbergleit, Durkalski et al. 2012), which is done either at the scene of the seizure or in the ambulance. If this is unsuccessful at abating the seizure, additional doses of the first-line therapy will be administered in the emergency room. Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line therapy, which is an IV anti-epileptic drug (AED) such as phenytoin or valproic acid (Novy, Logroscino et al. 2010; Shorvon 2011; Hocker, Britton et al. 2013).

Approximately 20-30% of patients refractory to first-line treatment will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to approximately 70-80% of patients who receive second-line therapy refractory to that therapy.

If a patient's SE continues after administration of BDZs and AEDs, the subject is diagnosed as having refractory status epilepticus (RSE), which must be treated quickly to terminate the seizure activity, maintain the patient's airway, and prevent cerebral damage. RSE patients are immediately admitted to the Intensive Care Unit (ICU) and placed in a medically-induced coma to stop all seizure-related activity. The drugs used to induce coma are continuously-infused IV agents,

commonly propofol, midazolam, or pentobarbital/thiopental, referred to as third-line agents (Brophy, Bell et al. 2012).

The RSE patient is continually monitored using electroencephalography (EEG) to ensure burst suppression is achieved. Burst suppression is a pattern of brain waves seen on an EEG, characterized by periods of activity alternating with periods of little or no activity in the brain, informing medical personnel of the effectiveness of the medically-induced coma. The goal of burst suppression is to allow the brain and corresponding neuronal tissue to restore function and reset to normal pre-seizure levels.

### **3.2.1. Epidemiology of RSE**

Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line AED therapy. In turn, approximately 20 – 30% of these patients treated with AEDs will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to 28% of the total estimated SE patient population refractory to second-line therapy. Based on the previously-cited estimated incidence in the US, this means that there are up to 42,000 incident cases of RSE in the USA, annually (DeLorenzo, Pellock et al. 1995).

### **3.3. Super-refractory SE**

After 24 hours of burst suppression, the patient is weaned off of the third-line therapy. If the weaning is unsuccessful (neuronal activity has not returned to normal), the third-line agent is re-administered or a different third-line agent is started, and the patient is considered to be in super-refractory status epilepticus (SRSE) (Chapman, Smith et al. 2001; Shorvon 2011; Brophy, Bell et al. 2012). SAGE-547 is being developed as an adjunct to third-line therapy in patients in RSE who have failed standard treatment. In this protocol, the term “RSE that has failed standard treatment” is deemed to be equivalent to the term “SRSE” and the two may be used interchangeably.

#### **3.3.1. Epidemiology of SRSE**

The incidence of SRSE is very poorly understood, mainly because the diagnostic codes used for SE do not generally differentiate its nature as responding or refractory to treatment. Based on the variable reporting of outcomes data, the incident cases of SRSE could represent between one and two-thirds of the RSE patients (Novy, Logroscino et al. 2010; Ferlisi and Shorvon 2012; Hocker, Britton et al. 2013; Sutter, Marsch et al. 2013). More detailed epidemiology studies are needed to better elucidate the proportion of RSE patients whose condition becomes super-refractory. A recent review of ICU discharge data in the USA suggests an annual incidence of approximately 35,000, based on patients who required at least three days in the ICU for SE [Sage data on file].

#### **3.3.2. Outcomes of SRSE**

SE has varying degrees of mortality depending on the underlying etiologies. Table 4 outlines the acute mortality in patients with SE by etiology (Neligan and Shorvon 2010). The mortality rate of SRSE is estimated to be 30% to 50% using current standard of care.

The causes of death from SE (and therefore SRSE) are heterogeneous, resulting from neuronal cell death, complications of underlying medical conditions, or adverse effects of the current standard treatments. Prognosis worsens and mortality increases with longer duration of SE, i.e. with SE that develops into RSE or SRSE (Neligan and Shorvon 2010), and with longer duration of

medically-induced coma ([Ferlisi and Shorvon 2012](#)). There is an obvious unmet medical need to improve upon the current standard of care treatment regimens.

Morbidity is high and survivors have outcomes ranging from poor function to vegetative state ([Shorvon 2011](#)). Approximately one third of patients with RSE and SRSE will recover, but with chronic neurologic or other deficits ([Neligan and Shorvon 2010](#); [Hocker, Britton et al. 2013](#)). In all, it is estimated that less than 25-30% of all SRSE patients have a favorable functional outcome.

**Table 4: Approximate Mortality of Status Epilepticus in Different Etiologies**

Underlying Etiology	Associated Acute Mortality in Patients with SE (%)
Drug reduction/withdrawal, poor AED compliance, or low AED levels	0-10
Cerebrovascular Disease	20-60
Metabolic Disorders	10-35
Acute CNS Infection	0-30
Anoxia	60-100
Alcohol Abuse	0-10
Head Trauma	0-25
Drug Overdose/Toxicity	10-25
Brain Tumors	0-20
Cryptogenic/Idiopathic	5-20

### 3.3.3. Unmet Medical Need in Super-refractory Status Epilepticus

Treatment approaches for SRSE consist of diagnosis and treatment of underlying medical conditions, adding and changing anti-seizure drugs, and repeated attempts at weaning from IV anesthetic agents. Treatment of SRSE has three aims:

- to prevent excitotoxicity, which begins within 24 hours of SE onset;
- to prevent cerebral damage by initiating neuroprotective burst suppression;
- to prevent the complications of extended periods of anesthesia or unconsciousness ([Shorvon 2011](#)).

Currently, there are no therapies that have been specifically approved for RSE or SRSE. The primary drugs used to induce coma are continuously infused IV anesthetics such as propofol, midazolam, or pentobarbital/thiopental, known as third-line agents. Use of these drugs to control SRSE has only been studied in small retrospective reviews or small prospective studies without controls ([Hocker, Britton et al. 2013](#)) therefore there is no agreement on which drug is optimal nor on an optimal dosing regimen for the treatments that are used.

The most common adverse effect of the third-line agents is hemodynamic instability; in addition, they are not universally effective, with breakthrough seizures and withdrawal seizures requiring dose adjustments and changes in third-line agent(s). The drug thought to be most effective in SRSE, pentobarbital, is also associated with the most toxic adverse effect profile, comprising



decreased blood pressure and cardiorespiratory collapse (Claassen, Hirsch et al. 2002). The ability to wean patients successfully off the third-line agents as quickly as possible is therefore paramount, and an adjunct to SRSE treatment that enhances the success of the third-line agents and supports their successful weaning in a short timeframe would be an important addition to the therapeutic armamentarium. Preliminary clinical data show that SAGE-547 has been a successful adjunct to third-line therapy in this regard.

### 3.4. SAGE-547 Injection

Allopregnanolone is an endogenous, naturally occurring neuroactive steroid formed in the corpus luteum of the ovary, adrenal cortex and central nervous system (CNS) (Holzbauer, Birmingham et al. 1985; Paul and Purdy 1992; Ottander, Poromaa et al. 2005). It is a metabolite of progesterone created by the actions of 5- $\alpha$  reductase and 3- $\alpha$  hydroxy-steroid dehydrogenase. Allopregnanolone is a potent positive allosteric modulator of both synaptic and extra-synaptic GABA<sub>A</sub> receptors.

SAGE-547 Injection (allopregnanolone aqueous formulation in Captisol<sup>®</sup>) is being developed for the treatment of patients in RSE who have not responded to standard treatment. SAGE-547 Injection is a solution of 5 mg/mL allopregnanolone in Sterile Water for Injection (SWFI), USP and 250 mg/mL betadex sulfobutyl-ether sodium, NF. It is further diluted with Sterile Water for Injection, USP (SWFI) in IV bags to achieve an allopregnanolone concentration of approximately 1.67 mg/mL in an approximately isotonic solution and will be administered intravenously.

#### 3.4.1. Scientific Rationale for SAGE-547 in SRSE

Ineffective recruitment of inhibitory neurotransmission, together with excessive neuronal excitation, likely plays a role in the initiation and propagation of the electrical disturbance occurring in SE. GABA ( $\gamma$ -aminobutyric acid), the major inhibitory neurotransmitter in the central nervous system (CNS), is released from GABAergic neurons and binds to several types of GABA receptors (GABA<sub>A</sub>, GABA<sub>B</sub>, and GABA<sub>C</sub>) on target neurons. GABA<sub>A</sub> receptors are macromolecular proteins that form a chloride ion channel complex and contain specific binding sites for GABA and a number of allosteric regulators, including barbiturates, benzodiazepines, and some anesthetic agents. GABA receptor-mediated inhibition contributes significantly to the normal termination of a seizure (Kapur and Macdonald 1997). SAGE-547 is a positive allosteric modulator of the GABA<sub>A</sub> receptor.

The importance of terminating seizure activity as soon as possible is underpinned by a growing body of evidence from research and clinical observation that SE becomes more difficult to control as its duration increases. It has been postulated that this occurs due to a mechanistic shift from inadequate GABAergic inhibitory receptor-mediated transmission to excessive N-methyl-D-aspartic acid (NMDA) excitatory receptor-mediated transmission (Kapur and Macdonald 1997). As prolonged epileptiform bursting results in a reduction of GABA<sub>A</sub>-mediated synaptic inhibition, antiepileptic treatments which rely on enhancing intrasynaptic GABA<sub>A</sub> neurotransmission become less effective the longer SE continues.

Furthermore, the constitutive process of synaptic GABA<sub>A</sub> receptor internalization is accelerated by the increased neuronal activity associated with seizures. These findings suggest that the rate of GABA<sub>A</sub> receptor internalization is regulated by neuronal activity, and its acceleration contributes to the reduction of inhibitory transmission observed during prolonged seizures (Kapur and Macdonald 1997). Of note is that SAGE-547 binds to extrasynaptic as well as intrasynaptic GABA<sub>A</sub> receptors;

extrasynaptic receptors remain active with ongoing seizure activity, resulting in a putative mode of action for SAGE-547 in SRSE.

Status epilepticus induces cerebral damage that includes neuronal cell necrosis, gliosis, and network reorganization. The major cause of cell death in cerebral damage is excitotoxicity, which is initiated by glutaminergic receptor over-activation, causing calcium to flood the cell, thereby leading to apoptosis and necrosis. This process is initiated within a few hours of the start of seizure activity, and provides the medical imperative to terminate SE as quickly as possible. To prevent the consequences of the excitotoxicity cascade, it is recommended that anesthesia be initiated within 1-2 hours of onset of seizures at doses designed to induce EEG burst suppression ([Shorvon and Ferlisi 2011](#)).

### **3.4.2. SAGE-547 Clinical Program in the Treatment of SRSE**

The current SAGE-547 development program includes:

- an ongoing Phase 2 open-label trial, Study 547-SSE-201;
- this proposed Phase 3 randomized, double-blind, placebo-controlled trial, Study 547-SSE-301;
- a planned open-label, expanded access protocol, Study 547-SSE-302;
- a number of EINDs for SAGE-547 in patients with SRSE.

The designs of these studies are all similar, with a five to six day infusion of SAGE-547 (or placebo), during which time attempts are made to wean the subject off all third-line agents. In the Phase 3 studies, those subjects who cannot be weaned off third-line agents while being administered SAGE-547 (or placebo) will be eligible for a second open-label infusion of SAGE-547 at a higher dose, which is also being employed for the latter patients being enrolled in the Phase 2 study. Follow up of subjects is for 21 – 30 days after the first infusion of study medication.

### **3.4.3. Data from the SAGE-547 Development Program**

The data from 30 subjects included in the on-going clinical evaluation of SAGE-547 for the treatment of adults and children with SRSE clearly offers preliminary evidence that SAGE-547 could provide substantial and clinically significant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate. These subjects comprise 20 from the ongoing Phase 2 trial (71% success rate in 12/17 evaluable subjects) and 10 subjects who received EIND treatments (78% success rate in 7/9 evaluable subjects).

Successful therapy of SRSE has been defined as “the SE is completely controlled by the therapy, without breakthrough of withdrawal seizures, or discontinuation due to side effects or death during therapy,” ([Ferlisi and Shorvon 2012](#)). By this definition, which is in accord with the efficacy assessments used in the overall clinical evaluation of SAGE-547, 19 of the 26 (73%) subjects with SRSE who completed the SAGE-547 infusion were treatment successes. As data collection is ongoing, this information is preliminary and subject to change upon further monitoring.

Published reports on RSE and SRSE have stated mortality rate ranges from 35% to 65%. The underlying etiologies of SE in the 547-SAGE-201 study and EINDs are heterogeneous, and each one conveys a different risk of mortality and longer term morbidity. However, the death rate in subjects who have received SAGE-547, 6 out of 30 (20%) subjects, appears to be lower than the published

rates. None of the deaths were considered related to SAGE-547: brain tumor, organophosphate toxicity, respiratory failure, respiratory arrest due to ventilator support withdrawal, and breast cancer.

In the Phase 2 study, 20 SAEs (15 non-fatal) have been reported in 13 (65%) subjects, and of these 3 events in 2 subjects (10%) were considered by the investigator to be related to SAGE-547: pulmonary emboli and tracheostomy dehiscence/infection. The Sponsor did not consider these events to be related to SAGE-547, rather to the underlying disease states. Four of the 20 subjects (20%) experienced AEs considered possibly related to SAGE-547 by the investigator, namely moderate myopathy and severe pulmonary emboli in 1 subject, moderate tracheostomy dehiscence and tracheostomy infection in 1 subject, moderate thrombocytosis in 1 subject and moderate BUN, ALT and AST elevation in 1 subject.

Review of the most current safety data from 547-SAGE-201 reveals that there were changes in serum chemistry, hematology, and urinalysis during the study, but that none of those changes were assessed as related to SAGE-547. There were also no SAGE-547-related changes to vital signs.

Despite the heterogeneity in the underlying causes of SE, the ages of the subject, comorbidities, which normally complicate the treatment of SE, and the fact that all subjects had failed current standard of care treatment, a large majority of subjects had a successful therapy outcome, with discontinuation of all third-line agents and resolution of SE.

Refer to the Investigational Brochure for further information on the pre-clinical and clinical data supporting the use of SAGE-547 in SRSE.

### **3.5. Study Rationale - SAGE-547 in SRSE**

#### **3.5.1. Justification for the Control Group**

Although SAGE-547 has demonstrated extremely promising activity in subjects with SRSE, both in the Phase 2 study and during the EINDs, these have been open-label investigations with no control data for comparison. Generally in the literature there are few data describing the success rates of wean attempts of third-line agents, and few comparative data on the effectiveness of the three main third-line agents, propofol, pentobarbital/thiopental, and midazolam.

Several options for a control group in Study 547-SSE-301 were considered:

- No control group was thought to be unacceptable since there are no reliable published data on success rates in this population that could be used for broad comparisons;
- An active control was considered but found to be impractical since none of the third-line agents are approved for their use in SRSE, no standardized dosing regimens or treatment guidelines have been adopted for the management of SRSE, and clinicians were unlikely to agree which of the available third-line agents would be reserved for the active control arm;
- Historical controls were considered but abandoned because of the practical difficulties of obtaining high quality data, the lack of ability to prospectively match cases, and a suspicion that clinical practice in the standard of care of SRSE is evolving, mandating the use of prospective, concurrent control data;
- Comparison to standard of care alone was considered as a feasible design. However, in a field where no widely adopted treatment guidelines exist, there was a concern that knowledge of the treatment group (SAGE-547 plus standard of care versus standard of care

alone) would alter the behavior of the investigators such that they could be more aggressive with weaning in the SAGE-547 group;

- Placebo control is not without its challenges since the preliminary efficacy data for SAGE-547 show that the compound exerts central pharmacological effects and is associated with positive outcomes in around 70% of patients. There is therefore a potential ethical concern about administering placebo to desperately ill patients who have often exhausted all treatment options for SRSE. This concern has been addressed in two ways: firstly all patients receive current standard of care; secondly, all subjects who fail to be weaned from their third-line agents at the end of the blinded infusion of study drug will be administered open-label SAGE-547 without un-blinding their initial treatment allocation, so treatment with the investigational product is not denied, but delayed about a week in the setting of ongoing receipt of full current standard of care.

It was therefore decided that a blinded, placebo-controlled design was appropriate for Study 547-SSE-301.

### **3.5.2. Justification for the Dose Regimen**

The standard dose regimen has been studied in 19 subjects in the 547-SSE-201 Phase 2 trial; the average peak plasma concentration of SAGE-547 at the end of the loading dose was approximately 144 ng/ml. The average plasma concentration during the maintenance infusion was approximately 70 ng/ml. At these concentrations, there were no clear safety signals although two-thirds of subjects experienced an SAE and there were four deaths, all related to the underlying comorbid conditions. The standard dosing regimen was associated with an approximate 70% successful treatment outcome. For these reasons, the standard dosing regimen has been adopted for the initial SAGE-547 infusion to be compared in a blinded fashion to placebo.

In the 547-SSE-201 trial, three subjects have thus far received the higher dose regimen. This dose regimen has also been well tolerated. The average peak plasma concentrations at the end of the loading dose for both dosing regimens will be in the same range, as the loading dose is the same for both regimens. The average plasma concentrations observed during the higher maintenance dose are 102 ng/ml (n=2). The rationale for adopting the higher dose regimen as the open-label infusion of SAGE-547 for subjects who are retreated in this 547-SSE-301 trial is that those who fail on the standard SAGE-547 dose regimen are afforded the opportunity to have access to a higher dose. The justification to also administer the higher dose regimen to failures on placebo is that the regimen has thus far been well tolerated, and this methodology preserves the blind for the initial infusion.

A five-day dosing regimen with SAGE-547 was investigated in the Phase 2 study, 547-SSE-201. There were some cases when weaning off all third-line agents was not possible within 48 hours, but weaning was completed after the end of the infusion of SAGE-547. For this reason, the duration of dosing with SAGE-547 has been increased from 120 hours (five days) in Phase 2 to 144 hours (six days) in this Phase 3 study.

### **3.5.3. Rationale for Genetic Testing Sub-study**

Sage Therapeutics intends to perform genetic research in the SAGE-547 development program in order to explore how genetic variations may affect the metabolism and activity of SAGE-547. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials, and, possibly, to genetically-guided

treatment strategies for optimizing decision making with respect to individual benefit:risk. Participation of subjects in genetic research as part of the overall clinical study is optional.

### **3.6. Benefit-Risk Evaluation of the Present Study**

Previous reports of human administration of exogenous allopregnanolone indicate that for exposures in men and women up to 150 nM, the most commonly reported AEs were sedation (recorded as sleepiness or tiredness), feelings of intoxication (like alcohol), flushing, and mild headache (Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007). No SAEs were reported (Navarro, Kaddouz et al. 2003; Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007; Kask, Backstrom et al. 2008; Kask, Backstrom et al. 2009; Timby, Hedstrom et al. 2011a). In view of the reduced consciousness and sedation of study subjects at entry into this protocol, none of these previously-reported events are likely to impact subjects in this study.

To date, in the SAGE-547 Phase 2 study and the EIND subjects, a majority of subjects demonstrated a successful therapy outcome (>70%). The majority in the clinical trial (65%) have also experienced SAEs, but none has been considered related to SAGE-547 by the Sponsor (SAEs in 2 subjects (10%) were considered possibly related by Investigator). Five deaths have been reported in 30 subjects (20%), all related to the underlying cause of SRSE and not related to SAGE-547 – this is in the context of published mortality rates between 35% and 65%. These preliminary data suggest that SAGE-547 has the potential to provide clinically relevant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate.

The underlying etiologies of SE are heterogeneous, and each one conveys a different risk of mortality. Subjects who survive SRSE still have a high risk of severe morbidity (Neligan and Shorvon 2010). The subjects treated with SAGE-547 in Study 547-SSE-201, are heterogeneous in factors such as age and etiology of SE, factors that usually complicate treatment and can increase morbidity and mortality. Even with this heterogeneity, the preliminary efficacy and safety data for SAGE-547 are very encouraging, and the mortality rate suggests that the risk to benefit assessment of this treatment rests on the side of benefit.

## **4. ETHICS**

### **4.1. Institutional Review Board or Independent Ethics Committee**

This protocol will be reviewed and approved by the Institutional Review Board (IRB) where the study is conducted. The IRB will meet all FDA requirements governing IRBs (CFR, Title 21, Part 56).

### **4.2. Ethical Conduct of the Study**

The Sponsor, the Medical Monitor, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable ICH and GCP guidelines, and must also conduct the study in accordance with local regulations.

### **4.3. Subject Information and Informed Consent**

Subjects prospectively enrolled in this study will be unable to give consent. Therefore, consent will be given by proxy by a legally authorized representative (LAR). Written informed consent is required for each subject prior to any testing under this protocol not considered standard of care,

including screening tests and evaluations. Should a subject gain the ability to sufficiently comprehend the situation and consent during the course of the study, written informed consent or verbal assent will be documented as required or recommended by the institution's IRB.

The form of consent to be obtained will depend on the condition of the subject as determined by the Principal Investigator. The informed consent form (ICF), as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50.

It is the responsibility of the Investigator to obtain consent and to provide the subject's LAR with a copy of the signed and dated informed consent form. The informed consent form for subject participation must also be available as part of the subject file for review by the site's dedicated study monitor or any authorized auditor of the Sponsor or regulatory authorities.

All ICFs used in this study must be approved by the appropriate IRB and by the Sponsor. The ICF must not be altered without the prior agreement of the relevant IRB and the Sponsor.

#### **4.4. Ethical and Regulatory Considerations for Pharmacogenetic Sub-study**

##### **4.4.1. Informed Consent for Pharmacogenetics**

The genetic component of this study is optional and subjects may participate in other components of the main study without having to agree to participate in the genetic component. If subject chooses to participate in the genetic component of the study, the subject or LAR must sign and date a specific consent form for the genetic component of the study in addition to the main study consent form. The principal investigator(s) is responsible for ensuring that consent is freely given and that the subject understands that they may discontinue from the genetic aspect of the study independent of their decision to remain within or withdrawal from the main study.

##### **4.4.2. Subject Data Protection Relative to Pharmacogenomics**

Sage Therapeutics will not provide individual genotype results to subjects, their family members, their general physician, their employer or any insurance company unless required to do so by law. While extra precautions will be taken to preserve confidentiality and to prevent genetic data from being linked to an individual's identity outside of a restricted access site, in certain exceptional situations (e.g. in case of a medical emergency or as a consequence of a specific regulatory need), certain individuals may see both genetic data and the personal identifiers of a subject; however in all cases a subject's medical information and genetic files will remain physically separated.

## **5. STUDY OBJECTIVES**

### **5.1. Primary Objective**

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult subjects with SRSE, and for the response to endure at least 24 hours after cessation of the SAGE-547 or placebo infusion (primary response).

## 5.2. Secondary Objectives

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in Clinical Global Impression Scale between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

## 5.3. Safety Objectives

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

## 5.4. Other Objectives

1. To evaluate the impact of retreatment with a higher dose of SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol<sup>®</sup> and identified SAGE-547 metabolite plasma concentrations;
3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;

6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS).

## **6. ENDPOINTS**

### **6.1. Primary Endpoint**

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### **6.2. Secondary Endpoints**

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) and to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### **6.3. Safety Endpoints**

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.



## 6.4. Other Endpoints

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who fail to respond to their randomized double blind treatment and are retreated with a higher dose of SAGE-547;
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS).

## 7. INVESTIGATIONAL PLAN

### 7.1. Overview of Study Design

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

Figure 1 provides an overview of the study design and Figure 2 gives the details of treatment and follow-up on the active treatment arm. Patients will follow one of three paths to entry to the study. The first path is for patients who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst suppression with a third-line agent. These patients will be consented for the study after admission to the intensive care unit, but before any third-line agents are administered for burst suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their LAR. Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours. Once burst suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see Table 3). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The second path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst suppression pattern on the EEG. These patients may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at

least 24 hours of continuous burst suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The third path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These patients may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within six hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third line agent wean attempts prior to randomization (one vs two or more).

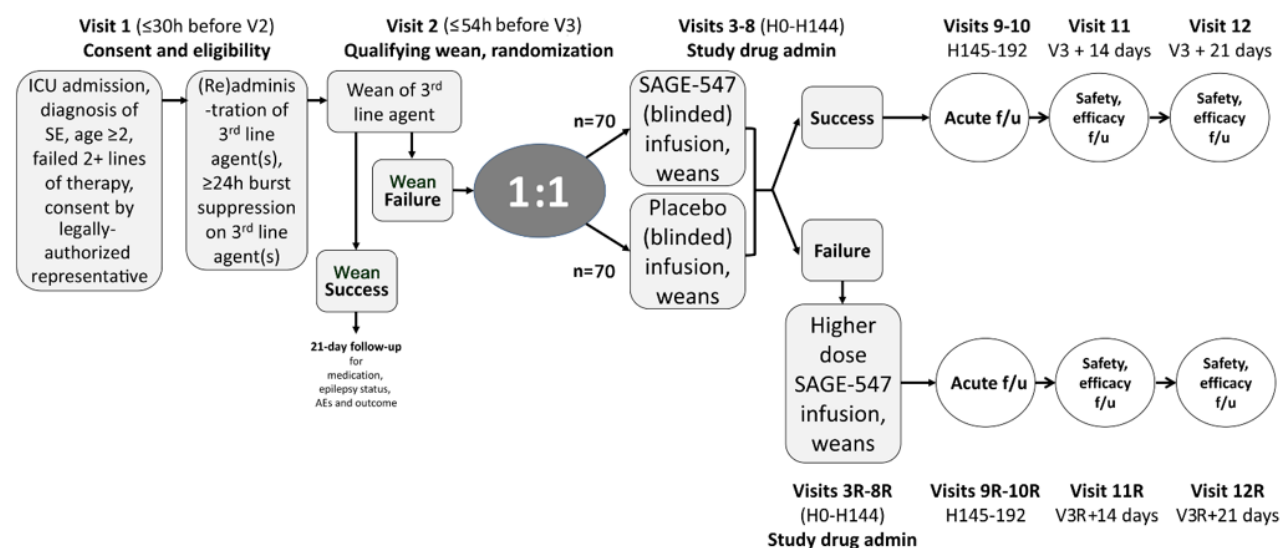
The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as the ability to wean the subject off all third-line agents before the end of the first infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication. Subjects must also have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) at the end of the primary endpoint assessment period as determined by EEG in order to be deemed a success. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#), [Table 2](#) and [Table 3](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. Eligibility for retreatment must be confirmed in writing by the medical monitor prior to the open-label infusion starting. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo will all subsequently be eligible to be administered SAGE-547 at the higher dose.

**Figure 1: Study Design**



## 7.2. Trial Conduct

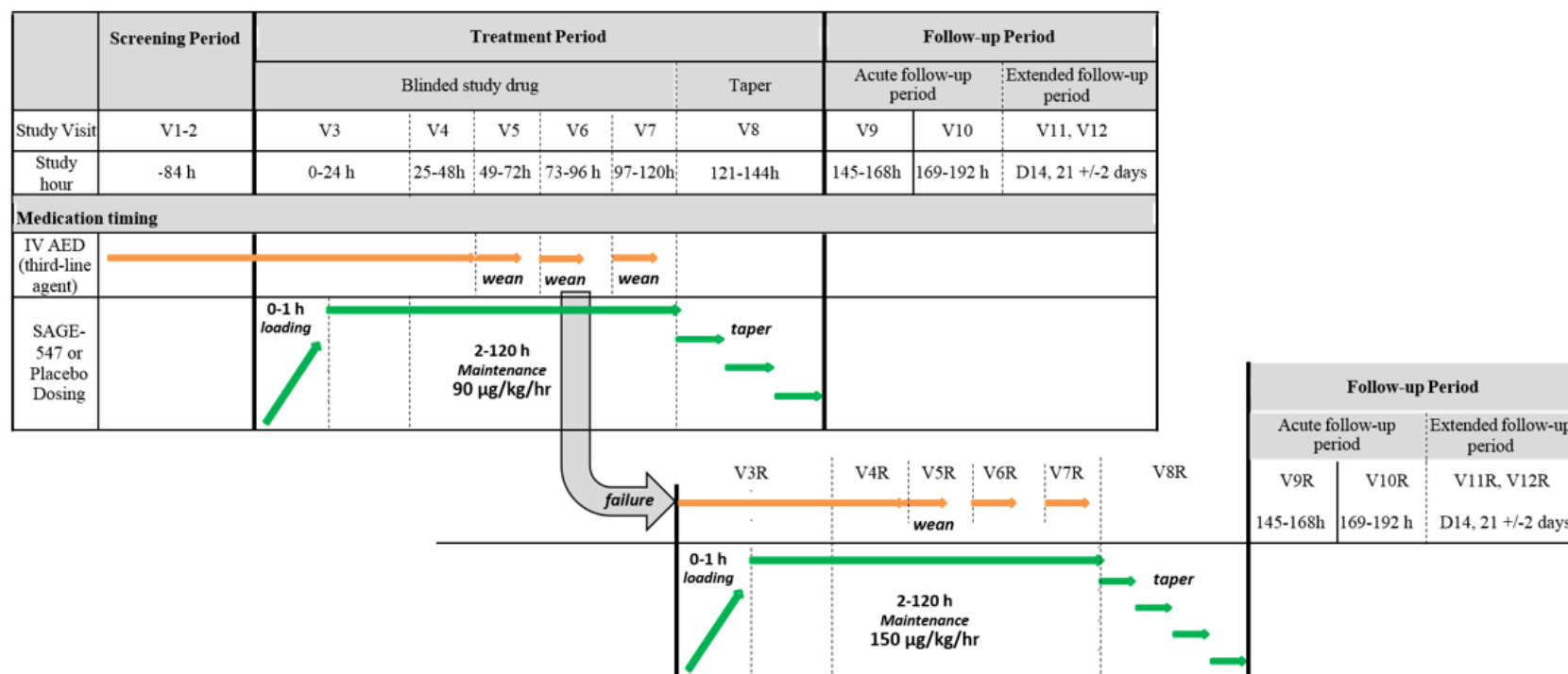
This study will be conducted according to the principles of the World Medical Association Declaration of Helsinki and most recent amendment, and in compliance with the protocol approved by the IRBs/Independent Ethics Committees (IECs), and in accordance with ICH Guidelines on GCP standards.

## 7.3. Blinding and Randomization

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo). Details of the dynamic randomization process will be included in the SAP.

The randomized portion of the study will be blinded, with the two treatment products (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

The second infusion of SAGE-547 will be administered on an open label basis to subjects who failed the primary endpoint wean.

**Figure 2: Details of Treatment Administration and Follow-up**

## 8. SELECTION AND WITHDRAWAL OF SUBJECTS

The study will randomize 140 patients at up to 180 sites. All subjects deemed eligible to enroll must have written Medical Monitor approval on a case-by-case basis prior to undertaking the qualifying wean.

### 8.1. Inclusion Criteria

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects 18 years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; *or* who have previously failed one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst suppression pattern; *or* who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst suppression pattern.

### 8.2. Exclusion Criteria

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy.
4. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis but for whatever reason, dialysis is not planned or non-continuous dialysis planned (that would not adequately remove Captisol®);
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the experience of the investigator, is less than 30 days;
  - e. a do not resuscitate (DNR) order.
5. Subjects who are being administered more than three third-line agents concomitantly or for whom the qualifying wean cannot be completed within 24 hours or who are being

administered a third-line agent for indications such as raised intra-cranial pressure that would preclude weaning according to this protocol.

6. Subjects with a living will that does not allow heroic measure.
7. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
8. Subjects who have been enrolled in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not withdraw or complete and then re-enroll).

### **8.3. Selection and Consent of Subjects for Pharmacogenetic Substudy**

All subjects will be asked to participate in pharmacogenetic research; however, participation in research is voluntary and a subject can decide to decline his/her participation without penalty or loss of benefit. Participation or lack thereof will not be a cause for exclusion from any aspect of the main study. In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **8.4. Subject Withdrawal / Study Termination**

#### **8.4.1. Withdrawal/Discontinuation of Individual Subjects**

The reasons for study drug discontinuation and/or subject withdrawal from the study must be recorded in the subject's electronic case report form (eCRF). The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject has been discontinued/withdrawn due to an AE.

##### **8.4.1.1. Withdrawal from the Study**

Subjects or their LAR may withdraw subjects from the study at any time for any reason without compromising the subject's medical care. The Investigator will also withdraw subjects upon the request of Sage Therapeutics or upon termination of the study.

Subjects who withdraw from the study prior to Visit 10 (or 10R) should complete the procedures scheduled for the day of study drug taper (hour 121-144; Visit8/8R) on the day of their withdrawal, including the SAGE-547 taper schedule, with the addition of the mortality assessment from Visit 12/12R. Subjects who withdraw from the study after Visit 10/10R should undergo study procedures as outlined for Visit 12/12R on the day of their withdrawal. In all cases, the reason for subject withdrawal will be recorded in the eCRF.

Withdrawal of subjects for any reason should be discussed with the Medical Monitor.

##### **8.4.1.2. Discontinuation of Study Drug**

If it is necessary to discontinue the study drug earlier than planned, subjects should continue to be followed per protocol to capture safety and efficacy assessments for the duration of the study period.

The investigator may withdraw the subject from the study drug for the following reasons:

- Upon subject's or LAR's request

- The subject or LAR is unwilling or unable to adhere to the protocol-specified visits
- The subject experiences an intolerable adverse event
- During the course of the study, the subject develops symptoms or conditions listed in the exclusion criteria.
- Other medical reason, at the discretion of the Investigator and/or the Medical Monitor

Subjects who discontinue the study due to an AE considered related to study drug should be followed until the event is resolved, considered stable, or the Investigator determines the event is no longer clinically significant. Study drug discontinuation due to AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

#### **8.4.2. Study Termination**

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of AEs or other findings suggesting unacceptable risk to subjects, administrative or operational reasons. In the event of study termination, Sage Therapeutics will provide written notification to the Investigator. Investigational sites must promptly notify their IRB and initiate withdrawal procedures for participating subjects.

## **9. INVESTIGATIONAL PRODUCT**

### **9.1. Identity of Investigational Product**

SAGE-547 Injection (allopregnanolone)

### **9.2. Clinical Supplies**

#### **9.2.1. SAGE-547**

Adequate supplies of SAGE-547 Injection and materials for intravenous administration will be provided to each site.

SAGE-547 Injection is a clear, colorless sterile solution of allopregnanolone intended for intravenous injection. SAGE-547 Injection is an aqueous solution of 5 mg/mL allopregnanolone in 250 mg/mL Captisol® (betadex sulfobutyl-ether sodium, NF). It is presented either un-buffered or buffered with 10 mM citrate at a pH of 6.0 in either 20 mL or 50 mL vials. SAGE-547 is further diluted according to the Pharmacy Manual to achieve an approximately isotonic solution and will be administered intravenously.

No preservatives are included in the drug product, which is intended to be used as a single-use vial. All inactive components (excipients) used in the formulation are compendial grade and conform to current USP/EP, and include sodium citrate, citric acid and betadex sulfobutyl-ether sodium (Captisol®).

#### **9.2.2. Placebo**

Placebo will be identical to SAGE-547 and presented in identical vials. Placebo will be manufactured in a similar way to SAGE-547 and comprises all excipients but no SAGE-547.

### 9.2.3. Blinding

The vials of SAGE-547 and placebo will be identical in every way so that they are indistinguishable by the pharmacist, investigator, anyone treating or managing the patient, the monitors, and the sponsor. In this way the first infusion of study drug administered to each patient will be double-blind.

For the blinded study drug infusions, subject-specific dosing kits will be provided. These dosing kits will be pre-labelled with kit number for the first blinded infusion. For the second-infusion, open-label kits will be provided, which will require subject assignment by the pharmacy for reconciliation purposes. The study kits must be stored under refrigerated conditions (2-8 °C). IV administration bags and lines may be provided for the blinded and open-label infusions. Refer to the Pharmacy Manual for additional details.

The label for the SAGE-547 Injection vials will include standard product identification information according to the Code of Federal Regulations, 21CFR 312.6. All study labels will also contain the following statement:

Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use.

### 9.3. Preparation of SAGE-547 or Placebo Injection for Dosing

The Pharmacy will be responsible for preparing the blinded and open-label study drug for subject dosing. The prepared admixture will be assigned a room temperature (20-25 °C) storage shelf life of 30 hours from time of compounding.

SAGE-547, which is hypertonic, will require dilution with SWFI to achieve an approximately isotonic solution according to the instructions provided in the Pharmacy Manual. Exactly the same procedures will be used to prepare the placebo admixture, so that all site staff remain blinded as to treatment allocation for the first infusion of study drug. SAGE-547 Injection is not intended to be administered to patients undiluted.

Refer to the Pharmacy Manual for specific instructions regarding infusion preparation.

### 9.4. Administration and Accountability

The Pharmacy will maintain accurate records of all investigational product supplies. Accurate records will be kept regarding the volume of SAGE-547 Injection or placebo used for each IV preparation, as well as the required infusion rate or rates, and the date and time of preparation. Reasons for departure from the expected dosing regimen must also be recorded. To satisfy regulatory requirements regarding drug accountability, all study medication will be reconciled in full. Refer to the Pharmacy Manual for additional details.

## 10. TREATMENT OF SUBJECTS

### 10.1. Dosing Schedule (Blinded Infusions)

SAGE-547 Injection or placebo will be administered according to the dosing schedules in [Table 5](#). The infusion rates to accomplish these µg/kg/h doses will be calculated according to the weight of the subject. The infusion rates will be applied to blinded study drug for the first infusion of study medication.



**Table 5: SAGE-547 or Placebo Dosing Schedule**

Hour	Type and Duration of Study Drug Infusion	Description
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	90 µg/kg/h
H121 – H128	8 hour taper	65 µg/kg/h
H129 – H136	8 hour taper	45 µg/kg/h
H137 – H144	8 hour taper	25 µg/kg/h

## 10.2. Dosing Schedule (Open-Label Infusions)

If a subject fails wean from third-line agent(s) or requires re-instatement of third-line therapy within 24 hours of discontinuing the initial infusion of study drug, SAGE-547 Injection will be re-administered according to the dosing schedule in Table 6. The infusion rates to accomplish these µg/kg/h doses will be calculated according to the weight of the subject. These infusion rates will be applied to SAGE-547 re-treatment for the open-label second infusions of study medication.

**Table 6: SAGE-547 Open Label Dosing Schedule**

Hour	Type and Duration of SAGE-547 Infusion	Description
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	150 µg/kg/h
H121 – H126	6 hour taper	125 µg/kg/h
H127 – H132	6 hour taper	95 µg/kg/h
H133 – H138	6 hour taper	65 µg/kg/h
H139 – H144	6 hour taper	35 µg/kg/h

## 10.3. Route of Administration

SAGE-547 Injection is intended for IV administration only. The compatibility of SAGE-547 with other drugs is unknown, and the product should be administered via a dedicated peripheral IV line using any Sage-supplied study-specific IV administration bags and lines. In order to preserve blinding, these instructions also apply to the blinded placebo infusions.

## 10.4. Treatment Period

The treatment period with double-blind SAGE-547 or placebo is six 24-hour periods (144 hours), which may encompass 6-7 calendar days. The retreatment period is of identical duration.

## 10.5. Concomitant Medications, Procedures and Treatments

Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. All concomitant medications, procedures, and treatments should be documented throughout the study from Screening through Visit 12/12R and recorded on the eCRF.

SAGE-547 has demonstrated inhibitory effects on cytochrome P450 isoenzyme 2C9 (CYP2C9).

Therefore, AEDs such as phenytoin and phenobarbital that are primarily metabolized by CYP2C9 should be closely monitored during SAGE-547 administration to ensure target exposures are maintained.

#### **10.5.1. Concomitant AEDs**

Subjects may enter the study on AEDs, and be administered AEDs during the study. All of these must be recorded on the eCRF with details including date and time of starting and stopping each AED, the route of administration, changes in doses, and frequency of administration. In addition, details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the eCRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.

#### **10.5.2. Concomitant Third-Line Agents**

All third-line agents (as defined in [Section 8](#)) administered since the diagnosis of SE will be recorded on the eCRF, whatever path the patient took for entry into the study. Details will include the name of the drug, the start and stop dates and times, and, after consent, the doses with start and stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

In addition, those changes in dose that constitute a wean attempt will be marked as such on the eCRF. In this way the start and stop dates and times of all wean attempts (see [Section 11](#) for definitions) will be recorded, as will the type of wean (QW, OW, or TW) and the outcome of the wean attempt (successful, failed and dose of this third-line agent increased or failed and this third-line agent stopped and another third-line agent started). Those wean attempts that occur after the TW up to and including Visit 12/12R will be marked “AW”.

Some third-line agents (such as propofol) are also used to induce sedation to facilitate a subject’s ability to tolerate the ventilator. For subjects requiring such sedation, propofol is the preferred agent unless there are contraindications. The eCRF will make clear from the indication for the third-line agent when it is being used for burst or seizure suppression and when it is being used as ventilator support or for another purpose. The investigator will add a note to the eCRF to justify that the doses used are appropriate for sedation and not for seizure or burst suppression. The doses used for ventilator support and other similar uses are usually much lower than those used for seizure or burst suppression, and use of these third-line agents for these other purposes does not constitute a wean failure under this protocol.

#### **10.5.3. Concomitant Pressors**

The start and stop dates and times of all pressors will be recorded as well as the start and stop dates and times of all dose changes.

#### **10.5.4. Other Concomitant Medications**

All other concomitant medications must be recorded on the eCRF with details including date and time of starting and stopping, the route of administration, dose, and frequency of administration.

## **11. STUDY ASSESSMENTS**

### **11.1. Efficacy Assessments**

#### **11.1.1. Primary Efficacy**

Success or failure will be determined, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo infusion and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the blinded (first) infusion of SAGE-547 or placebo. In addition, subjects must have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) to be deemed to be successes. All subjects who fail to complete their infusion of randomized treatment or do not have at least one attempt during study treatment to wean off all third-line agents will be considered as “failures” for the primary endpoint.

##### **11.1.1.1. Weaning**

Third-line agents are anesthetic agents that are administered in order to reach a seizure or burst suppression EEG pattern. For the purposes of this study, third-line agents are defined as continuous intravenous infusions of pentobarbital/thiopental, midazolam, propofol, and ketamine at maintenance doses alone or in combination sufficient to produce a burst suppression pattern on the EEG. The following are considered to be minimum maintenance doses of these agents that may be expected alone or in combination to achieve EEG burst suppression. If subjects are on lower doses than these and are not in EEG burst suppression for the 24 hours prior to the QW or the first 12 hours of the blinded study drug infusion, they will be considered to be screen failures/protocol violators and will exit the study.

- Pentobarbital: 1 mg/kg/hour
- Thiopental: 3 mg/kg/hour
- Midazolam: 0.1 mg/kg/hour
- Propofol: 3 mg/kg/hour
- Ketamine 1.2 mg/kg/hour

The timing and nature of the third-line agent weans will be guided by the Clinical Standardization Guidelines for the study, and the clinical judgment of the investigator, and will always be primarily done in the best medical interests of the subject. Advice about weaning may be sought from the Clinical Standardization Team, a group of fellow investigators with experience of performing clinical trials in subjects with SRSE. The Clinical Standardization Team will be able to discuss EEGs related to key study timepoints (qualifying wean, terminal wean, and the period after the end of the blinded study drug infusion if the terminal wean was successful) in a timely manner in order to provide advice about compliance with the Clinical Standardization Guidelines.

The following guidance for weaning applies to all weans of third-line agents undertaken during the study. These weans include the qualifying wean (QW); the terminal wean (TW), which is the wean of the third-line agent if the subject is on only one third-line agent or the wean of the last third-line agent if the subject is on more than one third-line agent; the other weans (OW), which are the weans of the third-line agents other than the TW if the subject is on more than one third-line agent. The guidance also applies to additional weans (AW), which are the weans from third line agents that take

place after the TW for the first blinded study drug infusion or the second open-label study drug infusion.

### **QW Guidance**

- Wean to be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace that third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Investigators should allow 24 hours to lapse after the end of a “successful” qualifying wean before finally declaring the QW a success. If a third-line agent needs to be re-instituted within that 24 hours, the QW is a failure, and the subject may then be randomized in the study.

### **OW Guidance**

- First OW should not begin before H49 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- If the subject is on two third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the TW. However the OW may be completed over a shorter or longer time period and may overlap if clinically indicated with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- If the subject is on three third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the wean of the second agent. The second agent should be weaned over 24 hours and that wean completed before starting the TW. However the OWs may be completed over a shorter or longer time period and may overlap if clinically indicated with each other and with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- All OWs should be completed before H96 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **TW Guidance**

- The TW is defined as the wean of the last third-line agent.
- If the subject is on one third-line agent, the TW should not begin before H49 and should begin no later than H97 after starting administration of study drug or starting the open-label infusion of SAGE-547. If the subject has had one or more OWs, the TW should ideally begin

as soon as the last OW is complete but in any case not later than H97 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

- The TW must be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace this third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Every effort must be made to complete the TW before H120 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547, but the TW must be complete before H144 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **AW Guidance**

- AWs will take place when medically indicated in the opinion of the investigator.
- Ideally the AW should take place over 24 hours, but completion may be over a shorter or longer time period than this. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.

#### **11.1.1.2. EEG**

Electroencephalographs (EEGs) that are representative of the intermittent or continuous EEG being used to support key investigator decisions will be collected at the following time points:

- A 24-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst suppression for the second path to eligibility, and a variable pattern for the third path to eligibility. This EEG will capture as much as possible of the burst suppression pattern that precedes the QW.
- EEG will be performed to cover the qualifying wean (QWEEG). EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for up to 24 hours after the end of the QW. The duration of the QWEEG will be up to 48.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s), the decision to re-institute a third-line agent(s) at doses intended to induce burst suppression, and the decision that the QW is a success.
- EEG will be performed from three hours prior to the start of the blinded infusion to 12 hours after the start of the blinded infusion. This will be called the BIEEG. The intent of this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG and to assess the depth of burst suppression in the first 12 hours of blinded study drug infusion.

- EEG will be performed to cover the final or terminal wean of third-line agent (TWEEG). The TW is the wean of the final third-line agent during the blinded administration of study drug or the open-label infusion of SAGE-547; if the subject was on one third-line agent, the TW is the wean of that agent. If the subject was on three third-line agents, the TW is the wean of the third and final agent. EEG recording will start 30 minutes prior to the start of the TW, continue for up to 24 hours during the TW, and then continue for the one hour after the end of the TW. The duration of the TWEEG will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the final third-line agent or the decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity could not be managed using intermittent bolus doses of AEDs.
- EEG will be performed during the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 (TAEED). The TAEED is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the start of the taper (at Hour 119.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours during the taper, and then continue for the one hour after the end of the taper (to Hour 145 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547). The duration of the TAEED will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity seen during the taper could not be managed using intermittent bolus doses of AEDs.
- EEG will be obtained to cover the end of the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 and the ensuing 24-hour period, during which the primary endpoint is assessed (PAEED). The PAEED is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the end of taper (at Hour 143.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours after the end of the blinded administration of study treatment or the open-label infusion of SAGE-547, and then continue for the one hour after the end of the 24-hour assessment period (to Hour 169 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547). The duration of the PAEED will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity seen in the 24 hours following the end of the blinded administration of study treatment or the open-label infusion of SAGE-547 that could not be managed using intermittent bolus doses of AEDs.

In practice, most subjects are on continuous EEG monitoring or long periods of intermittent EEG monitoring. However, this protocol does not mandate continuous EEG monitoring and breaks from EEG monitoring to provide relief to the scalp from the irritating effects of the electrodes are advised according to local practice. If a break in EEG monitoring is mandated by local practice guidelines at a time when one of the protocolled EEG segments is to be collected, the break in EEG monitoring will take precedence, with the reason for missing the EEG reading noted on the eCRF. The EEGs obtained for the study are therefore part of the existing EEG record rather than being obtained de-novo at each timepoint. For timepoints where there might be some ambiguity, such as the TWEEG,

the final EEG record is that of the final attempt to wean the last third-line agent, even if earlier attempts to wean that agent took place. In some cases (the TAEED and PAEEG, for instance), the EEG records will overlap, but different cuts are taken to service the different EEG record requirements.

The electronic EEG file will be de-identified, the date and time of the start and stop of the EEG and the subject number will be attached to the file, and the study time point will be indicated (CEEG, QWEEG, BIEEG, TWEEG, TAEED, and PAEEG). The PI will indicate on the eCRF what the EEG shows, as follows:

- For the CEEG, the PI will describe the EEG pattern that determined which path to eligibility the subject was on.
- For the QWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure or success on the qualifying wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the qualifying wean constitutes a failure); the QWEEG will extend to cover the 24 hours after the end of third line agents in order to confirm that the QW was a success.
- For the BIEEG, the PI will note the date and time of the start of the EEG and the pattern seen on the EEG.
- For the TWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure on the terminal wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the terminal wean).
- For the TAEED, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst suppression before the end of the SAGE-547 infusion).
- For the PAEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst suppression in the 24 hours following the end of the SAGE-547 infusion).

A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm the depth of burst suppression prior to the QW and during the first 12 hours of the blinded study drug infusion, the PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period (average EEG power at the end of Visit 9 of more than two microvolts):

- All subjects will have the CEEG and QWEEG collected and stored, and the CEEG and QWEEG read;
- Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;

- Those subjects randomized who are not retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the BIEEG, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read;
- Those subjects randomized who are retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion and the TWEEG, TAEED, and PAEEG related to the open-label study drug infusion collected and stored, and the BIEEG, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read.

All EEG records may be subject to quantitative EEG analysis.

### **11.1.2. Secondary Efficacy**

#### **11.1.2.1. Clinical Global Impression Scale (CGI)**

The clinical global impression scales are often utilized in clinical trials to allow clinicians to integrate several sources of information into a single rating of the subject's condition. Both the CGI-Severity (Question 1, CGI-S) and the CGI-Improvement (Question 2, CGI-I) employ a 7-point Likert scale measuring severity of the disease state in the subject and improvement, respectively. All severity assessments after initiation of SAGE-547 treatment should consider the general state of the subject over the preceding week. The third question on the scale will not be employed in this trial, and where the scale states "mental illness", this means "physical illness" in this trial.

The CGI-S will be evaluated at Visit 1 and at the last visit, Visit 12 or 12R. The CGI-I will be evaluated at Visit 12 or 12R.

#### **11.1.2.2. Epilepsy Status**

At Visit 1, the diagnosis of epilepsy will be documented as a no/yes question. If there was a previous diagnosis of epilepsy, further details will be documented, including:

- Date of diagnosis;
- Details of anti-epileptic drugs currently being taken;
- Type of epilepsy;
- Seizure frequency in the past month.

Information about the current (index) episode of status epilepticus will be obtained at Visit 1:

- Date of onset
- Date of failure to respond to first line agent(s) and the name(s) of the agent(s)
- Date of failure to respond to second line agent(s) and the name(s) of the agent(s)
- Any previous treatment with third line agents and the response to those agents (details of the third line agent drugs and previous wean attempts will be recorded on the Third Line Agent Medication CRF)
- The cause of the index episode of status epilepticus
- If the subject was transferred from another hospital or from within the hospital, the reason for the transfer will be recorded (such as for study enrollment, due to lack of medical options)



at original hospital or unit, due to lack of beds at the original hospital or unit, family request, other)

Previous (non-index) diagnosis of status epilepticus will be documented as a no/yes question. If SE did occur in the past, further information will be gathered, including:

- SE, RSE, or SRSE diagnosis, whichever was the most severe diagnosis for each episode;
- Cause;
- Treatment, including experimental treatments and need for intubation/ventilation;
- Dates of onset and duration if the episode of status epilepticus occurred in the past 12 months.

At Visit 12 or Visit 12R, the following information will be gathered:

- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of SE up to and including Visit 12 or Visit 12R;
- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of seizures (convulsive and non-convulsive) up to and including Visit 12 or Visit 12R;
- Number of separate episodes of SE after H144 at the end of Visit 8 or Visit 8R (no/yes); if yes,
  - SE, RSE, or SRSE diagnosis;
  - Cause;
  - Treatment, including experimental treatments and need for intubation/ventilation;
  - Dates of onset and duration.

Note that a separate episode of SE is defined as an episode of SE separated from other periods of status epilepticus by at least 24 hours.

- Diagnosis of epilepsy since Visit 11 or Visit 11R will be documented as a no/yes question. If a diagnosis of epilepsy has been made, further details will be documented, including:
  - Status as ongoing or new epilepsy since Visit 11 or Visit 11R after initiation of SAGE-547 treatment;
  - Details of anti-epileptic drugs currently being taken;
  - Type of epilepsy and seizure frequency in the past week.

## **11.2. Safety Assessments**

The safety and tolerability of SAGE-547 will be assessed using adverse events, clinical laboratory measures, vital signs, ECG intervals and morphology, and mortality. All safety assessments should be performed per hospital standard of care and will be collected periodically throughout the study according to [Table 1](#), [Table 2](#), and [Table 3](#) (Schedules of Assessments).

### **11.2.1. Adverse Events**

AEs will be collected after informed consent has been signed and prior to study-specific screening procedures not considered standard of care, during subject preparation for SAGE-547

administration and through Visit 12 or Visit 12R. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™) coding system (current version). See [Section 14](#) for additional details.

### **11.2.2. Clinical Laboratory Tests**

Blood samples will be taken for hematology, and serum chemistry and GFR will be calculated at:

- Visit 1 and then at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.
- Blood samples will be taken at Visit 11 or Visit 11R for serum chemistry (renal panel only).

Urine samples (20 ml) will be taken for urinalysis and urine NAG analysis at:

- Visit 1 and at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.

These samples will be analyzed at a central laboratory; hour-to-hour medical decisions will be based on sampling for laboratory testing done outside the protocol as part of normal standard of care. GFR will be calculated by the central laboratory.

Any out-of-range values will be flagged by the laboratory; the investigator will add a comment about whether the abnormality is clinically significant. Clinical significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

#### **11.2.2.1. Hematology and Serum Chemistry**

Hematology will include complete blood count (CBC) white blood cell count with differential, platelet count and red blood cell (RBC) count, hemoglobin and hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose. In addition triglycerides will be measured in serum chemistry samples (to aid assessment of lipemia in pharmacokinetic samples).

#### **11.2.2.2. Pregnancy Test**

Females of child-bearing potential will be tested for pregnancy by serum pregnancy test at Visit 1. In this study, since an accurate history of menstruation in girls and menopause in older women may not be available at Visit 1, “child-bearing potential” is taken to mean any female aged 18 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy. Female subjects with a positive pregnancy test will be ineligible for study participation.

#### **11.2.2.3. Urinalysis**

Urinalysis will include assessment of protein, blood, leukocytes, glucose, ketones, urobilinogen, pH, and specific gravity.

**11.2.3. Vital Signs**

Blood pressure, heart rate, and temperature will be recorded at the following time points relative to the first infusion of study drug, and to the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547:

- Visit 1;
- At 0, +30, +60 minutes (+/-15 minutes) and +2, +4 and +8 hours (+/- 30 minutes) after the start of the infusion;
- At +24, +48, +72, +96, +120, +144, +168, and +192 hours (+/- 2 hours) after the start of the infusion.

**11.2.4. Weight and Height**

Weight and height will be measured at Visit 1 and weight will also be measured once during each 24 hour period of the first infusion of study drug, and of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547. These daily weights will be used to modify the dose of SAGE-547 if required. If it is not possible to weigh the subject daily, an actual weight must be obtained prior to starting the blinded study drug, and that weight used to calculate the dose of study drug to be administered. If this is not possible, permission from the Monitor must be obtained to use another method to obtain the subject's weight (such as information from the LAR or estimating using an established local protocol).

**11.2.5. ECG**

12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours; at other times the allowed time window for ECGs is +/- 2 hours:

- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +128, +136, +144, +152, +160, and +192 hours after the start of the blinded (first) study drug infusion
- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +126, +132, +138, +144, +152, +160, and +192 hours after the start of the open-label (second) study drug

The heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm.

**11.2.6. Mortality**

Mortality will be recorded on the Visit 12 or Visit 12R case report form. If the subject has died, the following information will be collected:

- Date of death;
- Cause of death.

As accurate as possible cause of death will be collected, which will be further categorized as due to one of the following causes:

- SE;
- complications of long term intubation and third-line agent infusions;

- underlying cause of qualifying SE;
- co-morbidity existing at the time of the qualifying SE;
- new co-morbidity or trauma;
- study drug;
- other (specify).

### 11.2.7. Pharmacogenetic Samples

If a subject's LAR consents to pharmacogenetic sampling, a blood sample for genetic research will be collected at Visit 1 in order to avoid the possible introduction of bias through the exclusion of patients who may withdraw from study due to an AE (a subject population that may be of specific interest for subsequent genetic analysis). If for any reason a sample cannot be taken prior to treatment, a sample can be drawn at any point prior to completion with the restriction that no more than one genetic sample be taken per subject.

The objective of this research is to collect and store blood samples for possible DNA extraction and exploratory research into how genes or specific genetic variation may influence response (i.e. distribution, safety, tolerability, and efficacy) to SAGE-547. Specific genetic variations of interest include but are not limited to: classes of metabolizing enzymes (e.g. Cytochrome P450 supra-family genes), genes encoding enzymes involved in the production and metabolism of allopregnanolone (e.g. AKR1C4 (3 $\alpha$ -hydroxysteroid dehydrogenase)), genes associated with the GABA receptor (e.g. GABRA1-A6, GABRB1-B3, GABRD, GABRE, GABRG1-3) and genes associated with the production and degradation of GABA.

Future research may suggest other genes or gene categories as candidates for influencing not only response to SAGE-547 but also susceptibility to disorders for which SAGE-547 is being evaluated. Thus, the genetic research may involve study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.

#### 11.2.7.1. Biological Sampling and Coding Procedures (Pharmacogenetics)

To ensure patient confidentiality, utmost care will be taken in the coding and storage of pharmacogenetic samples.

*Extraction and coding:* DNA will be extracted from the blood sample and the DNA sample will be assigned a unique number replacing information from sampling tube. The assigned DNA number will be used to identify the sample and its corresponding information within Sage Therapeutics or at any designated contract laboratory for the purpose of sequencing of other DNA specific analysis. No personal details sufficient for individual identification will be available to any person (internal or external to Sage Therapeutics) working with the DNA.

*Genotype/Phenotype Analysis:* Samples and data from genetic analysis will be coded. The link between subject enrollment / randomization code and DNA number will be maintained and stored in a secure environment with restricted access. The established link will be used to identify relevant DNA samples for analysis, facilitated correlation of genotype results with clinical data, allow regulatory audit, and to trace samples for destruction in case of withdrawal of consent.

### 11.2.7.2. Retention of Biological Samples for Pharmacogenetic Analysis

Extracted DNA is a finite research that is destroyed in the process of being analyzed. Primary blood samples from which DNA can be extracted will be stored and used until no further analyses are possible, a maximum storage period of 25 years from time of last subject last visit has been reached, or an individual or LAR withdraws his/her or their consent.

### 11.2.8. Other Outcomes

#### 11.2.8.1. Pharmacokinetic Data

Formal plasma analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS)). In addition, all samples will be analyzed for important SAGE-547 metabolites (if and when these are identified) and Captisol® concentrations.

#### Plasma Analysis

Plasma will be collected to assay for SAGE-547 concentrations at the following time points relative to the start of each infusion of study drug:

- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion.
- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open label SAGE-547 study drug infusion.
- All samples will also be analyzed for plasma concentrations of important metabolites of SAGE-547 if and when these are identified.
- All samples will also be analyzed for plasma concentrations of Captisol®.

The plasma samples will be drawn from the arm contralateral to that used for drug administration. Drawing samples from peripheral arterial or venous lines or from a central line is permissible. PK collection times should be adhered to as strictly as possible. The allowed time window for all samples is: pre-dose in the two hours prior to starting the infusion of study drug; samples up to and including 1h, +/- 5 minutes; subsequent samples, +/- 15 minutes. Subject-specific PK kits for sampling including instructions on collection and processing methods, and storage and shipping conditions, will be provided separately. To maintain the blind, all subjects will have samples taken as outlined above: subjects receiving SAGE-547 will have all samples analyzed for all analytes. Subjects on placebo may have samples analyzed to investigate endogenous allopregnanolone and metabolite concentrations, as well as Captisol® concentrations; experience with the plasma concentration data will determine if and which placebo samples are analyzed.

Each blood sample will be 3 ml in volume for subjects weighing 30 kg or more, and 1 ml in volume for subjects weighing less than 30 kg. Separate aliquots will be obtained from each sample to service

the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum blood draw for PK analysis for a subject having two infusions of study drug will be 99 ml (33 ml for subjects weighing less than 30 kg).

Plasma PK parameters for SAGE-547 will be calculated where appropriate (e.g.,  $C_{max}$ ,  $C_{min}$ ,  $t_{max}$ ,  $AUC_{last}$ ,  $AUC_{\infty}$ ,  $CL_s$ ). In addition, similar PK parameters will be calculated for Captisol®. PK parameters for important metabolites of SAGE-547 may be calculated. An evaluation will be made of the feasibility of adopting a population-PK approach to assess drug-drug-interactions with SAGE-547 as victim of AEDs.

In addition, the Visit 9 sample may be analyzed for plasma concentrations of third-line agents.

#### Other Analysis

If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations. The minimum volume of cerebrospinal fluid for analysis is 100 microlitres.

Full details of all pharmacokinetic analyses will be described in the Pharmacokinetic Analysis Plan.

#### **11.2.8.2. Correlation of QT/QTc Changes and Plasma Concentrations of SAGE-547**

An analysis will be performed to determine whether there is any correlation between changes in QT/QTc interval and plasma concentrations of SAGE-547, in order to investigate any effect that SAGE-547 may have on QT/QTc interval.

#### **11.2.8.3. Pharmacoeconomic Data**

At Visit 12 or Visit 12R, the following information will be collected: number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital. If the subject dies before Visit 12 or Visit 12R, data will be collected up to the date of death. The definition of “hospital” is the institution that the subject was initially treated in. If the subject is transferred to another hospital, that hospital would be the “discharge destination from the hospital” and the “number of days in hospital” would be the number of days in the initial treating hospital.

For those subjects discharged from hospital before Visit 12/12R, the following questions will be asked:

- On what study day was the subject discharged from hospital?
- What type of facility was the subject discharged to (another hospital, a rehabilitation center, a supported care facility, home, other)?
- How many days did the subject stay in this facility?

The following questions will be answered regarding the stay in the ICU and hospital:

- Was the subject still in the ICU at the end of Visit 10/10R?
- If the FOUR Score was  $\geq 12$  at Visit 10/10R and the subject was in the ICU at Visit 10/10R, what was the reason for the subject not being discharged from the ICU (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, other)?
- Was the subject still an in-patient in the hospital at the end of Visit 12/12R?

- If the FOUR Score was  $\geq 15$  at Visit 12/12R and the subject was in the hospital at Visit 12/12R, what was the reason for the subject not being discharged from the hospital (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, unsuitable home circumstances, other)?

#### **11.2.8.4. STESS**

The STESS will be assessed during Visit 1 in order to assess the severity of the status epilepticus.

#### **11.2.8.5. FOUR Score**

The Full Outline of UnResponsiveness or FOUR Score is designed to assess conscious level and unlike other scores, is suitable for subjects who are intubated. It assesses four domains of neurological function (eye responses, motor responses, brainstem reflexes, and breathing pattern).

The FOUR Score will be collected at the following time points relative to each infusion of study drug (the initial blinded infusion and the second open-label infusion if this is administered):

- baseline, +24, +48, +72, +96, +120, +144, +168, and +192 hours (all +/- 2 hours) after the start of the infusion, and at Visit 11/11R and Visit 12/12R.

#### **11.2.8.6. Glasgow Outcome Scale (GOS)**

The GOS is a relatively common assessment scale used to standardize descriptions of the objective degree of recovery from brain injury such as cerebral trauma, or in this case SRSE. It was first used in 1975 ([Jennett and Bond 1975](#)) and allows a prediction of the long-term course of rehabilitation to return to work and everyday life. The scale classifies subjects into 5 groups:

- Death
- Persistent vegetative state
- Severe disability
- Moderate disability
- Good recovery

The GOS will be assessed at Visit 12 or Visit 12R.

#### **11.2.8.7. Supervision Rating Scale (SRS)**

The Supervision Rating (SRS) measures the level of supervision that a patient/subject receives from caregivers. The SRS rates level of supervision on a 13-point ordinal scale that can optionally be grouped into five ranked categories (Independent, Overnight Supervision, Part-Time Supervision, Full-Time Indirect Supervision, and Full-Time Direct Supervision). The SRS was designed to be rated by a clinician based on interviews with the subject and an informant who has observed at first hand the level of supervision received by the subject ([Boake 2000](#)). Scoring is a one-step procedure in which the clinician assigns the rating that is closest to the subject's level. Ratings are based on the level of supervision received, not on how much supervision a subject is judged or predicted to need.

The SRS will be assessed at Visit 1 and Visit 12 or Visit 12R. The Visit 1 assessment will be a retrospective assessment of the supervision required by the subject immediately prior to the admission that included the index episode of status epilepticus.

**11.2.8.8. Modified Rankin Scale – 9Q (mRS-9Q)**

The Modified Rankin Scale (mRS) is a commonly used scale to determine disability and functional dependence due to neurological insult such as stroke in adults. The 7-point scale (0 – 6) denotes functional capacity from no symptoms (0) to severe disability (5) and death (6). The Modified Rankin Scale – 9Q is a shortened version consisting of 9 questions that reliably determines the mRS score and was developed to both simplify the assessment and expand the rater base to non- medically trained personnel ([Patel, Rao et al. 2012](#)). The assessment is a web-based tool in the public domain with automatic score calculation and error checking found at [www.modifiedrankin.com](http://www.modifiedrankin.com).

The mRS will be assessed at Visit 1 and at Visit 12 or Visit 12R. The baseline assessment will be a retrospective assessment of the disability and dependence of the subject immediately prior to the admission that included the index episode of status epilepticus.



## 12. STUDY PROCEDURES

The study procedures listed below by study day reflect the required data collection times for this protocol. When a time window is necessary, this is specified below. If no time window is specified, the test may be performed at any time within the specified 24-hour period.

### 12.1. Visit 1 (V2-≤30h)

The baseline period will be up to approximately 84 hours prior to starting blinded study treatment and should include the assessments/procedures listed below and summarized in [Table 1 and Table 2 \(for retreatment\)](#), the Schedules of Events.

- Informed consent
- Eligibility checklist
- Verification of inclusion/exclusion criteria.
- Demographic information and medical history obtained by proxy and confirmed by the subject when possible.
- SE and wean history
- Blood will be collected from female subjects 18 years to 55 years for a serum pregnancy test unless they are known to be pre-menstrual or post-menopausal or to have had a hysterectomy.
- Blood and urine samples collected for clinical laboratory testing.
- Pharmacogenetic sample will be collected from consenting/eligible subjects.
- Vital signs
- Height
- Weight
- An ECG reading taken.
- Administration of the STESS.
- Administration of the FOUR Score.
- Administration of SRS.
- Administration of the mRS-9Q assessment.
- Assessment of the CGI scale.
- Evaluation of epilepsy status.
- Administration of continuous IV third-line agents.
- Perform EEG.
- Recording of adverse events.
- Recording of previous and concomitant anti-epileptic drugs.
- Recording of previous and concomitant third-line agents.
- Recording of concomitant pressors.

- Recording of other concomitant medications, procedures, and treatments.

## **12.2. Visit 2 (V3-≤54h)**

- Recording of adverse events.
- Recording of concomitant anti-epileptic drugs.
- Recording of concomitant third-line agents.
- Recording of concomitant pressors.
- Recording of other concomitant medications, procedures, and treatments.
- Wean of continuous third-line agent:
  - If wean is successful, subject is followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (these subjects are Qualifying Wean Success subjects or QWS subjects);
  - If wean is not successful, there is ongoing intravenous administration of at least one continuous IV third-line agent and EEG is performed and the subject is randomized.

## **12.3. SAGE-547 Treatment Period**

### **12.3.1. Visit 3/3R (0-24 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs will be recorded at:
  - 0, +30, +60 minutes (+/-15 minutes) and +2, +4, +8 (+/- 30 minutes) and +24 hours (+/- 2 hours) after the start of the infusion
- ECG readings will be recorded immediately after PK sampling at:
  - 0 (pre-dose) and at +0.5, +1, +3, +6, +12, and +24 hours after the start of the blinded study drug infusion.
- A blood sample for PK analysis should be collected at the following time points (all +/- 15 minutes except where otherwise stated):
  - 0 (pre-dose, within two hours of the start of the infusion) and at +0.5, +1 (+/- 5 minutes), +3, +6, +12, and +24 hours after the start of the blinded study drug infusion.
- Completion of the FOUR Score
  - +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the end of the 24 hour observation period following the QW)
- Ongoing intravenous administration of a continuous IV third-line agent.

- Study drug administration in loading (Hour 0-1) and maintenance infusions (at completion of Hour 1).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.3.2. Visit 4/4R (25-48 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +48 hours (+/- 2 hours) after the start of the infusion
- An ECG reading taken immediately after PK sampling:
  - +48 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +48 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +48 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent.
- Ongoing study drug maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.3.3. Visit 5/5R (49-72 hours)**

- Weight
- Vital signs should be recorded at:
  - +72 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +72 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +72 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +72 hours (+/- 2 hours) after the start of the infusion

- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.4. Visit 6/6R (73-96 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +96 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +96 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +96 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +96 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Perform EEG.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.5. Visit 7/7R (97-120 hours)**

- Weight
- Vital signs should be recorded at:
  - +120 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +120 hours after the start of the study drug infusion

- A blood sample for PK analysis should be collected:
  - +120 hours (+/- 15 minutes) after the start of study drug infusion, immediately prior to the end of the maintenance infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +120 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled. Complete wean by 120 hours if at all possible.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## **12.4. SAGE-547 Taper Period**

### **12.4.1. Visit 8/8R (121-144 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +144 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after each PK sampling:
  - +128, +136 hours and +144 hours after the start of the study drug infusion
  - During the open-label retreatment phase of the study ECG readings at: +126, +132, +138 hours and +144 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected (+/- 15 minutes unless otherwise stated):
  - +128 (immediately prior to the end of the first taper step), +136 hours (+/- 5 minutes, immediately prior to the end of the second taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of study drug infusion.
  - During the open-label retreatment phase of the study PK blood draws at: +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 hours (+/- 5 minutes, immediately prior to the end of the third taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of the study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +144 hours (+/- 2 hours) after the start of the infusion

- Complete wean of third line agents by H144 if not completed by H120.
- Perform EEG.
- Taper of SAGE-547 infusion begins at hour 121.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## **12.5. Follow-up Period**

### **12.5.1. Visit 9/9R (145-168 hours)**

- Vital signs should be recorded at:
  - +168 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +152, +160 hours (+/- 2 hours) after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +152 and +160 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +168 hours (+/- 2 hours) after the start of the infusion
- Perform EEG.
- Assessment of the presence of physiologic brain activity using EEG.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.5.2. Visit 10/10R (169-192 hours)**

- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +192 hours (+/- 2 hours) after the start of the infusion
- At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine eligibility for retreatment with the higher dose of study drug. This determination may occur at any point

during Visit 10: the retreatment infusion must begin within the Visit 10 window. All patients for retreatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.

- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.3. Visit 11/11R (Visit 3/3R + 14d (±2))**

- Blood samples collected for clinical laboratory testing (renal panel only).
- Completion of the FOUR Score (QWS subjects also).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.4. Visit 12/12R (Visit 3/3R + 21d (±2))**

All assessments also performed for QWS subjects.

- Completion of the FOUR Score.
- Administration of the GOS.
- Administration of the SRS.
- Administration of the mRS-9Q assessment.
- Evaluation of epilepsy status (see [Section 11.1.2.2](#) for details).
- Assessment of the CGI Scale.
- Recording of adverse events.
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications.
- Collection of pharmacoeconomic data.
- Mortality will be assessed throughout the study period.

## **13. STATISTICS**

### **13.1. Statistical Plan**

Complete details for the analysis and reporting of data from this study will be contained in the Statistical Analysis Plan (SAP).

#### **13.1.1. Interim Analysis**

When approximately 50% of subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment

will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### 13.1.2. Study Populations

The **Safety Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to actual treatment. This analysis population will be used for all safety analyses.

The **Intent to Treat Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to randomized treatment. This analysis population will be used for all efficacy analyses.

The **Modified Intent to Treat Population** is defined as all subjects who:

1. complete their initial course of blinded SAGE-547 or placebo treatment unless the non-completion was due a drug-related adverse event; and
2. have at least one attempt to wean from third-line agents prior to the end of blinded study treatment infusion unless the failure to wean was because seizures were not controlled.

Subjects will be classified according to randomized treatment. This analysis population will be used for sensitivity analyses of the primary endpoint and select secondary efficacy endpoints.

Narratives will be prepared for all subjects who do not complete the infusion of blinded study medication or were not subjected to any wean attempts. Narratives will include details of the cause of SE, the comorbid conditions, the adverse event(s), and reasons for non-completion of the infusion or failure to attempt weaning. This blinded narrative will be reviewed by the medical monitors and the patient adjudicated as MITT eligible or ineligible. Acceptable reasons for defining a subject as MITT ineligible include death or withdrawal of consent due to progression of the underlying cause of SE or comorbid conditions, unless the cause of death or progression of disease were thought by the investigator, sponsor, or DSMB to be related to study drug.

The **Per-Protocol (PP) Population** is defined as a subset of the MITT population but will exclude data from all subjects with significant protocol violations or deviations. Subjects will be classified according to actual treatment received. This data set will be used for sensitivity analyses to examine the robustness of results for the primary and key secondary efficacy endpoints.

The **Pharmacokinetics Population** is defined as all subjects who at least had an infusion of blinded SAGE-547 initiated and have at least one pharmacokinetic sample collected.

The **Pharmacogenetic Population** is defined all subjects who consent to being included in the pharmacogenetic assessment and provide a pharmacogenetic sample.

Summary statistics of all data collected will be presented for subjects who were QW successes.

### 13.1.3. General Aspects

Tabular displays of descriptive statistics will be provided for all variables. Summary tables will include n, mean, mean, standard deviation, minimum and maximum for continuous variable and frequency and percentage for categorical variables.



### **13.1.4. Analysis of Primary Endpoint**

The analysis of response to treatment (see Section 11.1.1 for definition of primary endpoint) between SAGE-547 treated subjects and placebo treated subjects will be performed on the ITT population using a Cochran-Mantel-Haenszel (CMH) test with variables for treatment, concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). The CMH general association statistic and its associated p-value will be presented. The comparison of treatment response rates will be conducted at the 5% level of significance. To confirm the CMH results, a permutation test will also be conducted.

An additional analysis of the primary endpoint will also be performed on the MITT population. In addition sensitivity analyses of the primary endpoint will be performed using the ITT population based on:

- the number of third-line agents (one, two, or three) subjects were administered post-randomization; and
- which third line agent was the subject of the first TW.

### **13.1.5. Analysis of Secondary Efficacy Endpoints**

Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section (Section 6). Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. The analysis of the secondary endpoints will also be performed on the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

### **13.1.6. Analysis of Other Endpoints**

Safety and “Other” endpoints will only be summarized by treatment group.

Summaries of safety endpoints will be based on the overall Safety Population.

### **13.1.7. Epilepsy and SRSE Status**

Diagnosis of epilepsy and recurrence of RSE or SRSE will be documented as the percentage of subjects by time point and overall. Kaplan-Meier curves may be plotted if sufficient data are available.

Utilization of AEDs during follow-up and during recurrence will be summarized.

**13.1.8. Questionnaires**

The data collected from each questionnaire will be interpreted according to the standard methodology for that questionnaire. There will be no adjustment for missing values.

**13.1.9. Pharmacokinetic Data Analysis**

Details of the pharmacokinetic data analysis will be described in detail in a separate Pharmacokinetic Analysis Plan.

**13.1.10. Pharmacogenetic Data Analysis**

Any genotype data generated in this study will be stored within a secured database within Sage Therapeutics and / or a third party contracted to work with Sage Therapeutics to analyze the samples. Because the number of subjects agreeing to participate in the genetic research component of the study is unknown, it is not possible to establish, a priori, whether sufficient samples will be obtained to support formal statistical evaluation of data. As a consequence a Pharmacogenetic Analysis Plan will only be prepared where appropriate and the results obtained from any genetic research will be reported in a report separate from the main study CSR.

**13.1.11. Retreated Subjects**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are retreated with SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo.

**13.1.12. EEG-Responders**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who are classified as EEG-responders/non-responders based on the independent assessment of the PAEEG. Summaries will be derived for the two randomized treatment groups.

**13.1.13. QT/QTc Assessment**

An analysis of the correlation between changes in QT/QTc intervals and SAGE-547 plasma levels will be performed to investigate if there is a potential effect that SAGE-547 may have on QT/QTc interval. A detailed description of the QT/QTc assessment will be included in the SAP.

**13.1.14. Quantitative EEG**

The six EEG records for each subject may be subjected to exploratory quantitative EEG analysis, the details of which will be included in the EEG Analysis Plan. In summary the following comparisons may be made, SAGE-547 versus placebo: the QWEEG versus the TWEEG (main analysis); the CEEG versus PAEEG (subsidiary analysis); and TAEEG versus PAEEG (exploratory analysis).

**13.2. Determination of Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between treatment groups at a 5% level of significance. Randomization will be stratified by concomitant

pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

### **13.3. Statistical Analysis Plan**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

## **14. ADVERSE EVENTS**

The safety procedures in this study will be detailed in a Safety Management Plan, which will be agreed and signed before the first subject is randomized in the study. [Section 14.1](#) summarizes Investigator responsibilities regarding the identification and documentation of AEs, the classification of AEs for relationship to study drug and severity, and the reporting of AE information to the Sponsor and the IRB.

[Section 14.2](#) summarizes Sponsor/Medical Monitor Responsibilities regarding monitoring of AE data and reporting relevant safety information to FDA.

[Section 14.3](#) lists important AE definitions.

### **14.1. Investigator Responsibilities**

#### **14.1.1. Identification and Documentation of Adverse Events by Investigator**

Subjects will be evaluated and questioned generally (if possible) to identify AEs during the course of the study. AEs will be collected from the signature of the consent form through Visit 12/12R. Adverse events that occur prior to completion of screening will be captured on the Medical History eCRF. Adverse events that occur after completion of screening will be recorded on the Adverse Event eCRF.

All AEs revealed by observation, other diagnostic procedures, or spontaneously reported by the subject and/or in response to an open question from study personnel will be recorded on the Adverse Event Form. Any clinically significant deterioration in laboratory assessments or other clinical findings are considered an AE and must be recorded on the Adverse Event Form, unless otherwise stated. AE information recorded will be entered into the database on an ongoing basis.

AEs with a relationship considered related to study drug (probable, possible) should be followed until the event is resolved or the Investigator determines the event is stable or no longer clinically significant. AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

For SAEs, an electronic Serious Adverse Event eCRF must be completed with as much information as possible and submitted in the time frame described below in [Section 14.1.3](#). When new significant information is obtained as well as when the outcome of an event is known, the electronic SAE eCRF should be updated within 24 hours. If the subject was an outpatient at the time of the SAE and was re-hospitalized due to the SAE, a copy of relevant hospital records (e.g., admission report, laboratory test results, discharge summary, etc.) may be requested to be included as part of the subject medical file.

All SAEs will be followed until resolved or until a stable status has been achieved.

**14.1.2. Adverse Event Classification****14.1.2.1. Relationship to Investigational Drug**

None:	No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state.
Possible:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject, but this is not known for sure.
Probable:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

**14.1.2.2. Severity**

Mild	Discomfort noticed, but no disruption to daily activity.  For subjects that are unconscious, this may be a slight or minor change in a lab result or clinical sign or symptom that does not require immediate corrective action.
Moderate	Discomfort sufficient to reduce or affect normal daily activity, but is not hazardous to health; prescription drug therapy may be employed to treat the AE.  For subjects that are unconscious, this may be a clinically meaningful change that may require immediate corrective action.
Severe	Inability to work or perform normal daily activity and represented a definite hazard to health; prescription drug therapy and/or hospitalization may be employed to treat the AE.  For unconscious subjects, this may be a significant clinical change that requires immediate corrective action.

**14.1.2.3. Action Taken with Investigational Drug**

None	Study medication was continued without change.
Discontinued	Study medication was terminated.
Dose adjusted	Study medication dose/infusion rate was changed and then continued per protocol.
Interrupted	Study medication was interrupted and then continued per protocol.
Unknown	The action taken with regard to study medication is unknown.
Not applicable	Administration of study medication was not ongoing.

**14.1.2.4. Assessment of Outcome**

Ongoing	At the end of the study, the event has not resolved or stabilized.
Ongoing and stable	The event is ongoing but has stabilized and is unlikely to change
Resolved	The event has resolved or the subject recovered without sequelae.
Resolved with sequelae	The event has at least one secondary outcome that may result in permanent disability and/or functional limitation.
Unknown	The status of the event is unknown.
Death	The subject has expired.

**14.1.3. Investigator Reporting to Sponsor and Sponsor Emergency Contact**

All new SAEs that come to the Investigator and/or Sponsor's notice during the course of the study (up to and including the last study visit) must be reported by the Investigator on the designated electronic report form within 24 hours of the point in time when the Investigator becomes aware of the SAE. As additional information becomes available, the designated electronic report form must be updated within 24 hours.

Investigators must report any SAE, whether or not considered drug related. The report must include an assessment of whether there is a reasonable possibility that the drug caused the event.

In a medical emergency (ie, an event that requires immediate attention regarding the treatment of a subject, operation of the clinical study, and/or the use of investigational drug), study site staff will apply appropriate medical intervention according to current standards of care, and contact the Medical Monitor.

**14.1.4. Medical Monitor and Emergency Contact Information**

[REDACTED], MD  
[REDACTED]

**14.1.5. SAE Reporting Contact Information**

Contact information and reporting instructions are provided in the Safety Management Plan.

**14.1.6. Reporting to Institutional Review Boards (IRBs)**

It is the responsibility of the Investigator to promptly notify the institution's IRB of all serious and unexpected suspected adverse reactions (see [Section 14.3](#) for definitions).

## **14.2. Sponsor/Medical Monitor Responsibilities**

### **14.2.1. Monitoring of Adverse Event Data**

The Medical Monitor will review any newly reported adverse events in an ongoing basis. If the aggregate assessment indicates that an event is occurring more frequently than would normally be expected in this population, or as previously observed, and the sponsor believes that the events are causally related to the administration of SAGE-547, the Sponsor will then report that information in an IND safety report.

### **14.2.2. Data Safety Monitoring Board**

An independent DSMB will monitor the clinical, PK and PD data for safety signals throughout the study and will be asked to assess the placebo response rate at the time of the interim analysis to determine final sample size. In order to perform their monitoring function the DSMB will have access to un-blinded safety data as necessary.

The composition and procedures for the board will be described in a separate DSMB Charter.

### **14.2.3. Reporting to FDA**

The Sponsor must report in an IND safety report any suspected adverse reaction to study treatment that is both serious and unexpected (21 CFR 312.32(c)(1)(i)). Before submitting an IND safety report, the Sponsor will ensure the event meets all three of the definitions: (1) suspected adverse reaction, (2) serious, (3) unexpected. If the AE does not meet all three of the definitions, it should not be submitted as an IND safety report. The Sponsor should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the adverse event and, therefore, that the event meets the definition of a suspected adverse reaction.

If there is a serious and unexpected suspected adverse reaction, the Sponsor will notify the appropriate regulatory agency(ies) and all appropriate parties on an expedited basis. In addition, Sponsors must submit expedited reports of an increased rate of occurrence or severity of serious suspected adverse reactions over that listed in the protocol or Investigational Brochure.

SUSARs will be unblinded prior to reporting to FDA. Unless it is necessary to unblind for the safety of the patient, the investigator will not be informed of the unblinding of the subject.

Under 21 CFR 312.32, Sponsors should identify in the protocol SAEs that it does not plan to report individually in an expedited manner, because they are known consequences of the disease or otherwise common in the study population. Given the grave condition and prognosis of SRSE being studied, individual occurrences of seizures or seizure activity will not be reported expeditiously in this study. Regardless of which events are reported in an expedited manner, all adverse events will be closely monitored throughout the study.

## **14.3. Adverse Event Definitions**

### **14.3.1. Adverse Event**

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

### **14.3.2. Suspected Adverse Reaction**

Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

### **14.3.3. Life-Threatening**

An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

### **14.3.4. Serious**

An AE or suspected adverse reaction is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE – see definition above
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disability
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

### **14.3.5. Unexpected**

An AE or suspected adverse reaction is considered “unexpected”:

- If it is not listed in the Investigational Brochure or is not listed at the specificity or severity that has been observed, or
- If an Investigational Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigational Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigational Brochure listed only cerebral vascular accidents.

“Unexpected,” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigational Brochure as occurring with a class of drugs or as anticipated from



the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

#### **14.4. Emergency Identification of Study Medication**

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject's treatment in the study via the IVRS; this normally requires prior approval by the medical monitor. However, if the subject is at immediate risk and the Investigator believes that immediate knowledge of the study treatment will alter medical management, discussion with the medical monitor may take place after unblinding. The Investigator will not unblind the medical monitor during that discussion. The process of unblinding will ensure that only the investigator is unblinded; the medical monitor, study management team, and data management team will not be made aware of the treatment allocation of an individual subject. All cases of emergency unblinding will be fully documented in a way that does not unblind the medical monitor, study management team, and data management team.

### **15. STUDY ADMINISTRATIVE CONSIDERATIONS**

#### **15.1. Quality Control and Quality Assurance**

The Investigators and institutions will permit trial related monitoring, audits, IRB review, and regulatory inspections as requested by FDA, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed informed consent forms, etc.) in addition to case report forms.

Quality assurance and quality control systems with written standard operating procedures (SOPs) will be followed to ensure this trial will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The site's dedicated study monitor will arrange to visit the Investigator at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be identified and resolved. The study monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality assurance officers named by Sage Therapeutics or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements, made by the Sponsor with the Investigator/institution and any other parties involved with the clinical trial, will be in writing in a separate agreement.

## **15.2. Data Handling and Recordkeeping**

### **15.2.1. Data Handling**

Procedures for data handling (including electronic data) used in this protocol will be documented in a Data Management Plan.

### **15.2.2. Case Report Form Completion**

eCRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of demographics, study drug administration, study procedures, AEs, questionnaire completion, efficacy assessments and subject status, including survival.

The Investigator will maintain copies of the eCRFs at the study site. For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate eCRF.

### **15.2.3. Retention of Study Records**

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval and until there are no pending or contemplated marketing applications or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to an appropriate person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

## **15.3. Confidentiality**

To maintain subject privacy, all eCRFs, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available trial registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by Sage Therapeutics to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

#### **15.4. Publication Policy**

All information concerning SAGE-547 is considered confidential and shall remain the sole property of Sage Therapeutics. The Investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval from Sage Therapeutics. No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between Sage Therapeutics and the Investigator.

#### **15.5. Protocol Amendments**

Changes to the conduct of the study should be prepared as a protocol amendment by the Sponsor. Protocol amendments should receive written IRB/IEC approval prior to implementation at the investigative site, except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the trial (eg, change of monitor, telephone numbers). In this case, Sage Therapeutics will amend and implement the protocol change and subsequently notify the regulatory authorities and the Investigative sites who will notify the respective IRB, as appropriate.

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## APPENDIX 1. FOUR SCORE

### FOUR score

#### Full Outline of UnResponsiveness

##### Eye response

- E4: eyelids open or opened, tracking, or blinking to command
- E3: eyelids open but not tracking
- E2: eyelids closed but open to loud voice
- E1: eyelids closed but open to pain
- E0: eyelids remain closed with pain

##### Motor response

- M4: thumbs-up, fist or peace sign
- M3: localizing to pain
- M2: flexion response to pain
- M1: extension response to pain
- M0: no response to pain or generalized myoclonus status

##### Brainstem reflexes

- B4: pupil and corneal reflexes present
- B3: one pupil wide and fixed
- B2: pupil or corneal reflexes absent
- B1: pupil and corneal reflexes absent
- B0: absent pupil, corneal and cough reflex

##### Respiration pattern

- R4: not intubated, regular breathing pattern
- R3: not intubated, Cheyne-Stokes breathing pattern
- R2: not intubated, irregular breathing
- R1: breathes above ventilatory rate
- R0: breathes at ventilator rate or apnea

Reference ([Iyer, Hoel et al. 2009](#)).

**APPENDIX 2. GLASGOW OUTCOME SCALE (GOS)****GLASGOW  
OUTCOME  
SCALE**

Patient Name: \_\_\_\_\_  
 Rater Name: \_\_\_\_\_  
 Date: \_\_\_\_\_

*Note:* The scale presented here is based on the original article by Jennett and Bond. It has become common practice in clinical trial administration, however, to use a modified version that places the scores in reverse order (i.e., "good recovery" = 1, "moderate disability" =2, etc.).

Score	Description
1	DEATH
2	PERSISTENT VEGETATIVE STATE Patient exhibits no <i>obvious cortical</i> function.
3	SEVERE DISABILITY (Conscious but disabled). Patient depends upon others for daily support due to mental or physical disability or both.
4	MODERATE DISABILITY (Disabled but independent). Patient is independent as far as daily life is concerned. The disabilities found include varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes.
5	GOOD RECOVERY Resumption of normal activities even though there may be minor neurological or psychological deficits.

**TOTAL (1-5):** \_\_\_\_\_

Reference ([Jennett and Bond 1975](#)).

## APPENDIX 3. SUPERVISION RATING SCALE (SRS)

### SUPERVISION RATING SCALE (SRS)

**Instructions:** Circle the rating that is closest to the amount of supervision that the patient *actually receives*. "Supervision" means that someone is responsible for being with the patient.

<u>Rating</u>	<u>Description</u>
<u>Level 1: INDEPENDENT</u>	
1	The patient lives alone or independently. Other persons can live with the patient, but they cannot take responsibility for supervision (for example, a child or elderly person).
2	The patient is unsupervised overnight. The patient lives with one or more persons who <i>could</i> be responsible for supervision (for example, a spouse or roommate), but they are <i>all</i> sometimes absent overnight.
<u>Level 2: OVERNIGHT SUPERVISION</u>	
3	The patient is only supervised overnight. One or more supervising persons are always present overnight but they are <i>all</i> sometimes absent for the rest of the day.
<u>Level 3: PART-TIME SUPERVISION</u>	
4	The patient is supervised overnight and part-time during waking hours, but is allowed on independent outings. One or more supervising persons are always present overnight and are also present during part of waking hours every day. However, the patient is sometimes allowed to leave the residence without being accompanied by someone who is responsible for supervision.
5	The patient is supervised overnight and part-time during waking hours, but is unsupervised during working hours. Supervising persons are <i>all</i> sometimes absent for enough time for them to work full-time outside the home.
6	The patient is supervised overnight and during most waking hours. Supervising persons are <i>all</i> sometimes absent for periods longer than one hour, but less than the time needed to hold a full-time job away from home.
7	The patient is supervised overnight and during almost all waking hours. Supervising persons are <i>all</i> sometimes absent for periods shorter than one hour.
<u>Level 4: FULL-TIME INDIRECT SUPERVISION</u>	
8	The patient is under full-time indirect supervision. At least one supervising person is <i>always</i> present, but the supervising person does not check on the patient more than once every 30 minutes.
9	Same as #8 plus requires overnight safety precautions (for example, a deadbolt on outside door).
<u>Level 5: FULL-TIME DIRECT SUPERVISION</u>	
10	The patient is under full-time direct supervision. At least one supervising person is always present and the supervising person checks on the patient more than once every thirty minutes.
11	The patient lives in a setting in which the exits are physically controlled by others (for example, a locked ward).
12	Same as #11 plus a supervising person is designated to provide full-time line-of-sight supervision (for example, an escape watch or suicide watch).
13	The patient is in physical restraints.

3/12/93

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## APPENDIX 4. MODIFIED RANKIN SCALE – LEVEL OF FUNCTION SURVEY (mRS-9Q)

1. Do you have any symptoms that are bothering you? (For example, trouble with reading or writing, trouble speaking, problems with vision, numbness, weakness, balance trouble, or problems with swallowing?)	YES <input type="radio"/>	NO <input type="radio"/>
2. Are you able to do the same work as before?	YES <input type="radio"/>	NO <input type="radio"/>
3. Are you able to keep up with your hobbies?	YES <input type="radio"/>	NO <input type="radio"/>
4. Have you maintained your ties to friends and family?	YES <input type="radio"/>	NO <input type="radio"/>
5. Do you need help making a simple meal, doing household chores, or balancing a checkbook?	YES <input type="radio"/>	NO <input type="radio"/>
6. Do you need help with shopping or traveling close to home?	YES <input type="radio"/>	NO <input type="radio"/>
7. Do you need another person to help you walk?	YES <input type="radio"/>	NO <input type="radio"/>
8. Do you need help with eating, going to the toilet, or bathing?	YES <input type="radio"/>	NO <input type="radio"/>
9. Do you stay in bed most of the day and need constant nursing care?	YES <input type="radio"/>	NO <input type="radio"/>

## APPENDIX 5. CLINICAL GLOBAL IMPRESSION (CGI)

### Clinical Global Impression (CGI)

#### 1. Severity of illness

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- |                             |   |
|-----------------------------|---|
| 0 = Not assessed            | 4 = Moderately ill                        |
| 1 = Normal, not at all ill  | 5 = Markedly ill                          |
| 2 = Borderline mentally ill | 6 = Severely ill                          |
| 3 = Mildly ill              | 7 = Among the most extremely ill patients |

#### 2. Global improvement: Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.

Compared to his condition at admission to the project, how much has he changed?

- |                        |                     |
|------------------------|---------------------|
| 0 = Not assessed       | 4 = No change       |
| 1 = Very much improved | 5 = Minimally worse |
| 2 = Much improved      | 6 = Much worse      |
| 3 = Minimally improved | 7 = Very much worse |

#### 3. Efficacy index: Rate this item on the basis of drug effect only.

Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.

EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect		Side effects			
		None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
<b>Marked</b>	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
<b>Moderate</b>	Decided improvement. Partial remission of symptoms	05	06	07	08
<b>Minimal</b>	Slight improvement which doesn't alter status of care of patient	09	10	11	12
<b>Unchanged or worse</b>		13	14	15	16
Not assessed = 00					

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

**APPENDIX 6. STATUS EPILEPTICUS SEVERITY SCORE (STESS)**

Outcome Predictor	Feature	Score
Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type (prior to first treatment)	Simple-partial, complex-parial, absence, myoclonic (complicating idiopathic generalized epilepsy)	0
	Generalized-convulsive	1
	Nonconvulsive status epilepticus in coma	2
Age	< 65 years	0
	≥ 65 years	2
History of previous seizures	Yes	0
	No or unknown	1
Summed Total		

**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY  
TO EVALUATE THE EFFICACY AND SAFETY OF SAGE-547 INJECTION  
IN THE TREATMENT OF SUBJECTS WITH SUPER-REFRACTORY  
STATUS EPILEPTICUS**

**PROTOCOL NUMBER: 547-SSE-301**

**IND NUMBER: 117901**

**EudraCT Number: 2015-002142-31**

Product: SAGE-547 Injection (allopregnanolone)

Sponsor Contact: [REDACTED], MD

[REDACTED]  
Sage Therapeutics  
215 First Street  
Cambridge, MA 02142  
[REDACTED]

Medical Monitor: [REDACTED], MD

Date of Protocol: 09 March 2015  
Date of Amendment One 27 May 2015  
Date of Amendment Two 17 November 2015

**Confidentiality Statement**

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

**PROTOCOL NUMBER: 547-SSE-301**

Sponsor [REDACTED]:

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]:

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

CRO [REDACTED]:

[REDACTED]

## 1. SIGNATURE PAGE

Title of Protocol:

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus

Protocol No: 547-SSE-301

### Sponsor Approval

[Redacted Signature]

18 November 2015

[Redacted Name] MD  
[Redacted Title]

Date (dd/mmm/yyyy)

Sage Therapeutics

### Investigator Agreement

By signing this page I attest that I have read and understand the contents of Clinical Protocol 547-SSE-301 and any current amendments. I agree to adhere to the design, conduct, and reporting requirements of the study as stated in the clinical protocol and to my obligations to the Sponsor as described in the protocol and executed contracts between myself, my Institution, and the Sponsor. I also agree to adhere to any subsequent amendments to the clinical protocol.

Investigator's Signature: \_\_\_\_\_

Investigator's Name: \_\_\_\_\_

Institution: \_\_\_\_\_

Date: \_\_\_\_\_

## 2. SYNOPSIS

<b>Name of Sponsor:</b> Sage Therapeutics 215 First Street Cambridge, MA 02142		
<b>Protocol No.</b> 547-SSE-301	<b>Phase:</b> 3	
<b>Name of Investigational Product:</b> SAGE-547 Injection		
<b>Name of Active Ingredient:</b> Allopregnanolone		
<b>Title of the Protocol:</b> A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus		
<b>Dosing Regimen: SAGE-547 or Placebo Dosing Schedule</b>		
<b>Hour</b>	<b>Type and Duration of SAGE-547 Infusions</b>	<b>Dose</b>
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	90 µg/kg/h
H121 – H128	8 hour taper	65 µg/kg/h
H129 – H136	8 hour taper	45 µg/kg/h
H137 – H144	8 hour taper	25 µg/kg/h
<b>Dosing Regimen: SAGE-547 Open Label Dosing Schedule</b>		
<b>Hour</b>	<b>Type and Duration of SAGE-547 Infusion</b>	<b>Dose</b>
H1	One hour loading infusion	300 µg/kg/h
H2 –H120	119 hour maintenance infusion	150 µg/kg/h
H121 – H126	6 hour taper	125 µg/kg/h
H127 – H132	6 hour taper	95 µg/kg/h
H133 – H138	6 hour taper	65 µg/kg/h
H139 – H144	6 hour taper	35 µg/kg/h
<b>Study Sites</b> Up to 180 sites in the USA, Europe, and Canada.		

**Number of Subjects**

The study will randomize 140 subjects at up to 180 sites.

**Study Population**

Subjects will be aged two years or more, in SRSE<sup>1</sup> (as defined in the Inclusion Criteria [Section 8.1](#)), and being managed in an intensive care setting.

**Duration of Subject Involvement**

Individual subject participation will be up to 30 days.

**Study Design**

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

Patients will follow one of three paths to entry to the study. The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst suppression with a third-line agent. These subjects will be consented for the study after admission to the intensive care unit, but before any third-line agents are administered for burst suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their legally authorized representative (LAR). Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours. Once burst suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The second path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst suppression pattern on the EEG. These subjects may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

<sup>1</sup> In this study, the term Super-Refractory Status Epilepticus or SRSE is equivalent to “Refractory Status Epilepticus (RSE) that has failed standard treatment” and the two terms are used interchangeably.



The third path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These subjects may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 treatment or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within six hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo).

The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that subjects, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as both the ability to wean the subject off all third-line agents before the end of the infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication infusion, and concurrent signs of physiologic brain activity as determined by EEG. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#) and [Table 2](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo will all subsequently be eligible to be administered SAGE-547 at the higher dose.

### Visit Schedule

The visit schedule and an overview of events at each visit is provided in [Table 1](#), [Table 2](#) and [Table 3](#) Schedule of Assessments.

**Study Objectives*****Primary objective:***

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult and pediatric subjects with SRSE, and for the response to endure at least 24 hours after the end of the SAGE-547 or placebo infusion (primary response).

***Secondary objectives:***

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in the Clinical Global Impression scale (CGI) between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

***Safety objectives:***

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

***Other objectives:***

1. To evaluate the impact of retreatment with a higher dose SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;

3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;
6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS) (age  $\geq 17$  years).

## Endpoints

### *Primary endpoint:*

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### *Secondary endpoints:*

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### *Safety endpoints:*

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.

**Other endpoints:**

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who fail to respond to their randomized double blind treatment and are retreated with a higher dose of SAGE-547.
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS) (age  $\geq 17$  years).

**Inclusion Criteria**

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects two (2) years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst suppression pattern; or who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst suppression pattern.

**Exclusion Criteria**

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone or any excipients in SAGE-547.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy.

4. Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing underlying neurological disorder.
5. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis for whatever reason, but dialysis is not planned or non-continuous dialysis is planned (that would not adequately remove Captisol<sup>®</sup>);
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the opinion of the investigator, of less than 30 days;
  - e. a do not resuscitate (DNR) order.
6. Subjects who are being administered more than three third-line agents concomitantly or in whom the qualifying wean cannot be completed within 24 hours, or who are being administered a third-line agent for other indications such as management of raised intra-cranial pressure that would preclude weaning according to this protocol.
7. Subjects with a living will that does not allow heroic measures.
8. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
9. Subjects who have been enrolled in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not withdraw or complete and then re-enroll).

### **Pharmacogenetic Research**

In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **Statistical Analysis**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

### **Interim Analysis**

When approximately 50% of the subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

**Analysis of Primary Endpoint**

The analysis of response to treatment between SAGE-547 treated subjects and placebo treated subjects will be performed using a Cochran-Mantel-Haenszel test with variables for treatment, concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). In this analysis, a treatment responder is a subject who is successfully weaned off all third-line agents and blinded study medication prior to the end of study treatment infusion and remains off third-line agents for at least 24 hours following cessation of the blinded study medication, and who has concurrent signs of physiologic brain activity as determined by EEG. The analysis will be based on the ITT Population. The comparison of treatment response rates will be conducted at the 5% level of significance.

**Analysis of Secondary Efficacy Endpoints**

The primary analysis will be repeated for the MITT population. Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section. Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. Secondary analyses will be repeated for the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from Baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third-line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

Summaries of safety endpoints will be based on the overall Safety Population which is defined as all subjects who at least initiated the infusion with blinded study treatment.

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are retreated with SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo. Summary statistics will be presented for subjects who were QW successes.

**Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

**Table 1: Schedule of Assessments for Protocol 547-SSE-301: One Infusion of Study Drug (blinded)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical/SE/Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X		X	X	X	X	X	X				
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X		X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X		X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X		X	X		X		X		X		
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X			
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>o</sup>											X
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV 3rd-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>p</sup>				
EEG	X	X				X		X	X			
Randomization		X										
Study Drug Administration <sup>q</sup>			X	X	X	X	X	X				
TW Outcome & Retreat Decision										X <sup>r</sup>		
Physiologic Brain Activity									X			
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

**Table 2: Schedule of Assessments for Protocol 547-SSE-301: Two Infusions of Study Drug (one blinded, one open-label)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V3R
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	0-24h
Eligibility Checklist	X										S
Informed Consent <sup>a</sup>	X										E
Inclusion/Exclusion Criteria	X										E
Demography <sup>b</sup>	X										
Medical and SE and Wean History <sup>c</sup>	X										T
Height	X										A
Weight <sup>d</sup>	X		X	X	X	X	X	X			B
Serum Pregnancy Test <sup>e</sup>	X										L
Hematology <sup>f</sup>	X		X	X		X		X		X	E
Serum Chemistry and GFR <sup>g</sup>	X		X	X		X		X		X	
Urinalysis <sup>h</sup>	X		X	X		X		X		X	E
Pharmacogenetic sample	X										X
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X	T
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X	E
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X		N
STESS	X										I
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	O
Glasgow Outcome Score (GOS)											N
Supervision Rating Scale (SRS)	X <sup>o</sup>										
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>										
Epilepsy Status	X										N
Clinical Global Impression (CGI)	X										E
Continuous IV Third-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>p</sup>			X
EEG	X	X				X		X	X		T
Randomization		X									
Study Drug Administration <sup>q</sup>			X	X	X	X	X	X			
TW Outcome and Retreat Decision										X <sup>r</sup>	P
Physiologic Brain Activity									X		
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	A
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	G
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	E
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X	
Pharmacoeconomic Data											
Mortality											



Table 2 continued

	V3R	V4R	V5R	V6R	V7R	V8R	V9R	V10R	V11R	V12R
	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3R+14d (±2d)	V3R+21d (±2d)
Weight <sup>d</sup>	X	X	X	X	X	X				
Serum Pregnancy Test <sup>e</sup>										
Hematology <sup>f</sup>	X	X		X		X		X		
Serum Chemistry and GFR <sup>g</sup>	X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X	X		X		X		X		
Vital Signs <sup>i</sup>	X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>	X	X	X	X	X	X	X			
STESS										
FOUR Score <sup>m</sup>	X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)										X
Supervision Rating Scale (SRS)										X
Modified Rankin Score (mRS) <sup>n</sup>										X
Epilepsy Status										X
Clinical Global Impression Scale (CGI)										X
Continuous IV Third-Line Agent(s)	X	X	Wean	Wean	Wean	Wean <sup>p</sup>				
EEG			X			X	X			
Randomization										
Study Drug Administration <sup>q</sup>	X	X	X	X	X	X				
TW Success and Physiologic Brain Activity							X			
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data										X
Mortality										X

**Table 3: Schedule of Assessments for Protocol 547-SSE-301: Qualifying Wean Successes**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical and SE and Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X											
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X											
Serum Chemistry and GFR <sup>f</sup>	X											
Urinalysis <sup>h</sup>	X											
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X											
ECG <sup>j</sup>	X											
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>o</sup>											X
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV Third-Line Agent(s)	X	Wean										
EEG	X	X										
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

<sup>a</sup> Written informed consent by proxy (LAR) will be obtained prior to starting any study-related procedures not considered standard of care.

<sup>b</sup> Demographic information will be obtained by proxy and confirmed by the subject when possible.

<sup>c</sup> Medical history will be obtained by proxy and confirmed by the subject when possible. All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Dosing changes with the third-line agent(s) that constitute a wean attempt will be marked as such on the CRF, and the start/stop dates and times of all wean attempts prior to V3 will be recorded, as well as the outcome of the wean attempt.

- <sup>d</sup> Weight will be collected at Screening (V1) and once during each 24 hour period of the initial study drug infusion period (V3-V8) and second infusion period (V3R-V8R, if applicable). Daily weight will be used to determine the appropriate infusion rate of each dose.
- <sup>e</sup> Serum pregnancy test for females aged 10 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy.
- <sup>f</sup> Blood samples will be taken for hematology and serum chemistry and GFR calculation at V1, at 24, 48, 96, 144 and 192 hours ( $\pm$  2 hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will document whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.
- <sup>g</sup> Blood samples will be taken at V11 or V11R for serum chemistry (renal panel only).
- <sup>h</sup> Urine samples will be taken for urinalysis and NAG at V1, at 24, 48, 96, 144 and 192 hours ( $\pm$  2 hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will add a comment about whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.
- <sup>i</sup> Vital signs will be recorded at the following time points relative to the start of each infusion of study drug: Screening (V1), at 0, 30, 60 minutes ( $\pm$  15 minutes), at 2, 4, and 8 hours ( $\pm$  30 minutes), and at 24, 48, 72, 96, 120, 144, 168, and 192 hours ( $\pm$  2 hours).
- <sup>j</sup> ECG (12-lead) should be performed at Screening (V1) and at the following times relative to the start of study drug infusion. For the blinded (first) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 128, 136, 144, 152, 160, and 192 hours ( $\pm$  2 hours). For the open label SAGE-547 (second) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 126, 132, 138, 144, 152, 160, and 192 hours ( $\pm$  2 hours). Heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours.
- <sup>k</sup> Plasma will be collected to assay for study drug concentrations at the following time points relative to the start of each infusion of study drug: For the blinded (first) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion. For the open label SAGE-547 (second) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open label SAGE-547 study drug infusion. Pre-dose samples may be taken within two hours before starting the infusion of study drug; timepoints up to and including 1h will have a time window of  $\pm$  5 minutes; all other timepoints will have a window of  $\pm$  15 minutes.
- <sup>m</sup> FOUR Score assessments will be performed at Screening (V1), 24, 48, 72, 96, 120, 144, 168, and 192 hours (all  $\pm$  2 hours) relative to the start of each infusion of study drug, and at V11 or V11R, and at V12 or V12R.
- <sup>n</sup> Modified Rankin Score (mRS) applicable for subjects  $\geq$  17 years old only.
- <sup>o</sup> SRS at V1 will be a retrospective assessment of the supervision required by the subject immediately prior to admission that includes the index episode of the SE, and mRS at V1 will be a retrospective assessment of the disability and dependence of the subject immediately prior to admission that includes the index episode of the SE.
- <sup>p</sup> Target for complete wean of all continuous IV third-line agents by 144 hours at V8/V8R if not completed by 120 hours at V7/V7R.
- <sup>q</sup> Study drug infusion is intended for IV administration only with a dedicated peripheral IV line using Sage-approved IV administration bags and lines.
- <sup>r</sup> At V10 only a decision to re-treat at a higher dose of SAGE-547 will be made by the Investigator if the continuous IV third-line agent wean has failed or the third-line agent requires re-introduction during V9. Subjects who become eligible for re-treatment at a higher dose of SAGE-547 will discontinue the planned visit schedule at V10, then repeat V3 (V3R) and all applicable subsequent visits.
- <sup>s</sup> AEs will be collected from the time Informed Consent is obtained and prior to the start of study-specific screening procedures not considered standard of care. Collection of AEs will continue throughout the study from V1 through V12 or V12R.
- <sup>t</sup> Subjects may enter the study on AEDs and be administered AEDs during the study. All Concomitant AEDs must be recorded on the CRF with details including date and time of starting/stopping each AED, the route of administration, changes in doses, and frequency of administration. Details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the CRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.
- <sup>u</sup> All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Details will include the name of the drug, the start/stop dates and times, and, after consent, the doses with start/stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

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**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
AE	adverse event
AED	anti-epileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the time-concentration curve
AW	additional weans
BDZ	benzodiazepine
BIEEG	blinded infusion electroencephalogram
BUN	blood urea nitrogen
CBC	complete blood count
CEEG	consent electroencephalogram
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
C <sub>max</sub>	maximum plasma concentration
C <sub>min</sub>	minimum plasma concentration
CNS	central nervous system
CRF	case report form
CSR	clinical study report
CYP2C9	cytochrome P450 enzyme involved in drug metabolism
DNR	do not resuscitate
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EEG	electroencephalogram
EIND	Emergency Use Investigational New Drug Application
EP	European Pharmacopeia
ESETT	Established Status Epilepticus Treatment Trial
FDA	Food and Drug Administration
FOUR	Full Outline of UnResponsiveness
GABA	$\gamma$ -aminobutyric acid
GABA <sub>A</sub>	$\gamma$ -aminobutyric acid-gated chloride channel

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GOS	Glasgow Outcome Scale
H	hour
HPLC	high performance liquid chromatography
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent to Treat
IV	intravenous
IVRS	Interactive Voice Randomization System
LAR	legally authorized representative
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent to Treat
mRS-9Q	Modified Rankin Score - 9Q
MS/MS	tandem mass spectrometry
nM	nanomolar
NMDA	n-methyl-D-aspartic acid
OW	other weans
PAEEG	primary endpoint electroencephalogram
PD	pharmacodynamics
PK	pharmacokinetic
QOL	quality of life
QW	qualifying wean
QWEEG	qualifying wean electroencephalogram
RBC	red blood cell

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
RSE	refractory status epilepticus
SAE	serious adverse event
SAP	Statistical Analysis Plan
SE	status epilepticus
SOP	standard operating procedure
SRS	Severity Rating Scale
SRSE	Super-refractory status epilepticus
SSRI	Selective serotonin re-uptake inhibitors
STESS	Status Epilepticus Severity Score
SUSAR	Suspected Unexpected Serious Adverse Reactions
SWFI	Sterile Water for Injection
TAEEG	taper electroencephalogram
T <sub>max</sub>	time at maximum plasma concentration
TW	terminal wean
TWEEG	terminal wean electroencephalogram
US	United States
USP	United States Pharmacopeia

### 3. INTRODUCTION AND RATIONALE

#### 3.1. Status Epilepticus

Status epilepticus (SE) is a life-threatening seizure condition in which the brain is in a state of persistent seizure triggered by neuronal hyperexcitability. The Neurocritical Care Society defines SE as one continuous unremitting seizure lasting longer than five minutes or recurrent seizures without regaining consciousness between seizures for greater than five minutes (Brophy, Bell et al. 2012). Common causes of SE include preexisting epilepsy, cerebrovascular disease (in adults), electrolyte and metabolic disturbances, anoxia, encephalopathies, head trauma, high fever (in children, especially in the first year of life) and drug or substance intoxication. SE is associated with substantial morbidity and mortality.

##### 3.1.1. Epidemiology of SE

Geography, sex, age, and race influence the epidemiology of SE, whose incidence has a bimodal distribution, peaking in infants/young children and the elderly (Hauser 1990; DeLorenzo, Pellock et al. 1995; Wu, Shek et al. 2002). The incidence of SE in the elderly population is at least twice that in the general population. Concurrent medical conditions often exist in the elderly population, which can complicate therapy and worsen the prognosis of SE (Chapman, Smith et al. 2001).

The annual incidence of SE in the US is generally quoted to be within the range of 18/100,000 to 61/100,000, based on a 19-year retrospective study in Rochester, Minnesota (Hesdorffer, Logroscino et al. 1998) and a 2-year prospective study in Richmond, Virginia (DeLorenzo, Pellock et al. 1995), respectively. Two studies from Europe give annual incidences of a similar magnitude, ranging between 9.9/100,000 and 15.8/100,000 (Coeytaux, Jallon et al. 2000; Knake, Rosenow et al. 2001). It is thus estimated that in the United States each year there are as many as 150,000 cases of SE (DeLorenzo, Pellock et al. 1995).

#### 3.2. Refractory SE

When a patient begins to seize, the emergency medical technician will administer a first-line intravenous (IV) benzodiazepine (BDZ), such as diazepam, lorazepam or midazolam (Silbergleit, Durkalski et al. 2012), which is done either at the scene of the seizure or in the ambulance. If this is unsuccessful at abating the seizure, additional doses of the first-line therapy will be administered in the emergency room. Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line therapy, which is an IV anti-epileptic drug (AED) such as phenytoin or valproic acid (Novy, Logroscino et al. 2010; Shorvon 2011; Hocker, Britton et al. 2013).

Approximately 20-30% of patients refractory to first-line treatment will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to approximately 70-80% of patients who receive second-line therapy refractory to that therapy.

If a patient's SE continues after administration of BDZs and AEDs, the subject is diagnosed as having refractory status epilepticus (RSE), which must be treated quickly to terminate the seizure activity, maintain the patient's airway, and prevent cerebral damage. RSE patients are immediately admitted to the Intensive Care Unit (ICU) and placed in a medically-induced coma to stop

all seizure-related activity. The drugs used to induce coma are continuously-infused IV agents, commonly propofol, midazolam, or pentobarbital/thiopental, referred to as third-line agents (Brophy, Bell et al. 2012).

The RSE patient is continually monitored using electroencephalography (EEG) to ensure burst suppression is achieved. Burst suppression is a pattern of brain waves seen on an EEG, characterized by periods of activity alternating with periods of little or no activity in the brain, informing medical personnel of the effectiveness of the medically-induced coma. The goal of burst suppression is to allow the brain and corresponding neuronal tissue to restore function and reset to normal pre-seizure levels.

### **3.2.1. Epidemiology of RSE**

Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line AED therapy. In turn, approximately 20 – 30% of these patients treated with AEDs will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to 28% of the total estimated SE patient population refractory to second-line therapy. Based on the previously-cited estimated incidence in the US, this means that there are up to 42,000 incident cases of RSE in the USA, annually (DeLorenzo, Pellock et al. 1995).

### **3.3. Super-refractory SE**

After 24 hours of burst suppression, the patient is weaned off of the third-line therapy. If the weaning is unsuccessful (neuronal activity has not returned to normal), the third-line agent is re-administered or a different third-line agent is started, and the patient is considered to be in super-refractory status epilepticus (SRSE) (Chapman, Smith et al. 2001; Shorvon 2011; Brophy, Bell et al. 2012). SAGE-547 is being developed as an adjunct to third-line therapy in patients in RSE who have failed standard treatment. In this protocol, the term “RSE that has failed standard treatment” is deemed to be equivalent to the term “SRSE” and the two may be used interchangeably.

#### **3.3.1. Epidemiology of SRSE**

The incidence of SRSE is very poorly understood, mainly because the diagnostic codes used for SE do not generally differentiate its nature as responding or refractory to treatment. Based on the variable reporting of outcomes data, the incident cases of SRSE could represent between one and two-thirds of the RSE patients (Novy, Logroscino et al. 2010; Ferlisi and Shorvon 2012; Hocker, Britton et al. 2013; Sutter, Marsch et al. 2013). More detailed epidemiology studies are needed to better elucidate the proportion of RSE patients whose condition becomes super-refractory. A recent review of ICU discharge data in the USA suggests an annual incidence of approximately 35,000, based on patients who required at least three days in the ICU for SE [Sage data on file].

#### **3.3.2. Outcomes of SRSE**

SE has varying degrees of mortality depending on the underlying etiologies. Table 4 outlines the acute mortality in patients with SE by etiology (Neligan and Shorvon 2010). The mortality rate of SRSE is estimated to be 30% to 50% using current standard of care.

The causes of death from SE (and therefore SRSE) are heterogeneous, resulting from neuronal cell death, complications of underlying medical conditions, or adverse effects of the current standard treatments. Prognosis worsens and mortality increases with longer duration of SE, i.e. with SE

that develops into RSE or SRSE (Neligan and Shorvon 2010), and with longer duration of medically-induced coma (Ferlisi and Shorvon 2012). There is an obvious unmet medical need to improve upon the current standard of care treatment regimens.

Morbidity is high and survivors have outcomes ranging from poor function to vegetative state (Shorvon 2011). Approximately one third of patients with RSE and SRSE will recover, but with chronic neurologic or other deficits (Neligan and Shorvon 2010; Hocker, Britton et al. 2013). In all, it is estimated that less than 25-30% of all SRSE patients have a favorable functional outcome.

**Table 4: Approximate Mortality of Status Epilepticus in Different Etiologies**

Underlying Etiology	Associated Acute Mortality in Patients with SE (%)
Drug reduction/withdrawal, poor AED compliance, or low AED levels	0-10
Cerebrovascular Disease	20-60
Metabolic Disorders	10-35
Acute CNS Infection	0-30
Anoxia	60-100
Alcohol Abuse	0-10
Head Trauma	0-25
Drug Overdose/Toxicity	10-25
Brain Tumors	0-20
Cryptogenic/Idiopathic	5-20

### 3.3.3. Unmet Medical Need in Super-refractory Status Epilepticus

Treatment approaches for SRSE consist of diagnosis and treatment of underlying medical conditions, adding and changing anti-seizure drugs, and repeated attempts at weaning from IV anesthetic agents. Treatment of SRSE has three aims:

- to prevent excitotoxicity, which begins within 24 hours of SE onset;
- to prevent cerebral damage by initiating neuroprotective burst suppression;
- to prevent the complications of extended periods of anesthesia or unconsciousness (Shorvon 2011).

Currently, there are no therapies that have been specifically approved for RSE or SRSE. The primary drugs used to induce coma are continuously infused IV anesthetics such as propofol, midazolam, or pentobarbital/thiopental, known as third-line agents. Use of these drugs to control SRSE has only been studied in small retrospective reviews or small prospective studies without controls (Hocker, Britton et al. 2013) therefore there is no agreement on which drug is optimal nor on an optimal dosing regimen for the treatments that are used.

The most common adverse effect of the third-line agents is hemodynamic instability; in addition, they are not universally effective, with breakthrough seizures and withdrawal seizures requiring



dose adjustments and changes in third-line agent(s). The drug thought to be most effective in SRSE, pentobarbital, is also associated with the most toxic adverse effect profile, comprising decreased blood pressure and cardiorespiratory collapse (Claassen, Hirsch et al. 2002). The ability to wean patients successfully off the third-line agents as quickly as possible is therefore paramount, and an adjunct to SRSE treatment that enhances the success of the third-line agents and supports their successful weaning in a short timeframe would be an important addition to the therapeutic armamentarium. Preliminary clinical data show that SAGE-547 has been a successful adjunct to third-line therapy in this regard.

### 3.4. SAGE-547 Injection

Allopregnanolone is an endogenous, naturally occurring neuroactive steroid formed in the corpus luteum of the ovary, adrenal cortex and central nervous system (CNS) (Holzbauer, Birmingham et al. 1985; Paul and Purdy 1992; Ottander, Poromaa et al. 2005). It is a metabolite of progesterone created by the actions of 5- $\alpha$  reductase and 3- $\alpha$  hydroxy-steroid dehydrogenase. Allopregnanolone is a potent positive allosteric modulator of both synaptic and extra-synaptic GABA<sub>A</sub> receptors.

SAGE-547 Injection (allopregnanolone aqueous formulation in Captisol<sup>®</sup>) is being developed for the treatment of patients in RSE who have not responded to standard treatment. SAGE-547 Injection is a solution of 5 mg/mL allopregnanolone in Sterile Water for Injection (SWFI), USP and 250 mg/mL betadex sulfobutyl-ether sodium, NF. It is further diluted with Sterile Water for Injection, USP (SWFI) in IV bags to achieve an allopregnanolone concentration of approximately 1.67 mg/mL in an approximately isotonic solution and will be administered intravenously.

#### 3.4.1. Scientific Rationale for SAGE-547 in SRSE

Ineffective recruitment of inhibitory neurotransmission, together with excessive neuronal excitation, likely plays a role in the initiation and propagation of the electrical disturbance occurring in SE. GABA ( $\gamma$ -aminobutyric acid), the major inhibitory neurotransmitter in the central nervous system (CNS), is released from GABAergic neurons and binds to several types of GABA receptors (GABA<sub>A</sub>, GABA<sub>B</sub>, and GABA<sub>C</sub>) on target neurons. GABA<sub>A</sub> receptors are macromolecular proteins that form a chloride ion channel complex and contain specific binding sites for GABA and a number of allosteric regulators, including barbiturates, benzodiazepines, and some anesthetic agents. GABA receptor-mediated inhibition contributes significantly to the normal termination of a seizure (Kapur and Macdonald 1997). SAGE-547 is a positive allosteric modulator of the GABA<sub>A</sub> receptor.

The importance of terminating seizure activity as soon as possible is underpinned by a growing body of evidence from research and clinical observation that SE becomes more difficult to control as its duration increases. It has been postulated that this occurs due to a mechanistic shift from inadequate GABAergic inhibitory receptor-mediated transmission to excessive N-methyl-D-aspartic acid (NMDA) excitatory receptor-mediated transmission (Kapur and Macdonald 1997). As prolonged epileptiform bursting results in a reduction of GABA<sub>A</sub>-mediated synaptic inhibition, antiepileptic treatments which rely on enhancing intrasynaptic GABA<sub>A</sub> neurotransmission become less effective the longer SE continues.

Furthermore, the constitutive process of synaptic GABA<sub>A</sub> receptor internalization is accelerated by the increased neuronal activity associated with seizures. These findings suggest that the rate of GABA<sub>A</sub> receptor internalization is regulated by neuronal activity, and its acceleration contributes to

the reduction of inhibitory transmission observed during prolonged seizures (Kapur and Macdonald 1997). Of note is that SAGE-547 binds to extrasynaptic as well as intrasynaptic GABA<sub>A</sub> receptors; extrasynaptic receptors remain active with ongoing seizure activity, resulting in a putative mode of action for SAGE-547 in SRSE.

Status epilepticus induces cerebral damage that includes neuronal cell necrosis, gliosis, and network reorganization. The major cause of cell death in cerebral damage is excitotoxicity, which is initiated by glutaminergic receptor over-activation, causing calcium to flood the cell, thereby leading to apoptosis and necrosis. This process is initiated within a few hours of the start of seizure activity, and provides the medical imperative to terminate SE as quickly as possible. To prevent the consequences of the excitotoxicity cascade, it is recommended that anesthesia be initiated within 1-2 hours of onset of seizures at doses designed to induce EEG burst suppression (Shorvon and Ferlisi 2011).

### **3.4.2. SAGE-547 Clinical Program in the Treatment of SRSE**

The current SAGE-547 development program includes:

- an ongoing Phase 2 open-label trial, Study 547-SSE-201;
- this proposed Phase 3 randomized, double-blind, placebo-controlled trial, Study 547-SSE-301;
- a planned open-label, expanded access protocol, Study 547-SSE-302;
- a number of EINDs for SAGE-547 in patients with SRSE.

The designs of these studies are all similar, with a five to six day infusion of SAGE-547 (or placebo), during which time attempts are made to wean the subject off all third-line agents. In the Phase 3 studies, those subjects who cannot be weaned off third-line agents while being administered SAGE-547 (or placebo) will be eligible for a second open-label infusion of SAGE-547 at a higher dose, which is also being employed for the latter patients being enrolled in the Phase 2 study. Follow up of subjects is for 21 – 30 days after the first infusion of study medication.

### **3.4.3. Data from the SAGE-547 Development Program**

The data from 30 subjects included in the on-going clinical evaluation of SAGE-547 for the treatment of adults and children with SRSE clearly offers preliminary evidence that SAGE-547 could provide substantial and clinically significant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate. These subjects comprise 20 from the ongoing Phase 2 trial (71% success rate in 12/17 evaluable subjects) and 10 subjects who received EIND treatments (78% success rate in 7/9 evaluable subjects).

Successful therapy of SRSE has been defined as “the SE is completely controlled by the therapy, without breakthrough of withdrawal seizures, or discontinuation due to side effects or death during therapy,” (Ferlisi and Shorvon 2012). By this definition, which is in accord with the efficacy assessments used in the overall clinical evaluation of SAGE-547, 19 of the 26 (73%) subjects with SRSE who completed the SAGE-547 infusion were treatment successes. As data collection is ongoing, this information is preliminary and subject to change upon further monitoring.

Published reports on RSE and SRSE have stated mortality rate ranges from 35% to 65%. The underlying etiologies of SE in the 547-SAGE-201 study and EINDs are heterogeneous, and each one

conveys a different risk of mortality and longer term morbidity. However, the death rate in subjects who have received SAGE-547, 6 out of 30 (20%) subjects, appears to be lower than the published rates. None of the deaths were considered related to SAGE-547: brain tumor, organophosphate toxicity, respiratory failure, respiratory arrest due to ventilator support withdrawal, and breast cancer.

In the Phase 2 study, 20 SAEs (15 non-fatal) have been reported in 13 (65%) subjects, and of these 3 events in 2 subjects (10%) were considered by the investigator to be related to SAGE-547: pulmonary emboli and tracheostomy dehiscence/infection. The Sponsor did not consider these events to be related to SAGE-547, rather to the underlying disease states. Four of the 20 subjects (20%) experienced AEs considered possibly related to SAGE-547 by the investigator, namely moderate myopathy and severe pulmonary emboli in 1 subject, moderate tracheostomy dehiscence and tracheostomy infection in 1 subject, moderate thrombocytosis in 1 subject and moderate BUN, ALT and AST elevation in 1 subject.

Review of the most current safety data from 547-SAGE-201 reveals that there were changes in serum chemistry, hematology, and urinalysis during the study, but that none of those changes were assessed as related to SAGE-547. There were also no SAGE-547-related changes to vital signs.

Despite the heterogeneity in the underlying causes of SE, the ages of the subject, comorbidities, which normally complicate the treatment of SE, and the fact that all subjects had failed current standard of care treatment, a large majority of subjects had a successful therapy outcome, with discontinuation of all third-line agents and resolution of SE.

Refer to the Investigational Brochure for further information on the pre-clinical and clinical data supporting the use of SAGE-547 in SRSE.

### **3.5. Study Rationale - SAGE-547 in SRSE**

#### **3.5.1. Justification for the Control Group**

Although SAGE-547 has demonstrated extremely promising activity in subjects with SRSE, both in the Phase 2 study and during the EINDs, these have been open-label investigations with no control data for comparison. Generally in the literature there are few data describing the success rates of wean attempts of third-line agents, and few comparative data on the effectiveness of the three main third-line agents, propofol, pentobarbital/thiopental, and midazolam.

Several options for a control group in Study 547-SSE-301 were considered:

- No control group was thought to be unacceptable since there are no reliable published data on success rates in this population that could be used for broad comparisons;
- An active control was considered but found to be impractical since none of the third-line agents are approved for their use in SRSE, no standardized dosing regimens or treatment guidelines have been adopted for the management of SRSE, and clinicians were unlikely to agree which of the available third-line agents would be reserved for the active control arm;
- Historical controls were considered but abandoned because of the practical difficulties of obtaining high quality data, the lack of ability to prospectively match cases, and a suspicion that clinical practice in the standard of care of SRSE is evolving, mandating the use of prospective, concurrent control data;

- Comparison to standard of care alone was considered as a feasible design. However, in a field where no widely adopted treatment guidelines exist, there was a concern that knowledge of the treatment group (SAGE-547 plus standard of care versus standard of care alone) would alter the behavior of the investigators such that they could be more aggressive with weaning in the SAGE-547 group;
- Placebo control is not without its challenges since the preliminary efficacy data for SAGE-547 show that the compound exerts central pharmacological effects and is associated with positive outcomes in around 70% of patients. There is therefore a potential ethical concern about administering placebo to desperately ill patients who have often exhausted all treatment options for SRSE. This concern has been addressed in two ways: firstly all patients receive current standard of care; secondly, all subjects who fail to be weaned from their third-line agents at the end of the blinded infusion of study drug will be administered open-label SAGE-547 without un-blinding their initial treatment allocation, so treatment with the investigational product is not denied, but delayed about a week in the setting of ongoing receipt of full current standard of care.

It was therefore decided that a blinded, placebo-controlled design was appropriate for Study 547-SSE-301.

### **3.5.2. Justification for the Dose Regimen**

The standard dose regimen has been studied in 19 subjects in the 547-SSE-201 Phase 2 trial; the average peak plasma concentration of SAGE-547 at the end of the loading dose was approximately 144 ng/ml. The average plasma concentration during the maintenance infusion was approximately 70 ng/ml. At these concentrations, there were no clear safety signals although two-thirds of subjects experienced an SAE and there were four deaths, all related to the underlying comorbid conditions. The standard dosing regimen was associated with an approximate 70% successful treatment outcome. For these reasons, the standard dosing regimen has been adopted for the initial SAGE-547 infusion to be compared in a blinded fashion to placebo.

In the 547-SSE-201 trial, three subjects have thus far received the higher dose regimen. This dose regimen has also been well tolerated. The average peak plasma concentrations at the end of the loading dose for both dosing regimens will be in the same range, as the loading dose is the same for both regimens. The average plasma concentrations observed during the higher maintenance dose are 102 ng/ml (n=2). The rationale for adopting the higher dose regimen as the open-label infusion of SAGE-547 for subjects who are retreated in this 547-SSE-301 trial is that those who fail on the standard SAGE-547 dose regimen are afforded the opportunity to have access to a higher dose. The justification to also administer the higher dose regimen to failures on placebo is that the regimen has thus far been well tolerated, and this methodology preserves the blind for the initial infusion.

A five-day dosing regimen with SAGE-547 was investigated in the Phase 2 study, 547-SSE-201. There were some cases when weaning off all third-line agents was not possible within 48 hours, but weaning was completed after the end of the infusion of SAGE-547. For this reason, the duration of dosing with SAGE-547 has been increased from 120 hours (five days) in Phase 2 to 144 hours (six days) in this Phase 3 study.

### **3.5.3. Rationale for Genetic Testing Sub-study**

Sage Therapeutics intends to perform genetic research in the SAGE-547 development program in order to explore how genetic variations may affect the metabolism and activity of SAGE-547. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials, and, possibly, to genetically-guided treatment strategies for optimizing decision making with respect to individual benefit:risk. Participation of subjects in genetic research as part of the overall clinical study is optional.

### **3.6. Benefit-Risk Evaluation of the Present Study**

Previous reports of human administration of exogenous allopregnanolone indicate that for exposures in men and women up to 150 nM, the most commonly reported AEs were sedation (recorded as sleepiness or tiredness), feelings of intoxication (like alcohol), flushing, and mild headache (Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007). No SAEs were reported (Navarro, Kaddouz et al. 2003; Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007; Kask, Backstrom et al. 2008; Kask, Backstrom et al. 2009; Timby, Hedstrom et al. 2011a). In view of the reduced consciousness and sedation of study subjects at entry into this protocol, none of these previously-reported events are likely to impact subjects in this study.

To date, in the SAGE-547 Phase 2 study and the EIND subjects, a majority of subjects demonstrated a successful therapy outcome (>70%). The majority in the clinical trial (65%) have also experienced SAEs, but none has been considered related to SAGE-547 by the Sponsor (SAEs in 2 subjects (10%) were considered possibly related by Investigator). Five deaths have been reported in 30 subjects (20%), all related to the underlying cause of SRSE and not related to SAGE-547 – this is in the context of published mortality rates between 35% and 65%. These preliminary data suggest that SAGE-547 has the potential to provide clinically relevant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate.

The underlying etiologies of SE are heterogeneous, and each one conveys a different risk of mortality. Subjects who survive SRSE still have a high risk of severe morbidity (Neligan and Shorvon 2010). The subjects treated with SAGE-547 in Study 547-SSE-201, are heterogeneous in factors such as age and etiology of SE, factors that usually complicate treatment and can increase morbidity and mortality. Even with this heterogeneity, the preliminary efficacy and safety data for SAGE-547 are very encouraging, and the mortality rate suggests that the risk to benefit assessment of this treatment rests on the side of benefit.

## **4. ETHICS**

### **4.1. Institutional Review Board or Independent Ethics Committee**

This protocol will be reviewed and approved by the Institutional Review Board (IRB) where the study is conducted. The IRB will meet all FDA requirements governing IRBs (CFR, Title 21, Part 56).

## **4.2. Ethical Conduct of the Study**

The Sponsor, the Medical Monitor, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable ICH and GCP guidelines, and must also conduct the study in accordance with local regulations.

## **4.3. Subject Information and Informed Consent**

Subjects prospectively enrolled in this study will be unable to give consent. Therefore, consent will be given by proxy by a legally authorized representative (LAR). Written informed consent is required for each subject prior to any testing under this protocol not considered standard of care, including screening tests and evaluations. Should a subject gain the ability to sufficiently comprehend the situation and consent during the course of the study, written informed consent or verbal assent will be documented as required or recommended by the institution's IRB.

The form of consent to be obtained will depend on the condition of the subject as determined by the Principal Investigator. The informed consent form (ICF), as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50.

It is the responsibility of the Investigator to obtain consent and to provide the subject's LAR with a copy of the signed and dated informed consent form. The informed consent form for subject participation must also be available as part of the subject file for review by the site's dedicated study monitor or any authorized auditor of the Sponsor or regulatory authorities.

All ICFs used in this study must be approved by the appropriate IRB and by the Sponsor. The ICF must not be altered without the prior agreement of the relevant IRB and the Sponsor.

## **4.4. Ethical and Regulatory Considerations for Pharmacogenetic Sub-study**

### **4.4.1. Informed Consent for Pharmacogenetics**

The genetic component of this study is optional and subjects may participate in other components of the main study without having to agree to participate in the genetic component. If subject chooses to participate in the genetic component of the study, the subject or LAR must sign and date a specific consent form for the genetic component of the study in addition to the main study consent form. The principal investigator(s) is responsible for ensuring that consent is freely given and that the subject understands that they may discontinue from the genetic aspect of the study independent of their decision to remain within or withdrawal from the main study.

### **4.4.2. Subject Data Protection Relative to Pharmacogenomics**

Sage Therapeutics will not provide individual genotype results to subjects, their family members, their general physician, their employer or any insurance company unless required to do so by law. While extra precautions will be taken to preserve confidentiality and to prevent genetic data from being linked to an individual's identity outside of a restricted access site, in certain exceptional situations (e.g. in case of a medical emergency or as a consequence of a specific regulatory need), certain individuals may see both genetic data and the personal identifiers of a subject; however in all cases a subject's medical information and genetic files will remain physically separated.

## **5. STUDY OBJECTIVES**

### **5.1. Primary Objective**

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult and pediatric subjects with SRSE, and for the response to endure at least 24 hours after cessation of the SAGE-547 or placebo infusion (primary response).

### **5.2. Secondary Objectives**

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in Clinical Global Impression Scale between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### **5.3. Safety Objectives**

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

## 5.4. Other Objectives

1. To evaluate the impact of retreatment with a higher dose of SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;
6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS) (age  $\geq 17$  years).

## 6. ENDPOINTS

### 6.1. Primary Endpoint

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### 6.2. Secondary Endpoints

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) and to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.



### 6.3. Safety Endpoints

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.

### 6.4. Other Endpoints

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who fail to respond to their randomized double blind treatment and are retreated with a higher dose of SAGE-547;
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS) (age  $\geq 17$  years).

## 7. INVESTIGATIONAL PLAN

### 7.1. Overview of Study Design

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

Figure 1 provides an overview of the study design and Figure 2 gives the details of treatment and follow-up on the active treatment arm. Patients will follow one of three paths to entry to the study. The first path is for patients who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst suppression with a third-line agent. These patients will be consented for the study after admission to the intensive care unit, but before any third-line agents are administered for burst suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their LAR. Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours. Once burst suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status,

adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The second path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst suppression pattern on the EEG. These patients may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

The third path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These patients may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of blinded study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within six hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. Randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third line agent wean attempts prior to randomization (one vs two or more).

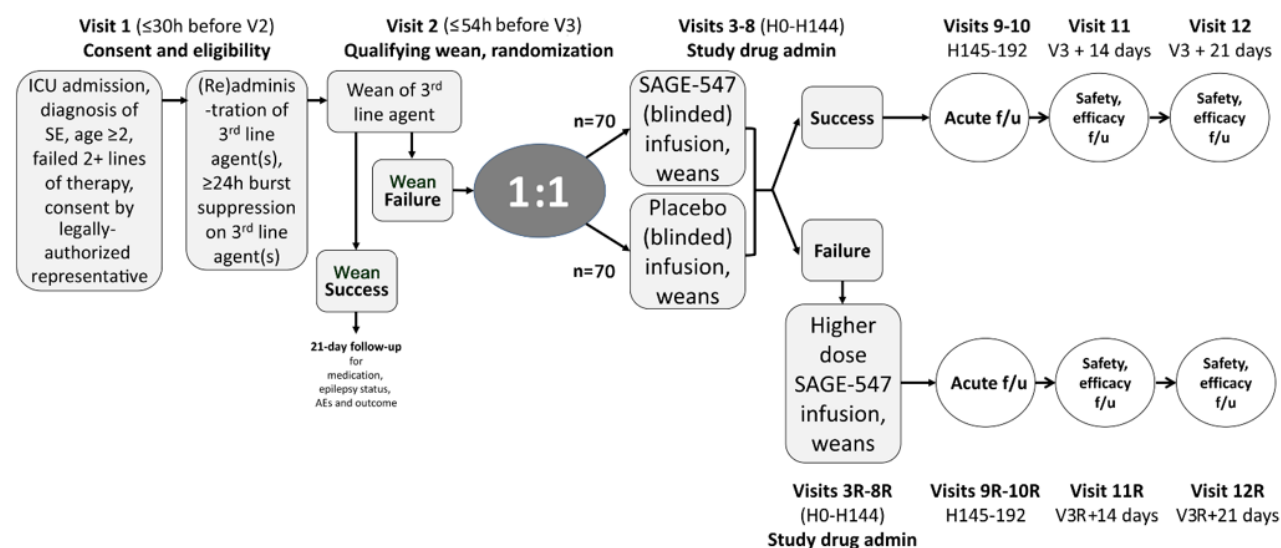
The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as the ability to wean the subject off all third-line agents before the end of the first infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication. Subjects must also have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) at the end of the primary endpoint assessment period as determined by EEG in order to be deemed a success. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#), [Table 2](#) and [Table 3](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. Eligibility for retreatment must be confirmed in writing by the medical monitor prior to the open-label infusion starting. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo will all subsequently be eligible to be administered SAGE-547 at the higher dose.

**Figure 1: Study Design**



## 7.2. Trial Conduct

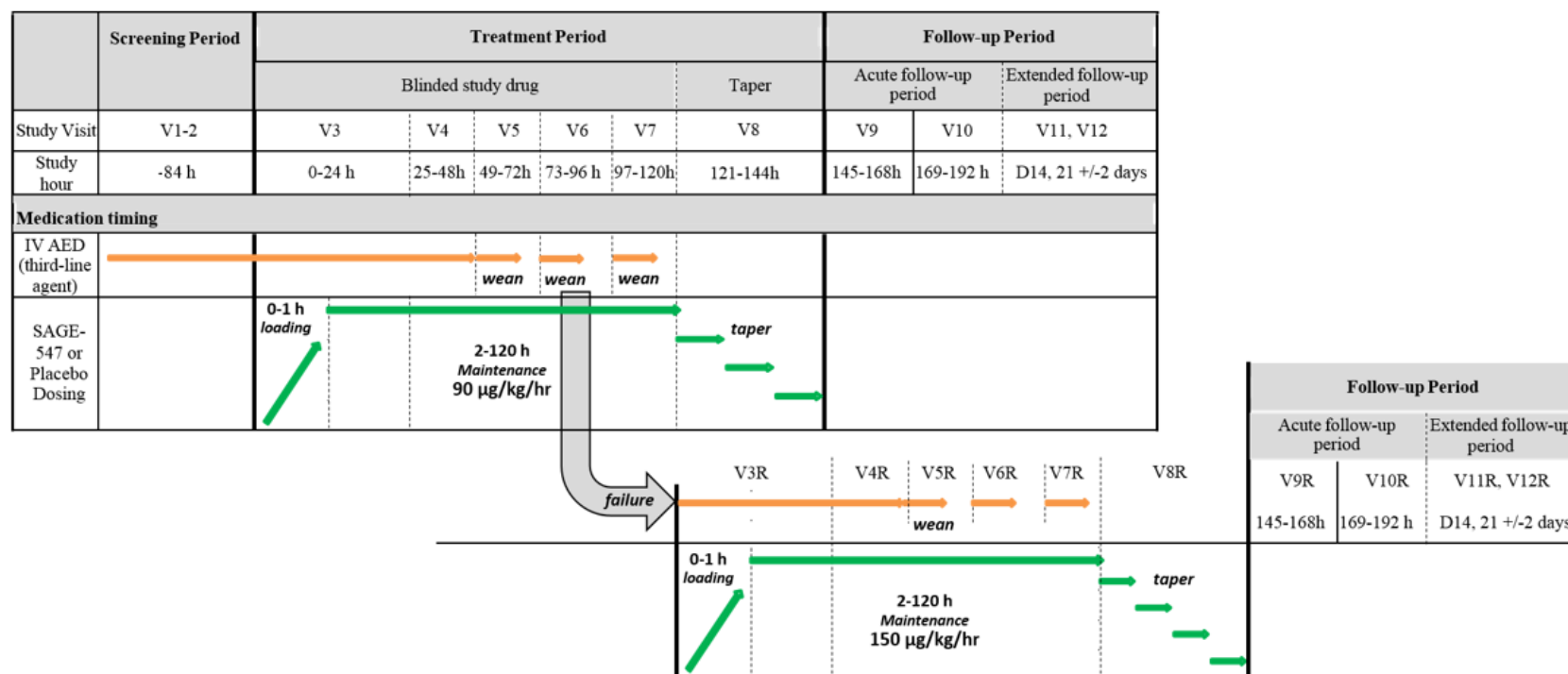
This study will be conducted according to the principles of the World Medical Association Declaration of Helsinki and most recent amendment, and in compliance with the protocol approved by the IRBs/Independent Ethics Committees (IECs), and in accordance with ICH Guidelines on GCP standards.

### **7.3. Blinding and Randomization**

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo). Details of the dynamic randomization process will be included in the SAP.

The randomized portion of the study will be blinded, with the two treatment products (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

The second infusion of SAGE-547 will be administered on an open label basis to subjects who failed the primary endpoint wean.

**Figure 2: Details of Treatment Administration and Follow-up**

## 8. SELECTION AND WITHDRAWAL OF SUBJECTS

The study will randomize 140 patients at up to 180 sites. All subjects deemed eligible to enroll must have written Medical Monitor approval on a case-by-case basis prior to undertaking the qualifying wean.

### 8.1. Inclusion Criteria

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects two (2) years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; *or* who have previously failed one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst suppression pattern; *or* who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst suppression pattern.

### 8.2. Exclusion Criteria

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy.
4. Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing underlying neurological disorder.
5. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis but for whatever reason, dialysis is not planned or non-continuous dialysis planned (that would not adequately remove Captisol®);
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the experience of the investigator, is less than 30 days;
  - e. a do not resuscitate (DNR) order.

6. Subjects who are being administered more than three third-line agents concomitantly or for whom the qualifying wean cannot be completed within 24 hours or who are being administered a third-line agent for indications such as raised intra-cranial pressure that would preclude weaning according to this protocol.
7. Subjects with a living will that does not allow heroic measure.
8. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
9. Subjects who have been enrolled in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not withdraw or complete and then re-enroll).

### **8.3. Selection and Consent of Subjects for Pharmacogenetic Substudy**

All subjects will be asked to participate in pharmacogenetic research; however, participation in research is voluntary and a subject can decide to decline his/her participation without penalty or loss of benefit. Participation or lack thereof will not be a cause for exclusion from any aspect of the main study. In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **8.4. Subject Withdrawal / Study Termination**

#### **8.4.1. Withdrawal/Discontinuation of Individual Subjects**

The reasons for study drug discontinuation and/or subject withdrawal from the study must be recorded in the subject's electronic case report form (eCRF). The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject has been discontinued/withdrawn due to an AE.

##### **8.4.1.1. Withdrawal from the Study**

Subjects or their LAR may withdraw subjects from the study at any time for any reason without compromising the subject's medical care. The Investigator will also withdraw subjects upon the request of Sage Therapeutics or upon termination of the study.

Subjects who withdraw from the study prior to Visit 10 (or 10R) should complete the procedures scheduled for the day of study drug taper (hour 121-144; Visit8/8R) on the day of their withdrawal, including the SAGE-547 taper schedule, with the addition of the mortality assessment from Visit 12/12R. Subjects who withdraw from the study after Visit 10/10R should undergo study procedures as outlined for Visit 12/12R on the day of their withdrawal. In all cases, the reason for subject withdrawal will be recorded in the eCRF.

Withdrawal of subjects for any reason should be discussed with the Medical Monitor.

##### **8.4.1.2. Discontinuation of Study Drug**

If it is necessary to discontinue the study drug earlier than planned, subjects should continue to be followed per protocol to capture safety and efficacy assessments for the duration of the study period.

The investigator may withdraw the subject from the study drug for the following reasons:

- Upon subject's or LAR's request
- The subject or LAR is unwilling or unable to adhere to the protocol-specified visits
- The subject experiences an intolerable adverse event
- During the course of the study, the subject develops symptoms or conditions listed in the exclusion criteria.
- Other medical reason, at the discretion of the Investigator and/or the Medical Monitor

Subjects who discontinue the study due to an AE considered related to study drug should be followed until the event is resolved, considered stable, or the Investigator determines the event is no longer clinically significant. Study drug discontinuation due to AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

#### **8.4.2. Study Termination**

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of AEs or other findings suggesting unacceptable risk to subjects, administrative or operational reasons. In the event of study termination, Sage Therapeutics will provide written notification to the Investigator. Investigational sites must promptly notify their IRB and initiate withdrawal procedures for participating subjects.

## **9. INVESTIGATIONAL PRODUCT**

### **9.1. Identity of Investigational Product**

SAGE-547 Injection (allopregnanolone)

### **9.2. Clinical Supplies**

#### **9.2.1. SAGE-547**

Adequate supplies of SAGE-547 Injection and materials for intravenous administration will be provided to each site.

SAGE-547 Injection is a clear, colorless sterile solution of allopregnanolone intended for intravenous injection. SAGE-547 Injection is an aqueous solution of 5 mg/mL allopregnanolone in 250 mg/mL Captisol® (betadex sulfobutyl-ether sodium, NF). It is presented either un-buffered or buffered with 10 mM citrate at a pH of 6.0 in either 20 mL or 50 mL vials. SAGE-547 is further diluted according to the Pharmacy Manual to achieve an approximately isotonic solution and will be administered intravenously.

No preservatives are included in the drug product, which is intended to be used as a single-use vial. All inactive components (excipients) used in the formulation are compendial grade and conform to current USP/EP, and include sodium citrate, citric acid and betadex sulfobutyl-ether sodium (Captisol®).



**9.2.2. Placebo**

Placebo will be identical to SAGE-547 and presented in identical vials. Placebo will be manufactured in a similar way to SAGE-547 and comprises all excipients but no SAGE-547.

**9.2.3. Blinding**

The vials of SAGE-547 and placebo will be identical in every way so that they are indistinguishable by the pharmacist, investigator, anyone treating or managing the patient, the monitors, and the sponsor. In this way the first infusion of study drug administered to each patient will be double-blind.

For the blinded study drug infusions, subject-specific dosing kits will be provided. These dosing kits will be pre-labelled with kit number for the first blinded infusion. For the second-infusion, open-label kits will be provided, which will require subject assignment by the pharmacy for reconciliation purposes. The study kits must be stored under refrigerated conditions (2-8 °C). IV administration bags and lines may be provided for the blinded and open-label infusions. Refer to the Pharmacy Manual for additional details.

The label for the SAGE-547 Injection vials will include standard product identification information according to the Code of Federal Regulations, 21CFR 312.6. All study labels will also contain the following statement:

Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use.

**9.3. Preparation of SAGE-547 or Placebo Injection for Dosing**

The Pharmacy will be responsible for preparing the blinded and open-label study drug for subject dosing. The prepared admixture will be assigned a room temperature (20-25 °C) storage shelf life of 30 hours from time of compounding.

SAGE-547, which is hypertonic, will require dilution with SWFI to achieve an approximately isotonic solution according to the instructions provided in the Pharmacy Manual. Exactly the same procedures will be used to prepare the placebo admixture, so that all site staff remain blinded as to treatment allocation for the first infusion of study drug. SAGE-547 Injection is not intended to be administered to patients undiluted.

Refer to the Pharmacy Manual for specific instructions regarding infusion preparation.

**9.4. Administration and Accountability**

The Pharmacy will maintain accurate records of all investigational product supplies. Accurate records will be kept regarding the volume of SAGE-547 Injection or placebo used for each IV preparation, as well as the required infusion rate or rates, and the date and time of preparation. Reasons for departure from the expected dosing regimen must also be recorded. To satisfy regulatory requirements regarding drug accountability, all study medication will be reconciled in full. Refer to the Pharmacy Manual for additional details.

## 10. TREATMENT OF SUBJECTS

### 10.1. Dosing Schedule (Blinded Infusions)

SAGE-547 Injection or placebo will be administered according to the dosing schedules in [Table 5](#). The infusion rates to accomplish these  $\mu\text{g/kg/h}$  doses will be calculated according to the weight of the subject. The infusion rates will be applied to blinded study drug for the first infusion of study medication.

**Table 5: SAGE-547 or Placebo Dosing Schedule**

Hour	Type and Duration of Study Drug Infusion	Description
H1	One hour loading Infusion	300 $\mu\text{g/kg/h}$
H2 – H120	119 hour maintenance infusion	90 $\mu\text{g/kg/h}$
H121 – H128	8 hour taper	65 $\mu\text{g/kg/h}$
H129 – H136	8 hour taper	45 $\mu\text{g/kg/h}$
H137 – H144	8 hour taper	25 $\mu\text{g/kg/h}$

### 10.2. Dosing Schedule (Open-Label Infusions)

If a subject fails wean from third-line agent(s) or requires re-instatement of third-line therapy within 24 hours of discontinuing the initial infusion of study drug, SAGE-547 Injection will be re-administered according to the dosing schedule in [Table 6](#). The infusion rates to accomplish these  $\mu\text{g/kg/h}$  doses will be calculated according to the weight of the subject. These infusion rates will be applied to SAGE-547 re-treatment for the open-label second infusions of study medication.

**Table 6: SAGE-547 Open Label Dosing Schedule**

Hour	Type and Duration of SAGE-547 Infusion	Description
H1	One hour loading Infusion	300 $\mu\text{g/kg/h}$
H2 – H120	119 hour maintenance infusion	150 $\mu\text{g/kg/h}$
H121 – H126	6 hour taper	125 $\mu\text{g/kg/h}$
H127 – H132	6 hour taper	95 $\mu\text{g/kg/h}$
H133 – H138	6 hour taper	65 $\mu\text{g/kg/h}$
H139 – H144	6 hour taper	35 $\mu\text{g/kg/h}$

### 10.3. Route of Administration

SAGE-547 Injection is intended for IV administration only. The compatibility of SAGE-547 with other drugs is unknown, and the product should be administered via a dedicated peripheral IV line using any Sage-supplied study-specific IV administration bags and lines. In order to preserve blinding, these instructions also apply to the blinded placebo infusions.

### 10.4. Treatment Period

The treatment period with double-blind SAGE-547 or placebo is six 24-hour periods (144 hours), which may encompass 6-7 calendar days. The retreatment period is of identical duration.

## **10.5. Concomitant Medications, Procedures and Treatments**

Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. All concomitant medications, procedures, and treatments should be documented throughout the study from Screening through Visit 12/12R and recorded on the eCRF.

SAGE-547 has demonstrated inhibitory effects on cytochrome P450 isoenzyme 2C9 (CYP2C9). Therefore, AEDs such as phenytoin and phenobarbital that are primarily metabolized by CYP2C9 should be closely monitored during SAGE-547 administration to ensure target exposures are maintained.

### **10.5.1. Concomitant AEDs**

Subjects may enter the study on AEDs, and be administered AEDs during the study. All of these must be recorded on the eCRF with details including date and time of starting and stopping each AED, the route of administration, changes in doses, and frequency of administration. In addition, details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the eCRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.

### **10.5.2. Concomitant Third-Line Agents**

All third-line agents (as defined in [Section 8](#)) administered since the diagnosis of SE will be recorded on the eCRF, whatever path the patient took for entry into the study. Details will include the name of the drug, the start and stop dates and times, and, after consent, the doses with start and stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

In addition, those changes in dose that constitute a wean attempt will be marked as such on the eCRF. In this way the start and stop dates and times of all wean attempts (see [Section 11](#) for definitions) will be recorded, as will the type of wean (QW, OW, or TW) and the outcome of the wean attempt (successful, failed and dose of this third-line agent increased or failed and this third-line agent stopped and another third-line agent started). Those wean attempts that occur after the TW up to and including Visit 12/12R will be marked “AW”.

Some third-line agents (such as propofol) are also used to induce sedation to facilitate a subject’s ability to tolerate the ventilator. For subjects requiring such sedation, propofol is the preferred agent unless there are contraindications. The eCRF will make clear from the indication for the third-line agent when it is being used for burst or seizure suppression and when it is being used as ventilator support or for another purpose. The investigator will add a note to the eCRF to justify that the doses used are appropriate for sedation and not for seizure or burst suppression. The doses used for ventilator support and other similar uses are usually much lower than those used for seizure or burst suppression, and use of these third-line agents for these other purposes does not constitute a wean failure under this protocol.

### **10.5.3. Concomitant Pressors**

The start and stop dates and times of all pressors will be recorded as well as the start and stop dates and times of all dose changes.

#### **10.5.4. Other Concomitant Medications**

All other concomitant medications must be recorded on the eCRF with details including date and time of starting and stopping, the route of administration, dose, and frequency of administration.

### **11. STUDY ASSESSMENTS**

#### **11.1. Efficacy Assessments**

##### **11.1.1. Primary Efficacy**

Success or failure will be determined, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo infusion and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the blinded (first) infusion of SAGE-547 or placebo. In addition, subjects must have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) to be deemed to be successes. All subjects who fail to complete their infusion of randomized treatment or do not have at least one attempt during study treatment to wean off all third-line agents will be considered as “failures” for the primary endpoint.

##### **11.1.1.1. Weaning**

Third-line agents are anesthetic agents that are administered in order to reach a seizure or burst suppression EEG pattern. For the purposes of this study, third-line agents are defined as continuous intravenous infusions of pentobarbital/thiopental, midazolam, propofol, and ketamine at maintenance doses alone or in combination sufficient to produce a burst suppression pattern on the EEG. The following are considered to be minimum maintenance doses of these agents that may be expected alone or in combination to achieve EEG burst suppression. If subjects are on lower doses than these and are not in EEG burst suppression for the 24 hours prior to the QW or the first 12 hours of the blinded study drug infusion, they will be considered to be screen failures/protocol violators and will exit the study.

- Pentobarbital: 1 mg/kg/hour
- Thiopental: 3 mg/kg/hour
- Midazolam: 0.1 mg/kg/hour
- Propofol: 3 mg/kg/hour
- Ketamine 1.2 mg/kg/hour

The timing and nature of the third-line agent weans will be guided by the Clinical Standardization Guidelines for the study, and the clinical judgment of the investigator, and will always be primarily done in the best medical interests of the subject. Advice about weaning may be sought from the Clinical Standardization Team, a group of fellow investigators with experience of performing clinical trials in subjects with SRSE. The Clinical Standardization Team will be able to discuss EEGs related to key study timepoints (qualifying wean, terminal wean, and the period after the end of the blinded study drug infusion if the terminal wean was successful) in a timely manner in order to provide advice about compliance with the Clinical Standardization Guidelines.

The following guidance for weaning applies to all weans of third-line agents undertaken during the study. These weans include the qualifying wean (QW); the terminal wean (TW), which is the wean of the third-line agent if the subject is on only one third-line agent or the wean of the last third-line agent if the subject is on more than one third-line agent; the other weans (OW), which are the weans of the third-line agents other than the TW if the subject is on more than one third-line agent. The guidance also applies to additional weans (AW), which are the weans from third line agents that take place after the TW for the first blinded study drug infusion or the second open-label study drug infusion.

### **QW Guidance**

- Wean to be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace that third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Investigators should allow 24 hours to lapse after the end of a “successful” qualifying wean before finally declaring the QW a success. If a third-line agent needs to be re-instituted within that 24 hours, the QW is a failure, and the subject may then be randomized in the study.

### **OW Guidance**

- First OW should not begin before H49 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- If the subject is on two third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the TW. However the OW may be completed over a shorter or longer time period and may overlap if clinically indicated with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- If the subject is on three third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the wean of the second agent. The second agent should be weaned over 24 hours and that wean completed before starting the TW. However the OWs may be completed over a shorter or longer time period and may overlap if clinically indicated with each other and with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- All OWs should be completed before H96 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

## **TW Guidance**

- The TW is defined as the wean of the last third-line agent.
- If the subject is on one third-line agent, the TW should not begin before H49 and should begin no later than H97 after starting administration of study drug or starting the open-label infusion of SAGE-547. If the subject has had one or more OWs, the TW should ideally begin as soon as the last OW is complete but in any case not later than H97 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- The TW must be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace this third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Every effort must be made to complete the TW before H120 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547, but the TW must be complete before H144 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

## **AW Guidance**

- AWs will take place when medically indicated in the opinion of the investigator.
- Ideally the AW should take place over 24 hours, but completion may be over a shorter or longer time period than this. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.

### **11.1.1.2. EEG**

Electroencephalographs (EEGs) that are representative of the intermittent or continuous EEG being used to support key investigator decisions will be collected at the following time points:

- A 24-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst suppression for the second path to eligibility, and a variable pattern for the third path to eligibility. This EEG will capture as much as possible of the burst suppression pattern that precedes the QW.
- EEG will be performed to cover the qualifying wean (QWEEG). EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for up to 24 hours after the end of the QW. The duration of the QWEEG will be up to 48.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s), the decision to re-institute a third-line agent(s) at doses intended to induce burst suppression, and the decision that the QW is a success.

- EEG will be performed from three hours prior to the start of the blinded infusion to 12 hours after the start of the blinded infusion. This will be called the BIEEG. The intent of this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG and to assess the depth of burst suppression in the first 12 hours of blinded study drug infusion.
- EEG will be performed to cover the final or terminal wean of third-line agent (TWEEN). The TW is the wean of the final third-line agent during the blinded administration of study drug or the open-label infusion of SAGE-547; if the subject was on one third-line agent, the TW is the wean of that agent. If the subject was on three third-line agents, the TW is the wean of the third and final agent. EEG recording will start 30 minutes prior to the start of the TW, continue for up to 24 hours during the TW, and then continue for the one hour after the end of the TW. The duration of the TWEEN will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the final third-line agent or the decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity could not be managed using intermittent bolus doses of AEDs.
- EEG will be performed during the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 (TAEEG). The TAEEG is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the start of the taper (at Hour 119.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours during the taper, and then continue for the one hour after the end of the taper (to Hour 145 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547). The duration of the TAEEG will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity seen during the taper could not be managed using intermittent bolus doses of AEDs.
- EEG will be obtained to cover the end of the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 and the ensuing 24-hour period, during which the primary endpoint is assessed (PAEEG). The PAEEG is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the end of taper (at Hour 143.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours after the end of the blinded administration of study treatment or the open-label infusion of SAGE-547, and then continue for the one hour after the end of the 24-hour assessment period (to Hour 169 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547). The duration of the PAEEG will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity seen in the 24 hours following the end of the blinded administration of study treatment or the open-label infusion of SAGE-547 that could not be managed using intermittent bolus doses of AEDs.

In practice, most subjects are on continuous EEG monitoring or long periods of intermittent EEG monitoring. However, this protocol does not mandate continuous EEG monitoring and breaks from EEG monitoring to provide relief to the scalp from the irritating effects of the electrodes are advised,

particularly in children, according to local practice. If a break in EEG monitoring is mandated by local practice guidelines at a time when one of the protocolled EEG segments is to be collected, the break in EEG monitoring will take precedence, with the reason for missing the EEG reading noted on the eCRF. The EEGs obtained for the study are therefore part of the existing EEG record rather than being obtained de-novo at each timepoint. For timepoints where there might be some ambiguity, such as the TWEEG, the final EEG record is that of the final attempt to wean the last third-line agent, even if earlier attempts to wean that agent took place. In some cases (the TAEEG and PAEEG, for instance), the EEG records will overlap, but different cuts are taken to service the different EEG record requirements.

The electronic EEG file will be de-identified, the date and time of the start and stop of the EEG and the subject number will be attached to the file, and the study time point will be indicated (CEEG, QWEEG, BIEEG, TWEEG, TAEEG, and PAEEG). The PI will indicate on the eCRF what the EEG shows, as follows:

- For the CEEG, the PI will describe the EEG pattern that determined which path to eligibility the subject was on.
- For the QWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure or success on the qualifying wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the qualifying wean constitutes a failure); the QWEEG will extend to cover the 24 hours after the end of third line agents in order to confirm that the QW was a success.
- For the BIEEG, the PI will note the date and time of the start of the EEG and the pattern seen on the EEG.
- For the TWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure on the terminal wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the terminal wean).
- For the TAEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst suppression before the end of the SAGE-547 infusion).
- For the PAEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst suppression in the 24 hours following the end of the SAGE-547 infusion).

A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm the depth of burst suppression prior to the QW and during the first 12 hours of the blinded study drug infusion, the PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period (average EEG power at the end of Visit 9 of more than two microvolts):



- All subjects will have the CEEG and QWEEG collected and stored, and the CEEG and QWEEG read;
- Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;
- Those subjects randomized who are not retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the BIEEG, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read;
- Those subjects randomized who are retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion and the TWEEG, TAEED, and PAEEG related to the open-label study drug infusion collected and stored, and the BIEEG, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read.

All EEG records may be subject to quantitative EEG analysis.

### **11.1.2. Secondary Efficacy**

#### **11.1.2.1. Clinical Global Impression Scale (CGI)**

The clinical global impression scales are often utilized in clinical trials to allow clinicians to integrate several sources of information into a single rating of the subject's condition. Both the CGI-Severity (Question 1, CGI-S) and the CGI-Improvement (Question 2, CGI-I) employ a 7-point Likert scale measuring severity of the disease state in the subject and improvement, respectively. All severity assessments after initiation of SAGE-547 treatment should consider the general state of the subject over the preceding week. The third question on the scale will not be employed in this trial, and where the scale states "mental illness", this means "physical illness" in this trial.

The CGI-S will be evaluated at Visit 1 and at the last visit, Visit 12 or 12R. The CGI-I will be evaluated at Visit 12 or 12R.

#### **11.1.2.2. Epilepsy Status**

At Visit 1, the diagnosis of epilepsy will be documented as a no/yes question. If there was a previous diagnosis of epilepsy, further details will be documented, including:

- Date of diagnosis;
- Details of anti-epileptic drugs currently being taken;
- Type of epilepsy;
- Seizure frequency in the past month.

Information about the current (index) episode of status epilepticus will be obtained at Visit 1:

- Date of onset
- Date of failure to respond to first line agent(s) and the name(s) of the agent(s)
- Date of failure to respond to second line agent(s) and the name(s) of the agent(s)
- Any previous treatment with third line agents and the response to those agents (details of the third line agent drugs and previous wean attempts will be recorded on the Third Line Agent Medication CRF)

- The cause of the index episode of status epilepticus
- If the subject was transferred from another hospital or from within the hospital, the reason for the transfer will be recorded (such as for study enrollment, due to lack of medical options at original hospital or unit, due to lack of beds at the original hospital or unit, family request, other)

Previous (non-index) diagnosis of status epilepticus will be documented as a no/yes question. If SE did occur in the past, further information will be gathered, including:

- SE, RSE, or SRSE diagnosis, whichever was the most severe diagnosis for each episode;
- Cause;
- Treatment, including experimental treatments and need for intubation/ventilation;
- Dates of onset and duration if the episode of status epilepticus occurred in the past 12 months.

At Visit 12 or Visit 12R, the following information will be gathered:

- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of SE up to and including Visit 12 or Visit 12R;
- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of seizures (convulsive and non-convulsive) up to and including Visit 12 or Visit 12R;
- Number of separate episodes of SE after H144 at the end of Visit 8 or Visit 8R (no/yes); if yes,
  - SE, RSE, or SRSE diagnosis;
  - Cause;
  - Treatment, including experimental treatments and need for intubation/ventilation;
  - Dates of onset and duration.

Note that a separate episode of SE is defined as an episode of SE separated from other periods of status epilepticus by at least 24 hours.

- Diagnosis of epilepsy since Visit 11 or Visit 11R will be documented as a no/yes question. If a diagnosis of epilepsy has been made, further details will be documented, including:
  - Status as ongoing or new epilepsy since Visit 11 or Visit 11R after initiation of SAGE-547 treatment;
  - Details of anti-epileptic drugs currently being taken;
  - Type of epilepsy and seizure frequency in the past week.

## 11.2. Safety Assessments

The safety and tolerability of SAGE-547 will be assessed using adverse events, clinical laboratory measures, vital signs, ECG intervals and morphology, and mortality. All safety assessments should be performed per hospital standard of care and will be collected periodically throughout the study according to [Table 1](#), [Table 2](#), and [Table 3](#) (Schedules of Assessments).

### 11.2.1. Adverse Events

AEs will be collected after informed consent has been signed and prior to study-specific screening procedures not considered standard of care, during subject preparation for SAGE-547 administration and through Visit 12 or Visit 12R. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™) coding system (current version). See [Section 14](#) for additional details.

### 11.2.2. Clinical Laboratory Tests

Blood samples will be taken for hematology, and serum chemistry and GFR will be calculated at:

- Visit 1 and then at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.
- Blood samples will be taken at Visit 11 or Visit 11R for serum chemistry (renal panel only).

Urine samples (20 ml) will be taken for urinalysis and urine NAG analysis at:

- Visit 1 and at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.

For adults and children  $\geq 30$  kg, these samples will be analyzed at a central laboratory; hour-to-hour medical decisions will be based on sampling for laboratory testing done outside the protocol as part of normal standard of care. GFR will be calculated by the central laboratory. For children under 30 kg, results of local laboratory testing undertaken at the protocolled timepoints may be sent to the central laboratory for inclusion in the central study laboratory database; this obviates the need for additional blood sampling for central laboratory testing.

Any out-of-range values will be flagged by the laboratory; the investigator will add a comment about whether the abnormality is clinically significant. Clinical significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

#### 11.2.2.1. Hematology and Serum Chemistry

Hematology will include complete blood count (CBC) white blood cell count with differential, platelet count and red blood cell (RBC) count, hemoglobin and hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose. In addition triglycerides will be measured in serum chemistry samples (to aid assessment of lipemia in pharmacokinetic samples).

#### 11.2.2.2. Pregnancy Test

Females of child-bearing potential will be tested for pregnancy by serum pregnancy test at Visit 1. In this study, since an accurate history of menstruation in girls and menopause in older women may not be available at Visit 1, “child-bearing potential” is taken to mean any female aged 10 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had

a hysterectomy. Female subjects with a positive pregnancy test will be ineligible for study participation.

#### **11.2.2.3. Urinalysis**

Urinalysis will include assessment of protein, blood, leukocytes, glucose, ketones, urobilinogen, pH, and specific gravity.

#### **11.2.3. Vital Signs**

Blood pressure, heart rate, and temperature will be recorded at the following time points relative to the first infusion of study drug, and to the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547:

- Visit 1;
- At 0, +30, +60 minutes (+/-15 minutes) and +2, +4 and +8 hours (+/- 30 minutes) after the start of the infusion;
- At +24, +48, +72, +96, +120, +144, +168, and +192 hours (+/- 2 hours) after the start of the infusion.

#### **11.2.4. Weight and Height**

Weight and height will be measured at Visit 1 and weight will also be measured once during each 24 hour period of the first infusion of study drug, and of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547. These daily weights will be used to modify the dose of SAGE-547 if required. If it is not possible to weigh the subject daily, an actual weight must be obtained prior to starting the blinded study drug, and that weight used to calculate the dose of study drug to be administered. If this is not possible, permission from the Monitor must be obtained to use another method to obtain the subject's weight (such as information from the LAR or estimating using an established local protocol).

#### **11.2.5. ECG**

12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours; at other times the allowed time window for ECGs is +/- 2 hours:

- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +128, +136, +144, +152, +160, and +192 hours after the start of the blinded (first) study drug infusion
- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +126, +132, +138, +144, +152, +160, and +192 hours after the start of the open-label (second) study drug

The heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm.

#### **11.2.6. Mortality**

Mortality will be recorded on the Visit 12 or Visit 12R case report form. If the subject has died, the following information will be collected:

- Date of death;

- Cause of death.

As accurate as possible cause of death will be collected, which will be further categorized as due to one of the following causes:

- SE;
- complications of long term intubation and third-line agent infusions;
- underlying cause of qualifying SE;
- co-morbidity existing at the time of the qualifying SE;
- new co-morbidity or trauma;
- study drug;
- other (specify).

#### **11.2.7. Pharmacogenetic Samples**

If a subject's LAR consents to pharmacogenetic sampling, a blood sample for genetic research will be collected at Visit 1 in order to avoid the possible introduction of bias through the exclusion of patients who may withdraw from study due to an AE (a subject population that may be of specific interest for subsequent genetic analysis). If for any reason a sample cannot be taken prior to treatment, a sample can be drawn at any point prior to completion with the restriction that no more than one genetic sample be taken per subject.

The objective of this research is to collect and store blood samples for possible DNA extraction and exploratory research into how genes or specific genetic variation may influence response (i.e. distribution, safety, tolerability, and efficacy) to SAGE-547. Specific genetic variations of interest include but are not limited to: classes of metabolizing enzymes (e.g. Cytochrome P450 supra-family genes), genes encoding enzymes involved in the production and metabolism of allopregnanolone (e.g. AKR1C4 (3 $\alpha$ -hydroxysteroid dehydrogenase)), genes associated with the GABA receptor (e.g. GABRA1-A6, GABRB1-B3, GABRD, GABRE, GABRG1-3) and genes associated with the production and degradation of GABA.

Future research may suggest other genes or gene categories as candidates for influencing not only response to SAGE-547 but also susceptibility to disorders for which SAGE-547 is being evaluated. Thus, the genetic research may involve study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.

##### **11.2.7.1. Biological Sampling and Coding Procedures (Pharmacogenetics)**

To ensure patient confidentiality, utmost care will be taken in the coding and storage of pharmacogenetic samples.

*Extraction and coding:* DNA will be extracted from the blood sample and the DNA sample will be assigned a unique number replacing information from sampling tube. The assigned DNA number will be used to identify the sample and its corresponding information within Sage Therapeutics or at any designated contract laboratory for the purpose of sequencing of other DNA specific analysis. No personal details sufficient for individual identification will be available to any person (internal or external to Sage Therapeutics) working with the DNA.

*Genotype/Phenotype Analysis:* Samples and data from genetic analysis will be coded. The link between subject enrollment / randomization code and DNA number will be maintained and stored in a secure environment with restricted access. The established link will be used to identify relevant DNA samples for analysis, facilitated correlation of genotype results with clinical data, allow regulatory audit, and to trace samples for destruction in case of withdrawal of consent.

#### **11.2.7.2. Retention of Biological Samples for Pharmacogenetic Analysis**

Extracted DNA is a finite research that is destroyed in the process of being analyzed. Primary blood samples from which DNA can be extracted will be stored and used until no further analyses are possible, a maximum storage period of 25 years from time of last subject last visit has been reached, or an individual or LAR withdraws his/her or their consent.

#### **11.2.8. Other Outcomes**

##### **11.2.8.1. Pharmacokinetic Data**

Formal plasma analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS)). In addition, all samples will be analyzed for important SAGE-547 metabolites (if and when these are identified) and Captisol® concentrations.

##### Plasma Analysis

Plasma will be collected to assay for SAGE-547 concentrations at the following time points relative to the start of each infusion of study drug:

- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion.
- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open label SAGE-547 study drug infusion.
- All samples will also be analyzed for plasma concentrations of important metabolites of SAGE-547 if and when these are identified.
- All samples will also be analyzed for plasma concentrations of Captisol®.

The plasma samples will be drawn from the arm contralateral to that used for drug administration. Drawing samples from peripheral arterial or venous lines or from a central line is permissible. PK collection times should be adhered to as strictly as possible. The allowed time window for all samples is: pre-dose in the two hours prior to starting the infusion of study drug; samples up to and including 1h, +/- 5 minutes; subsequent samples, +/- 15 minutes. Subject-specific PK kits for sampling including instructions on collection and processing methods, and storage and shipping conditions, will be provided separately. To maintain the blind, all subjects will have samples taken as outlined above: subjects receiving SAGE-547 will have all samples analyzed for all analytes.

Subjects on placebo may have samples analyzed to investigate endogenous allopregnanolone and metabolite concentrations, as well as Captisol® concentrations; experience with the plasma concentration data will determine if and which placebo samples are analyzed.

Each blood sample will be 3 ml in volume for adults and children weighing 30 kg or more, and 1 ml in volume for children weighing less than 30 kg. Separate aliquots will be obtained from each sample to service the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum blood draw for PK analysis for a subject having two infusions of study drug will be 99 ml (33 ml for children weighing less than 30 kg).

Plasma PK parameters for SAGE-547 will be calculated where appropriate (e.g.,  $C_{max}$ ,  $C_{min}$ ,  $t_{max}$ ,  $AUC_{last}$ ,  $AUC_{\infty}$ ,  $CL_s$ ). In addition, similar PK parameters will be calculated for Captisol®. PK parameters for important metabolites of SAGE-547 may be calculated. An evaluation will be made of the feasibility of adopting a population-PK approach to assess drug-drug-interactions with SAGE-547 as victim of AEDs.

In addition, the Visit 9 sample may be analyzed for plasma concentrations of third-line agents.

#### Other Analysis

If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations. The minimum volume of cerebrospinal fluid for analysis is 100 microlitres.

Full details of all pharmacokinetic analyses will be described in the Pharmacokinetic Analysis Plan.

#### **11.2.8.2. Correlation of QT/QTc Changes and Plasma Concentrations of SAGE-547**

An analysis will be performed to determine whether there is any correlation between changes in QT/QTc interval and plasma concentrations of SAGE-547, in order to investigate any effect that SAGE-547 may have on QT/QTc interval.

#### **11.2.8.3. Pharmacoeconomic Data**

At Visit 12 or Visit 12R, the following information will be collected: number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital. If the subject dies before Visit 12 or Visit 12R, data will be collected up to the date of death. The definition of “hospital” is the institution that the subject was initially treated in. If the subject is transferred to another hospital, that hospital would be the “discharge destination from the hospital” and the “number of days in hospital” would be the number of days in the initial treating hospital.

For those subjects discharged from hospital before Visit 12/12R, the following questions will be asked:

- On what study day was the subject discharged from hospital?
- What type of facility was the subject discharged to (another hospital, a rehabilitation center, a supported care facility, home, other)?
- How many days did the subject stay in this facility?

The following questions will be answered regarding the stay in the ICU and hospital:

- Was the subject still in the ICU at the end of Visit 10/10R?
- If the FOUR Score was  $\geq 12$  at Visit 10/10R and the subject was in the ICU at Visit 10/10R, what was the reason for the subject not being discharged from the ICU (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, other)?
- Was the subject still an in-patient in the hospital at the end of Visit 12/12R?
- If the FOUR Score was  $\geq 15$  at Visit 12/12R and the subject was in the hospital at Visit 12/12R, what was the reason for the subject not being discharged from the hospital (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, unsuitable home circumstances, other)?

#### **11.2.8.4. STESS**

The STESS will be assessed during Visit 1 in order to assess the severity of the status epilepticus.

#### **11.2.8.5. FOUR Score**

The Full Outline of UnResponsiveness or FOUR Score is designed to assess conscious level and unlike other scores, is suitable for subjects who are intubated. It assesses four domains of neurological function (eye responses, motor responses, brainstem reflexes, and breathing pattern).

The FOUR Score will be collected at the following time points relative to each infusion of study drug (the initial blinded infusion and the second open-label infusion if this is administered):

- baseline, +24, +48, +72, +96, +120, +144, +168, and +192 hours (all +/- 2 hours) after the start of the infusion, and at Visit 11/11R and Visit 12/12R.

#### **11.2.8.6. Glasgow Outcome Scale (GOS)**

The GOS is a relatively common assessment scale used to standardize descriptions of the objective degree of recovery from brain injury such as cerebral trauma, or in this case SRSE. It was first used in 1975 ([Jennett and Bond 1975](#)) and allows a prediction of the long-term course of rehabilitation to return to work and everyday life. The scale classifies subjects into 5 groups:

- Death
- Persistent vegetative state
- Severe disability
- Moderate disability
- Good recovery

The GOS will be assessed at Visit 12 or Visit 12R.

#### **11.2.8.7. Supervision Rating Scale (SRS)**

The Supervision Rating (SRS) measures the level of supervision that a patient/subject receives from caregivers. The SRS rates level of supervision on a 13-point ordinal scale that can optionally be grouped into five ranked categories (Independent, Overnight Supervision, Part-Time Supervision, Full-Time Indirect Supervision, and Full-Time Direct Supervision). The SRS was designed to be rated by a clinician based on interviews with the subject and an informant who has observed at first hand the level of supervision received by the subject ([Boake 2000](#)). Scoring is a one-step procedure



in which the clinician assigns the rating that is closest to the subject's level. Ratings are based on the level of supervision received, not on how much supervision a subject is judged or predicted to need.

The SRS will be assessed at Visit 1 and Visit 12 or Visit 12R. The Visit 1 assessment will be a retrospective assessment of the supervision required by the subject immediately prior to the admission that included the index episode of status epilepticus.

#### **11.2.8.8. Modified Rankin Scale – 9Q (mRS-9Q)**

The Modified Rankin Scale (mRS) is a commonly used scale to determine disability and functional dependence due to neurological insult such as stroke in adults. The 7-point scale (0 – 6) denotes functional capacity from no symptoms (0) to severe disability (5) and death (6). The Modified Rankin Scale – 9Q is a shortened version consisting of 9 questions that reliably determines the mRS score and was developed to both simplify the assessment and expand the rater base to non- medically trained personnel ([Patel, Rao et al. 2012](#)). The assessment is a web-based tool in the public domain with automatic score calculation and error checking found at [www.modifiedrankin.com](http://www.modifiedrankin.com).

The mRS will be assessed at Visit 1 and at Visit 12 or Visit 12R in subjects  $\geq 17$  years of age. The baseline assessment will be a retrospective assessment of the disability and dependence of the subject immediately prior to the admission that included the index episode of status epilepticus.

## 12. STUDY PROCEDURES

The study procedures listed below by study day reflect the required data collection times for this protocol. When a time window is necessary, this is specified below. If no time window is specified, the test may be performed at any time within the specified 24-hour period.

### 12.1. Visit 1 (V2-≤30h)

The baseline period will be up to approximately 84 hours prior to starting blinded study treatment and should include the assessments/procedures listed below and summarized in [Table 1 and Table 2 \(for retreatment\)](#), the Schedules of Events.

- Informed consent
- Eligibility checklist
- Verification of inclusion/exclusion criteria.
- Demographic information and medical history obtained by proxy and confirmed by the subject when possible.
- SE and wean history
- Blood will be collected from female subjects 10 years to 55 years for a serum pregnancy test unless they are known to be pre-menstrual or post-menopausal or to have had a hysterectomy.
- Blood and urine samples collected for clinical laboratory testing.
- Pharmacogenetic sample will be collected from consenting/eligible subjects.
- Vital signs
- Height
- Weight
- An ECG reading taken.
- Administration of the STESS.
- Administration of the FOUR Score.
- Administration of SRS.
- Administration of the mRS-9Q assessment.
- Assessment of the CGI scale.
- Evaluation of epilepsy status.
- Administration of continuous IV third-line agents.
- Perform EEG.
- Recording of adverse events.
- Recording of previous and concomitant anti-epileptic drugs.
- Recording of previous and concomitant third-line agents.
- Recording of concomitant pressors.

- Recording of other concomitant medications, procedures, and treatments.

## **12.2. Visit 2 (V3-≤54h)**

- Recording of adverse events.
- Recording of concomitant anti-epileptic drugs.
- Recording of concomitant third-line agents.
- Recording of concomitant pressors.
- Recording of other concomitant medications, procedures, and treatments.
- Wean of continuous third-line agent:
  - If wean is successful, subject is followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (these subjects are Qualifying Wean Success subjects or QWS subjects);
  - If wean is not successful, there is ongoing intravenous administration of at least one continuous IV third-line agent and EEG is performed and the subject is randomized.

## **12.3. SAGE-547 Treatment Period**

### **12.3.1. Visit 3/3R (0-24 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs will be recorded at:
  - 0, +30, +60 minutes (+/-15 minutes) and +2, +4, +8 (+/- 30 minutes) and +24 hours (+/- 2 hours) after the start of the infusion
- ECG readings will be recorded immediately after PK sampling at:
  - 0 (pre-dose) and at +0.5, +1, +3, +6, +12, and +24 hours after the start of the blinded study drug infusion.
- A blood sample for PK analysis should be collected at the following time points (all +/- 15 minutes except where otherwise stated):
  - 0 (pre-dose, within two hours of the start of the infusion) and at +0.5, +1 (+/- 5 minutes), +3, +6, +12, and +24 hours after the start of the blinded study drug infusion.
- Completion of the FOUR Score
  - +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the end of the 24 hour observation period following the QW)
- Ongoing intravenous administration of a continuous IV third-line agent.

- Study drug administration in loading (Hour 0-1) and maintenance infusions (at completion of Hour 1).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.3.2. Visit 4/4R (25-48 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +48 hours (+/- 2 hours) after the start of the infusion
- An ECG reading taken immediately after PK sampling:
  - +48 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +48 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +48 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent.
- Ongoing study drug maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.3.3. Visit 5/5R (49-72 hours)**

- Weight
- Vital signs should be recorded at:
  - +72 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +72 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +72 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +72 hours (+/- 2 hours) after the start of the infusion

- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.4. Visit 6/6R (73-96 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +96 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +96 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +96 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +96 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Perform EEG.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.5. Visit 7/7R (97-120 hours)**

- Weight
- Vital signs should be recorded at:
  - +120 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +120 hours after the start of the study drug infusion

- A blood sample for PK analysis should be collected:
  - +120 hours (+/- 15 minutes) after the start of study drug infusion, immediately prior to the end of the maintenance infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +120 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled. Complete wean by 120 hours if at all possible.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## **12.4. SAGE-547 Taper Period**

### **12.4.1. Visit 8/8R (121-144 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +144 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after each PK sampling:
  - +128, +136 hours and +144 hours after the start of the study drug infusion
  - During the open-label retreatment phase of the study ECG readings at: +126, +132, +138 hours and +144 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected (+/- 15 minutes unless otherwise stated):
  - +128 (immediately prior to the end of the first taper step), +136 hours (+/- 5 minutes, immediately prior to the end of the second taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of study drug infusion.
  - During the open-label retreatment phase of the study PK blood draws at: +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 hours (+/- 5 minutes, immediately prior to the end of the third taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of the study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +144 hours (+/- 2 hours) after the start of the infusion

- Complete wean of third line agents by H144 if not completed by H120.
- Perform EEG.
- Taper of SAGE-547 infusion begins at hour 121.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## **12.5. Follow-up Period**

### **12.5.1. Visit 9/9R (145-168 hours)**

- Vital signs should be recorded at:
  - +168 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +152, +160 hours (+/- 2 hours) after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +152 and +160 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +168 hours (+/- 2 hours) after the start of the infusion
- Perform EEG.
- Assessment of the presence of physiologic brain activity using EEG.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.5.2. Visit 10/10R (169-192 hours)**

- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +192 hours (+/- 2 hours) after the start of the infusion
- At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine eligibility for retreatment with the higher dose of study drug. This determination may occur at any point

during Visit 10: the retreatment infusion must begin within the Visit 10 window. All patients for retreatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.

- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.3. Visit 11/11R (Visit 3/3R + 14d (±2))**

- Blood samples collected for clinical laboratory testing (renal panel only).
- Completion of the FOUR Score (QWS subjects also).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.4. Visit 12/12R (Visit 3/3R + 21d (±2))**

All assessments also performed for QWS subjects.

- Completion of the FOUR Score.
- Administration of the GOS.
- Administration of the SRS.
- Administration of the mRS-9Q assessment.
- Evaluation of epilepsy status (see [Section 11.1.2.2](#) for details).
- Assessment of the CGI Scale.
- Recording of adverse events.
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications.
- Collection of pharmacoeconomic data.
- Mortality will be assessed throughout the study period.

## **13. STATISTICS**

### **13.1. Statistical Plan**

Complete details for the analysis and reporting of data from this study will be contained in the Statistical Analysis Plan (SAP).

#### **13.1.1. Interim Analysis**

When approximately 50% of subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment



will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### 13.1.2. Study Populations

The **Safety Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to actual treatment. This analysis population will be used for all safety analyses.

The **Intent to Treat Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to randomized treatment. This analysis population will be used for all efficacy analyses.

The **Modified Intent to Treat Population** is defined as all subjects who:

1. complete their initial course of blinded SAGE-547 or placebo treatment unless the non-completion was due a drug-related adverse event; and
2. have at least one attempt to wean from third-line agents prior to the end of blinded study treatment infusion unless the failure to wean was because seizures were not controlled.

Subjects will be classified according to randomized treatment. This analysis population will be used for sensitivity analyses of the primary endpoint and select secondary efficacy endpoints.

Narratives will be prepared for all subjects who do not complete the infusion of blinded study medication or were not subjected to any wean attempts. Narratives will include details of the cause of SE, the comorbid conditions, the adverse event(s), and reasons for non-completion of the infusion or failure to attempt weaning. This blinded narrative will be reviewed by the medical monitors and the patient adjudicated as MITT eligible or ineligible. Acceptable reasons for defining a subject as MITT ineligible include death or withdrawal of consent due to progression of the underlying cause of SE or comorbid conditions, unless the cause of death or progression of disease were thought by the investigator, sponsor, or DSMB to be related to study drug.

The **Per-Protocol (PP) Population** is defined as a subset of the MITT population but will exclude data from all subjects with significant protocol violations or deviations. Subjects will be classified according to actual treatment received. This data set will be used for sensitivity analyses to examine the robustness of results for the primary and key secondary efficacy endpoints.

The **Pharmacokinetics Population** is defined as all subjects who at least had an infusion of blinded SAGE-547 initiated and have at least one pharmacokinetic sample collected.

The **Pharmacogenetic Population** is defined all subjects who consent to being included in the pharmacogenetic assessment and provide a pharmacogenetic sample.

Summary statistics of all data collected will be presented for subjects who were QW successes.

### 13.1.3. General Aspects

Tabular displays of descriptive statistics will be provided for all variables. Summary tables will include n, mean, mean, standard deviation, minimum and maximum for continuous variable and frequency and percentage for categorical variables.

### **13.1.4. Analysis of Primary Endpoint**

The analysis of response to treatment (see Section 11.1.1 for definition of primary endpoint) between SAGE-547 treated subjects and placebo treated subjects will be performed on the ITT population using a Cochran-Mantel-Haenszel (CMH) test with variables for treatment, concomitant pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). The CMH general association statistic and its associated p-value will be presented. The comparison of treatment response rates will be conducted at the 5% level of significance. To confirm the CMH results, a permutation test will also be conducted.

An additional analysis of the primary endpoint will also be performed on the MITT population. In addition sensitivity analyses of the primary endpoint will be performed using the ITT population based on:

- the number of third-line agents (one, two, or three) subjects were administered post-randomization; and
- which third line agent was the subject of the first TW.

### **13.1.5. Analysis of Secondary Efficacy Endpoints**

Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section (Section 6). Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. The analysis of the secondary endpoints will also be performed on the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital/thiopental use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

### **13.1.6. Analysis of Other Endpoints**

Safety and “Other” endpoints will only be summarized by treatment group.

Summaries of safety endpoints will be based on the overall Safety Population.

### **13.1.7. Epilepsy and SRSE Status**

Diagnosis of epilepsy and recurrence of RSE or SRSE will be documented as the percentage of subjects by time point and overall. Kaplan-Meier curves may be plotted if sufficient data are available.

Utilization of AEDs during follow-up and during recurrence will be summarized.

### **13.1.8. Questionnaires**

The data collected from each questionnaire will be interpreted according to the standard methodology for that questionnaire. There will be no adjustment for missing values.

### **13.1.9. Pharmacokinetic Data Analysis**

Details of the pharmacokinetic data analysis will be described in detail in a separate Pharmacokinetic Analysis Plan.

### **13.1.10. Pharmacogenetic Data Analysis**

Any genotype data generated in this study will be stored within a secured database within Sage Therapeutics and / or a third party contracted to work with Sage Therapeutics to analyze the samples. Because the number of subjects agreeing to participate in the genetic research component of the study is unknown, it is not possible to establish, a priori, whether sufficient samples will be obtained to support formal statistical evaluation of data. As a consequence a Pharmacogenetic Analysis Plan will only be prepared where appropriate and the results obtained from any genetic research will be reported in a report separate from the main study CSR.

### **13.1.11. Retreated Subjects**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are retreated with SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo.

### **13.1.12. EEG-Responders**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who are classified as EEG-responders/non-responders based on the independent assessment of the PAEEG. Summaries will be derived for the two randomized treatment groups.

### **13.1.13. QT/QTc Assessment**

An analysis of the correlation between changes in QT/QTc intervals and SAGE-547 plasma levels will be performed to investigate if there is a potential effect that SAGE-547 may have on QT/QTc interval. A detailed description of the QT/QTc assessment will be included in the SAP.

### **13.1.14. Quantitative EEG**

The six EEG records for each subject may be subjected to exploratory quantitative EEG analysis, the details of which will be included in the EEG Analysis Plan. In summary the following comparisons may be made, SAGE-547 versus placebo: the QWEEG versus the TWEEG (main analysis); the CEEG versus PAEEG (subsidiary analysis); and TAEEG versus PAEEG (exploratory analysis).

## **13.2. Determination of Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between treatment groups at a 5% level of significance. Randomization will be stratified by concomitant

pentobarbital/thiopental use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

### **13.3. Statistical Analysis Plan**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

## 14. ADVERSE EVENTS

The safety procedures in this study will be detailed in a Safety Management Plan, which will be agreed and signed before the first subject is randomized in the study. [Section 14.1](#) summarizes Investigator responsibilities regarding the identification and documentation of AEs, the classification of AEs for relationship to study drug and severity, and the reporting of AE information to the Sponsor and the IRB.

[Section 14.2](#) summarizes Sponsor/Medical Monitor Responsibilities regarding monitoring of AE data and reporting relevant safety information to FDA.

[Section 14.3](#) lists important AE definitions.

### 14.1. Investigator Responsibilities

#### 14.1.1. Identification and Documentation of Adverse Events by Investigator

Subjects will be evaluated and questioned generally (if possible) to identify AEs during the course of the study. AEs will be collected from the signature of the consent form through Visit 12/12R. Adverse events that occur prior to completion of screening will be captured on the Medical History eCRF. Adverse events that occur after completion of screening will be recorded on the Adverse Event eCRF.

All AEs revealed by observation, other diagnostic procedures, or spontaneously reported by the subject and/or in response to an open question from study personnel will be recorded on the Adverse Event Form. Any clinically significant deterioration in laboratory assessments or other clinical findings are considered an AE and must be recorded on the Adverse Event Form, unless otherwise stated. AE information recorded will be entered into the database on an ongoing basis.

AEs with a relationship considered related to study drug (probable, possible) should be followed until the event is resolved or the Investigator determines the event is stable or no longer clinically significant. AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

For SAEs, an electronic Serious Adverse Event eCRF must be completed with as much information as possible and submitted in the time frame described below in [Section 14.1.3](#). When new significant information is obtained as well as when the outcome of an event is known, the electronic SAE eCRF should be updated within 24 hours. If the subject was an outpatient at the time of the SAE and was re-hospitalized due to the SAE, a copy of relevant hospital records (e.g., admission report, laboratory test results, discharge summary, etc.) may be requested to be included as part of the subject medical file.

All SAEs will be followed until resolved or until a stable status has been achieved.

**14.1.2. Adverse Event Classification****14.1.2.1. Relationship to Investigational Drug**

None:	No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state.
Possible:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject, but this is not known for sure.
Probable:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

**14.1.2.2. Severity**

Mild	Discomfort noticed, but no disruption to daily activity.  For subjects that are unconscious, this may be a slight or minor change in a lab result or clinical sign or symptom that does not require immediate corrective action.
Moderate	Discomfort sufficient to reduce or affect normal daily activity, but is not hazardous to health; prescription drug therapy may be employed to treat the AE.  For subjects that are unconscious, this may be a clinically meaningful change that may require immediate corrective action.
Severe	Inability to work or perform normal daily activity and represented a definite hazard to health; prescription drug therapy and/or hospitalization may be employed to treat the AE.  For unconscious subjects, this may be a significant clinical change that requires immediate corrective action.

**14.1.2.3. Action Taken with Investigational Drug**

None	Study medication was continued without change.
Discontinued	Study medication was terminated.
Dose adjusted	Study medication dose/infusion rate was changed and then continued per protocol.
Interrupted	Study medication was interrupted and then continued per protocol.
Unknown	The action taken with regard to study medication is unknown.
Not applicable	Administration of study medication was not ongoing.

**14.1.2.4. Assessment of Outcome**

Ongoing	At the end of the study, the event has not resolved or stabilized.
Ongoing and stable	The event is ongoing but has stabilized and is unlikely to change
Resolved	The event has resolved or the subject recovered without sequelae.
Resolved with sequelae	The event has at least one secondary outcome that may result in permanent disability and/or functional limitation.
Unknown	The status of the event is unknown.
Death	The subject has expired.

**14.1.3. Investigator Reporting to Sponsor and Sponsor Emergency Contact**

All new SAEs that come to the Investigator and/or Sponsor's notice during the course of the study (up to and including the last study visit) must be reported by the Investigator on the designated electronic report form within 24 hours of the point in time when the Investigator becomes aware of the SAE. As additional information becomes available, the designated electronic report form must be updated within 24 hours.

Investigators must report any SAE, whether or not considered drug related. The report must include an assessment of whether there is a reasonable possibility that the drug caused the event.

In a medical emergency (ie, an event that requires immediate attention regarding the treatment of a subject, operation of the clinical study, and/or the use of investigational drug), study site staff will apply appropriate medical intervention according to current standards of care, and contact the Medical Monitor.

**14.1.4. Medical Monitor and Emergency Contact Information**

[REDACTED], MD  
[REDACTED]

**14.1.5. SAE Reporting Contact Information**

Contact information and reporting instructions are provided in the Safety Management Plan.

**14.1.6. Reporting to Institutional Review Boards (IRBs)**

It is the responsibility of the Investigator to promptly notify the institution's IRB of all serious and unexpected suspected adverse reactions (see [Section 14.3](#) for definitions).

## **14.2. Sponsor/Medical Monitor Responsibilities**

### **14.2.1. Monitoring of Adverse Event Data**

The Medical Monitor will review any newly reported adverse events in an ongoing basis. If the aggregate assessment indicates that an event is occurring more frequently than would normally be expected in this population, or as previously observed, and the sponsor believes that the events are causally related to the administration of SAGE-547, the Sponsor will then report that information in an IND safety report.

### **14.2.2. Data Safety Monitoring Board**

An independent DSMB will monitor the clinical, PK and PD data for safety signals throughout the study and will be asked to assess the placebo response rate at the time of the interim analysis to determine final sample size. In order to perform their monitoring function the DSMB will have access to un-blinded safety data as necessary.

The composition and procedures for the board will be described in a separate DSMB Charter.

### **14.2.3. Reporting to FDA**

The Sponsor must report in an IND safety report any suspected adverse reaction to study treatment that is both serious and unexpected (21 CFR 312.32(c)(1)(i)). Before submitting an IND safety report, the Sponsor will ensure the event meets all three of the definitions: (1) suspected adverse reaction, (2) serious, (3) unexpected. If the AE does not meet all three of the definitions, it should not be submitted as an IND safety report. The Sponsor should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the adverse event and, therefore, that the event meets the definition of a suspected adverse reaction.

If there is a serious and unexpected suspected adverse reaction, the Sponsor will notify the appropriate regulatory agency(ies) and all appropriate parties on an expedited basis. In addition, Sponsors must submit expedited reports of an increased rate of occurrence or severity of serious suspected adverse reactions over that listed in the protocol or Investigational Brochure.

SUSARs will be unblinded prior to reporting to FDA. Unless it is necessary to unblind for the safety of the patient, the investigator will not be informed of the unblinding of the subject.

Under 21 CFR 312.32, Sponsors should identify in the protocol SAEs that it does not plan to report individually in an expedited manner, because they are known consequences of the disease or otherwise common in the study population. Given the grave condition and prognosis of SRSE being studied, individual occurrences of seizures or seizure activity will not be reported expeditiously in this study. Regardless of which events are reported in an expedited manner, all adverse events will be closely monitored throughout the study.

## **14.3. Adverse Event Definitions**

### **14.3.1. Adverse Event**

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.



### **14.3.2. Suspected Adverse Reaction**

Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

### **14.3.3. Life-Threatening**

An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

### **14.3.4. Serious**

An AE or suspected adverse reaction is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE – see definition above
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disability
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

### **14.3.5. Unexpected**

An AE or suspected adverse reaction is considered “unexpected”:

- If it is not listed in the Investigational Brochure or is not listed at the specificity or severity that has been observed, or
- If an Investigational Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigational Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigational Brochure listed only cerebral vascular accidents.

“Unexpected,” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigational Brochure as occurring with a class of drugs or as anticipated from

the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

#### **14.4. Emergency Identification of Study Medication**

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject's treatment in the study via the IVRS; this normally requires prior approval by the medical monitor. However, if the subject is at immediate risk and the Investigator believes that immediate knowledge of the study treatment will alter medical management, discussion with the medical monitor may take place after unblinding. The Investigator will not unblind the medical monitor during that discussion. The process of unblinding will ensure that only the investigator is unblinded; the medical monitor, study management team, and data management team will not be made aware of the treatment allocation of an individual subject. All cases of emergency unblinding will be fully documented in a way that does not unblind the medical monitor, study management team, and data management team.

### **15. STUDY ADMINISTRATIVE CONSIDERATIONS**

#### **15.1. Quality Control and Quality Assurance**

The Investigators and institutions will permit trial related monitoring, audits, IRB review, and regulatory inspections as requested by FDA, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed informed consent forms, etc.) in addition to case report forms.

Quality assurance and quality control systems with written standard operating procedures (SOPs) will be followed to ensure this trial will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The site's dedicated study monitor will arrange to visit the Investigator at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be identified and resolved. The study monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality assurance officers named by Sage Therapeutics or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements, made by the Sponsor with the Investigator/institution and any other parties involved with the clinical trial, will be in writing in a separate agreement.

## **15.2. Data Handling and Recordkeeping**

### **15.2.1. Data Handling**

Procedures for data handling (including electronic data) used in this protocol will be documented in a Data Management Plan.

### **15.2.2. Case Report Form Completion**

eCRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of demographics, study drug administration, study procedures, AEs, questionnaire completion, efficacy assessments and subject status, including survival.

The Investigator will maintain copies of the eCRFs at the study site. For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate eCRF.

### **15.2.3. Retention of Study Records**

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval and until there are no pending or contemplated marketing applications or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to an appropriate person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

## **15.3. Confidentiality**

To maintain subject privacy, all eCRFs, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available trial registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by Sage Therapeutics to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

#### **15.4. Publication Policy**

All information concerning SAGE-547 is considered confidential and shall remain the sole property of Sage Therapeutics. The Investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval from Sage Therapeutics. No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between Sage Therapeutics and the Investigator.

#### **15.5. Protocol Amendments**

Changes to the conduct of the study should be prepared as a protocol amendment by the Sponsor. Protocol amendments should receive written IRB/IEC approval prior to implementation at the investigative site, except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the trial (eg, change of monitor, telephone numbers). In this case, Sage Therapeutics will amend and implement the protocol change and subsequently notify the regulatory authorities and the Investigative sites who will notify the respective IRB, as appropriate.

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**APPENDIX 1. APPENDIX 1: FOUR SCORE****FOUR score****Full Outline of UnResponsiveness****Eye response**

- E4: eyelids open or opened, tracking, or blinking to command
- E3: eyelids open but not tracking
- E2: eyelids closed but open to loud voice
- E1: eyelids closed but open to pain
- E0: eyelids remain closed with pain

**Motor response**

- M4: thumbs-up, fist or peace sign
- M3: localizing to pain
- M2: flexion response to pain
- M1: extension response to pain
- M0: no response to pain or generalized myoclonus status

**Brainstem reflexes**

- B4: pupil and corneal reflexes present
- B3: one pupil wide and fixed
- B2: pupil or corneal reflexes absent
- B1: pupil and corneal reflexes absent
- B0: absent pupil, corneal and cough reflex

**Respiration pattern**

- R4: not intubated, regular breathing pattern
- R3: not intubated, Cheyne-Stokes breathing pattern
- R2: not intubated, irregular breathing
- R1: breathes above ventilatory rate
- R0: breathes at ventilator rate or apnea

Reference ([Iyer, Hoel et al. 2009](#)).

**APPENDIX 2. GLASGOW OUTCOME SCALE (GOS)****GLASGOW  
OUTCOME  
SCALE**

Patient Name: \_\_\_\_\_  
 Rater Name: \_\_\_\_\_  
 Date: \_\_\_\_\_

*Note:* The scale presented here is based on the original article by Jennett and Bond. It has become common practice in clinical trial administration, however, to use a modified version that places the scores in reverse order (i.e., "good recovery" = 1, "moderate disability" =2, etc.).

Score	Description
1	DEATH
2	PERSISTENT VEGETATIVE STATE Patient exhibits no <i>obvious cortical</i> function.
3	SEVERE DISABILITY (Conscious but disabled). Patient depends upon others for daily support due to mental or physical disability or both.
4	MODERATE DISABILITY (Disabled but independent). Patient is independent as far as daily life is concerned. The disabilities found include varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes.
5	GOOD RECOVERY Resumption of normal activities even though there may be minor neurological or psychological deficits.

**TOTAL (1-5):** \_\_\_\_\_

Reference ([Jennett and Bond 1975](#)).



## APPENDIX 3. SUPERVISION RATING SCALE (SRS)

### SUPERVISION RATING SCALE (SRS)

**Instructions:** Circle the rating that is closest to the amount of supervision that the patient *actually receives*. "Supervision" means that someone is responsible for being with the patient.

<u>Rating</u>	<u>Description</u>
<b>Level 1: INDEPENDENT</b>	
1	The patient lives alone or independently. Other persons can live with the patient, but they cannot take responsibility for supervision (for example, a child or elderly person).
2	The patient is unsupervised overnight. The patient lives with one or more persons who <i>could</i> be responsible for supervision (for example, a spouse or roommate), but they are <i>all</i> sometimes absent overnight.
<b>Level 2: OVERNIGHT SUPERVISION</b>	
3	The patient is only supervised overnight. One or more supervising persons are always present overnight but they are <i>all</i> sometimes absent for the rest of the day.
<b>Level 3: PART-TIME SUPERVISION</b>	
4	The patient is supervised overnight and part-time during waking hours, but is allowed on independent outings. One or more supervising persons are always present overnight and are also present during part of waking hours every day. However, the patient is sometimes allowed to leave the residence without being accompanied by someone who is responsible for supervision.
5	The patient is supervised overnight and part-time during waking hours, but is unsupervised during working hours. Supervising persons are <i>all</i> sometimes absent for enough time for them to work full-time outside the home.
6	The patient is supervised overnight and during most waking hours. Supervising persons are <i>all</i> sometimes absent for periods longer than one hour, but less than the time needed to hold a full-time job away from home.
7	The patient is supervised overnight and during almost all waking hours. Supervising persons are <i>all</i> sometimes absent for periods shorter than one hour.
<b>Level 4: FULL-TIME INDIRECT SUPERVISION</b>	
8	The patient is under full-time indirect supervision. At least one supervising person is <i>always</i> present, but the supervising person does not check on the patient more than once every 30 minutes.
9	Same as #8 plus requires overnight safety precautions (for example, a deadbolt on outside door).
<b>Level 5: FULL-TIME DIRECT SUPERVISION</b>	
10	The patient is under full-time direct supervision. At least one supervising person is always present and the supervising person checks on the patient more than once every thirty minutes.
11	The patient lives in a setting in which the exits are physically controlled by others (for example, a locked ward).
12	Same as #11 plus a supervising person is designated to provide full-time line-of-sight supervision (for example, an escape watch or suicide watch).
13	The patient is in physical restraints.

3/12/93

Corwin Boake, Ph.D., TIRR, 1333 Moursund, Houston, TX 77030-3405, 713/799-6990

## APPENDIX 4. MODIFIED RANKIN SCALE – LEVEL OF FUNCTION SURVEY (mRS-9Q)

1. Do you have any symptoms that are bothering you? (For example, trouble with reading or writing, trouble speaking, problems with vision, numbness, weakness, balance trouble, or problems with swallowing?)	YES <input type="radio"/>	NO <input type="radio"/>
2. Are you able to do the same work as before?	YES <input type="radio"/>	NO <input type="radio"/>
3. Are you able to keep up with your hobbies?	YES <input type="radio"/>	NO <input type="radio"/>
4. Have you maintained your ties to friends and family?	YES <input type="radio"/>	NO <input type="radio"/>
5. Do you need help making a simple meal, doing household chores, or balancing a checkbook?	YES <input type="radio"/>	NO <input type="radio"/>
6. Do you need help with shopping or traveling close to home?	YES <input type="radio"/>	NO <input type="radio"/>
7. Do you need another person to help you walk?	YES <input type="radio"/>	NO <input type="radio"/>
8. Do you need help with eating, going to the toilet, or bathing?	YES <input type="radio"/>	NO <input type="radio"/>
9. Do you stay in bed most of the day and need constant nursing care?	YES <input type="radio"/>	NO <input type="radio"/>

## APPENDIX 5. CLINICAL GLOBAL IMPRESSION (CGI)

### Clinical Global Impression (CGI)

#### 1. Severity of illness

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- |                             |   |
|-----------------------------|---|
| 0 = Not assessed            | 4 = Moderately ill                        |
| 1 = Normal, not at all ill  | 5 = Markedly ill                          |
| 2 = Borderline mentally ill | 6 = Severely ill                          |
| 3 = Mildly ill              | 7 = Among the most extremely ill patients |

#### 2. Global improvement: Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.

Compared to his condition at admission to the project, how much has he changed?

- |                        |                     |
|------------------------|---------------------|
| 0 = Not assessed       | 4 = No change       |
| 1 = Very much improved | 5 = Minimally worse |
| 2 = Much improved      | 6 = Much worse      |
| 3 = Minimally improved | 7 = Very much worse |

#### 3. Efficacy index: Rate this item on the basis of drug effect only.

Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.

EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

#### Therapeutic effect

#### Side effects

		None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
<b>Marked</b>	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
<b>Moderate</b>	Decided improvement. Partial remission of symptoms	05	06	07	08
<b>Minimal</b>	Slight improvement which doesn't alter status of care of patient	09	10	11	12
<b>Unchanged or worse</b>		13	14	15	16

Not assessed = 00

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

**APPENDIX 6. STATUS EPILEPTICUS SEVERITY SCORE (STESS)**

Outcome Predictor	Feature	Score
Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type (prior to first treatment)	Simple-partial, complex-parial, absence, myoclonic (complicating idiopathic generalized epilepsy)	0
	Generalized-convulsive	1
	Nonconvulsive status epilepticus in coma	2
Age	< 65 years	0
	≥ 65 years	2
History of previous seizures	Yes	0
	No or unknown	1
Summed Total		

**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY  
TO EVALUATE THE EFFICACY AND SAFETY OF SAGE-547 INJECTION  
IN THE TREATMENT OF SUBJECTS WITH SUPER-REFRACTORY  
STATUS EPILEPTICUS**

**PROTOCOL NUMBER: 547-SSE-301**

**IND NUMBER: 117901**

**EudraCT Number: 2015-002142-31**

Product: SAGE-547 Injection (allopregnanolone)

Sponsor Contact: [REDACTED], MD

[REDACTED]  
Sage Therapeutics  
215 First Street  
Cambridge, MA 02142

Medical Monitor: [REDACTED], MD

Date of Protocol: 09 March 2015

Date of Amendment One 27 May 2015

Date of Amendment One 02 Dec 2015

(Italy Specific)

**Confidentiality Statement**

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

**PROTOCOL NUMBER: 547-SSE-301**

Sponsor [REDACTED]:

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]:

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

CRO [REDACTED]:

[REDACTED]

## 1. SIGNATURE PAGE

Title of Protocol:

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus

Protocol No: 547-SSE-301

### Sponsor Approval

[Redacted Signature]

[Redacted Name] MD

Sage Therapeutics

02 DEC 2015

Date (dd/mmm/yyyy)

### Investigator Agreement

By signing this page I attest that I have read and understand the contents of Clinical Protocol 547-SSE-301 and any current amendments. I agree to adhere to the design, conduct, and reporting requirements of the study as stated in the clinical protocol and to my obligations to the Sponsor as described in the protocol and executed contracts between myself, my Institution, and the Sponsor. I also agree to adhere to any subsequent amendments to the clinical protocol.

Investigator's Signature: \_\_\_\_\_

Investigator's Name: \_\_\_\_\_

Institution: \_\_\_\_\_

Date: \_\_\_\_\_

## 2. SYNOPSIS

<b>Name of Sponsor:</b> Sage Therapeutics 215 First Street Cambridge, MA 02142		
<b>Protocol No.</b> 547-SSE-301		<b>Phase:</b> 3
<b>Name of Investigational Product:</b> SAGE-547 Injection		
<b>Name of Active Ingredient:</b> Allopregnanolone		
<b>Title of the Protocol:</b> A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus		
<b>Dosing Regimen: SAGE-547 or Placebo Dosing Schedule</b>		
<b>Hour</b>	<b>Type and Duration of SAGE-547 Infusions</b>	<b>Dose</b>
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	90 µg/kg/h
H121 – H128	8 hour taper	65 µg/kg/h
H129 – H136	8 hour taper	45 µg/kg/h
H137 – H144	8 hour taper	25 µg/kg/h
<b>Dosing Regimen: SAGE-547 Open Label Dosing Schedule</b>		
<b>Hour</b>	<b>Type and Duration of SAGE-547 Infusion</b>	<b>Dose</b>
H1	One hour loading infusion	300 µg/kg/h
H2 –H120	119 hour maintenance infusion	150 µg/kg/h
H121 – H126	6 hour taper	125 µg/kg/h
H127 – H132	6 hour taper	95 µg/kg/h
H133 – H138	6 hour taper	65 µg/kg/h
H139 – H144	6 hour taper	35 µg/kg/h
<b>Study Sites</b> Up to 150 sites in the USA, Europe, and Canada.		



**Number of Subjects**

The study will randomize 140 subjects at up to 150 sites.

**Study Population**

Subjects will be aged two years or more, in SRSE<sup>1</sup> (as defined in the Inclusion Criteria [Section 8.1](#)), and being managed in an intensive care setting. Pediatric patients (those < 14 years of age) will be managed in a pediatric intensive care setting.

**Duration of Subject Involvement**

Individual subject participation will be up to 30 days.

**Study Design**

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

Patients will follow one of three paths to entry to the study. The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst suppression with a third-line agent. These subjects will be consented for the study after admission to the intensive care unit, but before any third-line agents are administered for burst suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their legally authorized representative (LAR). Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours. Once burst suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of study drug.

The second path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst suppression pattern on the EEG. These subjects may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in

<sup>1</sup> In this study, the term Super-Refractory Status Epilepticus or SRSE is equivalent to “Refractory Status Epilepticus (RSE) that has failed standard treatment” and the two terms are used interchangeably.

EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of study drug.

The third path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These subjects may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 treatment or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within six hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo).

The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that subjects, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as both the ability to wean the subject off all third-line agents before the end of the infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication infusion, and concurrent signs of physiologic brain activity as determined by EEG. Details of the assessments and time points are provided in the schedule of assessments ([Table 1 and Error! Not a valid result for table.](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo will all subsequently be eligible to be administered SAGE-547 at the higher dose.

## Visit Schedule

The visit schedule and an overview of events at each visit is provided in [Table 1](#), **Error! Not a valid result for table.** and [Table 3](#) Schedule of Assessments.

## Study Objectives

### *Primary objective:*

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult and pediatric subjects with SRSE, and for the response to endure at least 24 hours after the end of the SAGE-547 or placebo infusion (primary response).

### *Secondary objectives:*

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in the Clinical Global Impression scale (CGI) between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### *Safety objectives:*

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

**Other objectives:**

1. To evaluate the impact of retreatment with a higher dose SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;
6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS) (age  $\geq 17$  years).

**Endpoints****Primary endpoint:**

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

**Secondary endpoints:**

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

**Safety endpoints:**

1. Adverse events and medications;

2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.

***Other endpoints:***

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who fail to respond to their randomized double blind treatment and are retreated with a higher dose of SAGE-547.
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS) (age  $\geq 17$  years).

**Inclusion Criteria**

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects two (2) years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst suppression pattern; or who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst suppression pattern.

**Exclusion Criteria**

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.

2. Subjects with a known allergy to progesterone or allopregnanolone or any excipients in SAGE-547.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy.
4. Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing underlying neurological disorder.
5. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis for whatever reason, but dialysis is not planned or non-continuous dialysis is planned (that would not adequately remove Captisol<sup>®</sup>);
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the opinion of the investigator, of less than 30 days;
  - e. a do not resuscitate (DNR) order.
6. Subjects who are being administered more than three third-line agents concomitantly or in whom the qualifying wean cannot be completed within 24 hours, or who are being administered a third-line agent for other indications such as management of raised intra-cranial pressure that would preclude weaning according to this protocol.
7. Subjects with a living will that does not allow heroic measures.
8. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
9. Subjects who have been enrolled in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not withdraw or complete and then re-enroll).

### Pharmacogenetic Research

In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### Statistical Analysis

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

### Interim Analysis

When approximately 50% of the subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made

to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### **Analysis of Primary Endpoint**

The analysis of response to treatment between SAGE-547 treated subjects and placebo treated subjects will be performed using a Cochran-Mantel-Haenszel test with variables for treatment, concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). In this analysis, a treatment responder is a subject who is successfully weaned off all third-line agents and blinded study medication prior to the end of study treatment infusion and remains off third-line agents for at least 24 hours following cessation of the blinded study medication, and who has concurrent signs of physiologic brain activity as determined by EEG. The analysis will be based on the ITT Population. The comparison of treatment response rates will be conducted at the 5% level of significance.

### **Analysis of Secondary Efficacy Endpoints**

The primary analysis will be repeated for the MITT population. Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section. Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. Secondary analyses will be repeated for the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from Baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third-line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

Summaries of safety endpoints will be based on the overall Safety Population which is defined as all subjects who at least initiated the infusion with blinded study treatment.

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are retreated with SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo. Summary statistics will be presented for subjects who were QW successes.

### **Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

**Table 1: Schedule of Assessments for Protocol 547-SSE-301: One Infusion of Study Drug (blinded)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical/SE/Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X		X	X	X	X	X	X				
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X		X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X		X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X		X	X		X		X		X		
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X			
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>o</sup>											X
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV 3rd-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>p</sup>				
EEG	X	X				X		X	X			
Randomization		X										
Study Drug Administration <sup>q</sup>			X	X	X	X	X	X				
TW Outcome & Retreat Decision										X <sup>r</sup>		
Physiologic Brain Activity									X			
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X



**Table 2: Schedule of Assessments for Protocol 547-SSE-301: Two Infusions of Study Drug (one blinded, one open-label)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V3R
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	0-24h
Eligibility Checklist	X										S
Informed Consent <sup>a</sup>	X										E
Inclusion/Exclusion Criteria	X										E
Demography <sup>b</sup>	X										
Medical and SE and Wean History <sup>c</sup>	X										T
Height	X										A
Weight <sup>d</sup>	X		X	X	X	X	X	X			B
Serum Pregnancy Test <sup>e</sup>	X										L
Hematology <sup>f</sup>	X		X	X		X		X		X <sup>g</sup>	E
Serum Chemistry and GFR	X		X	X		X		X		X	
Urinalysis <sup>h</sup>	X		X	X		X		X		X	E
Pharmacogenetic sample	X										X
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X	T
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X	E
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X		N
STESS	X										I
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	O
Glasgow Outcome Score (GOS)											N
Supervision Rating Scale (SRS)	X <sup>o</sup>										
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>										
Epilepsy Status	X										N
Clinical Global Impression (CGI)	X										E
Continuous IV Third-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>p</sup>			X
EEG	X	X				X		X	X		T
Randomization		X									
Study Drug Administration <sup>q</sup>			X	X	X	X	X	X			
TW Outcome and Retreat Decision										X <sup>r</sup>	P
Physiologic Brain Activity									X		
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	A
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	G
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	E
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X	
Pharmacoeconomic Data											
Mortality											

Table 2 continued

	V3R	V4R	V5R	V6R	V7R	V8R	V9R	V10R	V11R	V12R
	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3R+14d (±2d)	V3R+21d (±2d)
Weight <sup>d</sup>	X	X	X	X	X	X				
Serum Pregnancy Test <sup>e</sup>										
Hematology <sup>f</sup>	X	X		X		X		X <sup>g</sup>		
Serum Chemistry and GFR	X	X		X		X		X	X	
Urinalysis <sup>h</sup>	X	X		X		X		X		
Vital Signs <sup>i</sup>	X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>	X	X	X	X	X	X	X			
STESS										
FOUR Score <sup>m</sup>	X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)										X
Supervision Rating Scale (SRS)										X
Modified Rankin Score (mRS) <sup>n</sup>										X
Epilepsy Status										X
Clinical Global Impression Scale (CGI)										X
Continuous IV Third-Line Agent(s)	X	X	Wean	Wean	Wean	Wean <sup>p</sup>				
EEG			X			X	X			
Randomization										
Study Drug Administration <sup>q</sup>	X	X	X	X	X	X				
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data										X
Mortality										X

**Table 3: Schedule of Assessments for Protocol 547-SSE-301: Qualifying Wean Successes**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical and SE and Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X											
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X											
Serum Chemistry and GFR <sup>f</sup>	X											
Urinalysis <sup>h</sup>	X											
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X											
ECG <sup>j</sup>	X											
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>o</sup>											X
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV Third-Line Agent(s)	X	Wean										
EEG	X	X										
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

<sup>a</sup> Written informed consent by proxy (LAR) will be obtained prior to starting any study-related procedures not considered standard of care.

<sup>b</sup> Demographic information will be obtained by proxy and confirmed by the subject when possible.

<sup>c</sup> Medical history will be obtained by proxy and confirmed by the subject when possible. All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Dosing changes with the third-line agent(s) that constitute a wean attempt will be marked as such on the CRF, and the start/stop dates and times of all wean attempts prior to V3 will be recorded, as well as the outcome of the wean attempt.

- <sup>d</sup> Weight will be collected at Screening (V1) and once during each 24 hour period of the initial study drug infusion period (V3-V8) and second infusion period (V3R-V8R, if applicable). Daily weight will be used to determine the appropriate infusion rate of each dose.
- <sup>e</sup> Serum pregnancy test for females aged 10 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy. .
- <sup>f</sup> Blood samples will be taken for hematology and serum chemistry and GFR calculation at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will document whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.
- <sup>g</sup> Blood samples will be taken at V11 or V11R for serum chemistry (renal panel only).
- <sup>h</sup> Urine samples will be taken for urinalysis and NAG at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will add a comment about whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.
- <sup>i</sup> Vital signs will be recorded at the following time points relative to the start of each infusion of study drug: Screening (V1), at 0, 30, 60 minutes ( $\pm 15$  minutes), at 2, 4, and 8 hours ( $\pm 30$  minutes), and at 24, 48, 72, 96, 120, 144, 168, and 192 hours ( $\pm 2$  hours).
- <sup>j</sup> ECG (12-lead) should be performed at Screening (V1) and at the following times relative to the start of study drug infusion. For the blinded (first) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 128, 136, 144, 152, 160, and 192 hours ( $\pm 2$  hours). For the open label SAGE-547 (second) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 126, 132, 138, 144, 152, 160, and 192 hours ( $\pm 2$  hours). Heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours.
- <sup>k</sup> Plasma will be collected to assay for study drug concentrations at the following time points relative to the start of each infusion of study drug: For the blinded (first) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion. For the open label SAGE-547 (second) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open label SAGE-547 study drug infusion. Pre-dose samples may be taken within two hours before starting the infusion of study drug; timepoints up to and including 1h will have a time window of  $\pm 5$  minutes; all other timepoints will have a window of  $\pm 15$  minutes.
- <sup>m</sup> FOUR Score assessments will be performed at Screening (V1), 24, 48, 72, 96, 120, 144, 168, and 192 hours (all  $\pm 2$  hours) relative to the start of each infusion of study drug, and at V11 or V11R, and at V12 or V12R.
- <sup>n</sup> Modified Rankin Score (mRS) applicable for subjects  $\geq 17$  years old only.
- <sup>o</sup> SRS at V1 will be a retrospective assessment of the supervision required by the subject immediately prior to admission that includes the index episode of the SE, and mRS at V1 will be a retrospective assessment of the disability and dependence of the subject immediately prior to admission that includes the index episode of the SE.
- <sup>p</sup> Target for complete wean of all continuous IV third-line agents by 144 hours at V8/V8R if not completed by 120 hours at V7/V7R.
- <sup>q</sup> Study drug infusion is intended for IV administration only with a dedicated peripheral IV line using Sage-approved IV administration bags and lines.
- <sup>r</sup> At V10 only a decision to re-treat at a higher dose of SAGE-547 will be made by the Investigator if the continuous IV third-line agent wean has failed or the third-line agent requires re-introduction during V9. Subjects who become eligible for re-treatment at a higher dose of SAGE-547 will discontinue the planned visit schedule at V10, then repeat V3 (V3R) and all applicable subsequent visits.
- <sup>s</sup> AEs will be collected from the time Informed Consent is obtained and prior to the start of study-specific screening procedures not considered standard of care. Collection of AEs will continue throughout the study from V1 through V12 or V12R.
- <sup>t</sup> Subjects may enter the study on AEDs and be administered AEDs during the study. All Concomitant AEDs must be recorded on the CRF with details including date and time of starting/stopping each AED, the route of administration, changes in doses, and frequency of administration. Details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the CRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.
- <sup>u</sup> All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Details will include the name of the drug, the start/stop dates and times, and, after consent, the doses with start/stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

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**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
AE	adverse event
AED	anti-epileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the time-concentration curve
AW	additional weans
BDZ	benzodiazepine
BIEEG	blinded infusion electroencephalogram
BUN	blood urea nitrogen
CBC	complete blood count
CEEG	consent electroencephalogram
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
C <sub>max</sub>	maximum plasma concentration
C <sub>min</sub>	minimum plasma concentration
CNS	central nervous system
CRF	case report form
CSR	clinical study report
CYP2C9	cytochrome P450 enzyme involved in drug metabolism
DNR	do not resuscitate
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EEG	electroencephalogram
EIND	Emergency Use Investigational New Drug Application
EP	European Pharmacopeia
ESETT	Established Status Epilepticus Treatment Trial
FDA	Food and Drug Administration
FOUR	Full Outline of UnResponsiveness
GABA	$\gamma$ -aminobutyric acid
GABA <sub>A</sub>	$\gamma$ -aminobutyric acid-gated chloride channel

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GOS	Glasgow Outcome Scale
H	hour
HPLC	high performance liquid chromatography
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent to Treat
IV	intravenous
IVRS	Interactive Voice Randomization System
LAR	legally authorized representative
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent to Treat
mRS-9Q	Modified Rankin Score - 9Q
MS/MS	tandem mass spectrometry
nM	nanomolar
NMDA	n-methyl-D-aspartic acid
OW	other weans
PAEEG	primary endpoint electroencephalogram
PD	pharmacodynamics
PK	pharmacokinetic
QOL	quality of life
QW	qualifying wean
QWEEG	qualifying wean electroencephalogram
RBC	red blood cell

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
RSE	refractory status epilepticus
SAE	serious adverse event
SAP	Statistical Analysis Plan
SE	status epilepticus
SOP	standard operating procedure
SRS	Severity Rating Scale
SRSE	Super-refractory status epilepticus
SSRI	Selective serotonin re-uptake inhibitors
STESS	Status Epilepticus Severity Score
SUSAR	Suspected Unexpected Serious Adverse Reactions
SWFI	Sterile Water for Injection
TAEED	taper electroencephalogram
T <sub>max</sub>	time at maximum plasma concentration
TW	terminal wean
TWEEG	terminal wean electroencephalogram
US	United States
USP	United States Pharmacopeia

### 3. INTRODUCTION AND RATIONALE

#### 3.1. Status Epilepticus

Status epilepticus (SE) is a life-threatening seizure condition in which the brain is in a state of persistent seizure triggered by neuronal hyperexcitability. The Neurocritical Care Society defines SE as one continuous unremitting seizure lasting longer than five minutes or recurrent seizures without regaining consciousness between seizures for greater than five minutes (Brophy, Bell et al. 2012). Common causes of SE include preexisting epilepsy, cerebrovascular disease (in adults), electrolyte and metabolic disturbances, anoxia, encephalopathies, head trauma, high fever (in children, especially in the first year of life) and drug or substance intoxication. SE is associated with substantial morbidity and mortality.

##### 3.1.1. Epidemiology of SE

Geography, sex, age, and race influence the epidemiology of SE, whose incidence has a bimodal distribution, peaking in infants/young children and the elderly (Hauser 1990; DeLorenzo, Pellock et al. 1995; Wu, Shek et al. 2002). The incidence of SE in the elderly population is at least twice that in the general population. Concurrent medical conditions often exist in the elderly population, which can complicate therapy and worsen the prognosis of SE (Chapman, Smith et al. 2001).

The annual incidence of SE in the US is generally quoted to be within the range of 18/100,000 to 61/100,000, based on a 19-year retrospective study in Rochester, Minnesota (Hesdorffer, Logroscino et al. 1998) and a 2-year prospective study in Richmond, Virginia (DeLorenzo, Pellock et al. 1995), respectively. Two studies from Europe give annual incidences of a similar magnitude, ranging between 9.9/100,000 and 15.8/100,000 (Coeytaux, Jallon et al. 2000; Knake, Rosenow et al. 2001). It is thus estimated that in the United States each year there are as many as 150,000 cases of SE (DeLorenzo, Pellock et al. 1995).

#### 3.2. Refractory SE

When a patient begins to seize, the emergency medical technician will administer a first-line intravenous (IV) benzodiazepine (BDZ), such as diazepam, lorazepam or midazolam (Silbergleit, Durkalski et al. 2012), which is done either at the scene of the seizure or in the ambulance. If this is unsuccessful at abating the seizure, additional doses of the first-line therapy will be administered in the emergency room. Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line therapy, which is an IV anti-epileptic drug (AED) such as phenytoin or valproic acid (Novy, Logroscino et al. 2010; Shorvon 2011; Hocker, Britton et al. 2013).

Approximately 20-30% of patients refractory to first-line treatment will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to approximately 70-80% of patients who receive second-line therapy refractory to that therapy.

If a patient's SE continues after administration of BDZs and AEDs, the subject is diagnosed as having refractory status epilepticus (RSE), which must be treated quickly to terminate the seizure activity, maintain the patient's airway, and prevent cerebral damage. RSE patients are immediately admitted to the Intensive Care Unit (ICU) and placed in a medically-induced coma to stop all seizure-related activity. The drugs used to induce coma are continuously-infused IV agents,

commonly propofol, midazolam, or pentobarbital, referred to as third-line agents (Brophy, Bell et al. 2012).

The RSE patient is continually monitored using electroencephalography (EEG) to ensure burst suppression is achieved. Burst suppression is a pattern of brain waves seen on an EEG, characterized by periods of activity alternating with periods of little or no activity in the brain, informing medical personnel of the effectiveness of the medically-induced coma. The goal of burst suppression is to allow the brain and corresponding neuronal tissue to restore function and reset to normal pre-seizure levels.

### 3.2.1. Epidemiology of RSE

Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line AED therapy. In turn, approximately 20 – 30% of these patients treated with AEDs will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to 28% of the total estimated SE patient population refractory to second-line therapy. Based on the previously-cited estimated incidence in the US, this means that there are up to 42,000 incident cases of RSE in the USA, annually (DeLorenzo, Pellock et al. 1995).

### 3.3. Super-refractory SE

After 24 hours of burst suppression, the patient is weaned off of the third-line therapy. If the weaning is unsuccessful (neuronal activity has not returned to normal), the third-line agent is re-administered or a different third-line agent is started, and the patient is considered to be in super-refractory status epilepticus (SRSE) (Chapman, Smith et al. 2001; Shorvon 2011; Brophy, Bell et al. 2012). SAGE-547 is being developed as an adjunct to third-line therapy in patients in RSE who have failed standard treatment. In this protocol, the term “RSE that has failed standard treatment” is deemed to be equivalent to the term “SRSE” and the two may be used interchangeably.

#### 3.3.1. Epidemiology of SRSE

The incidence of SRSE is very poorly understood, mainly because the diagnostic codes used for SE do not generally differentiate its nature as responding or refractory to treatment. Based on the variable reporting of outcomes data, the incident cases of SRSE could represent between one and two-thirds of the RSE patients (Novy, Logroscino et al. 2010; Ferlisi and Shorvon 2012; Hocker, Britton et al. 2013; Sutter, Marsch et al. 2013). More detailed epidemiology studies are needed to better elucidate the proportion of RSE patients whose condition becomes super-refractory. A recent review of ICU discharge data in the USA suggests an annual incidence of approximately 35,000, based on patients who required at least three days in the ICU for SE [Sage data on file].

#### 3.3.2. Outcomes of SRSE

SE has varying degrees of mortality depending on the underlying etiologies. Table 4 outlines the acute mortality in patients with SE by etiology (Neligan and Shorvon 2010). The mortality rate of SRSE is estimated to be 30% to 50% using current standard of care.

The causes of death from SE (and therefore SRSE) are heterogeneous, resulting from neuronal cell death, complications of underlying medical conditions, or adverse effects of the current standard treatments. Prognosis worsens and mortality increases with longer duration of SE, i.e. with SE that develops into RSE or SRSE (Neligan and Shorvon 2010), and with longer duration of



medically-induced coma ([Ferlisi and Shorvon 2012](#)). There is an obvious unmet medical need to improve upon the current standard of care treatment regimens.

Morbidity is high and survivors have outcomes ranging from poor function to vegetative state ([Shorvon 2011](#)). Approximately one third of patients with RSE and SRSE will recover, but with chronic neurologic or other deficits ([Neligan and Shorvon 2010](#); [Hocker, Britton et al. 2013](#)). In all, it is estimated that less than 25-30% of all SRSE patients have a favorable functional outcome.

**Table 4: Approximate Mortality of Status Epilepticus in Different Etiologies**

Underlying Etiology	Associated Acute Mortality in Patients with SE (%)
Drug reduction/withdrawal, poor AED compliance, or low AED levels	0-10
Cerebrovascular Disease	20-60
Metabolic Disorders	10-35
Acute CNS Infection	0-30
Anoxia	60-100
Alcohol Abuse	0-10
Head Trauma	0-25
Drug Overdose/Toxicity	10-25
Brain Tumors	0-20
Cryptogenic/Idiopathic	5-20

### 3.3.3. Unmet Medical Need in Super-refractory Status Epilepticus

Treatment approaches for SRSE consist of diagnosis and treatment of underlying medical conditions, adding and changing anti-seizure drugs, and repeated attempts at weaning from IV anesthetic agents. Treatment of SRSE has three aims:

- to prevent excitotoxicity, which begins within 24 hours of SE onset;
- to prevent cerebral damage by initiating neuroprotective burst suppression;
- to prevent the complications of extended periods of anesthesia or unconsciousness ([Shorvon 2011](#)).

Currently, there are no therapies that have been specifically approved for RSE or SRSE. The primary drugs used to induce coma are continuously infused IV anesthetics such as propofol, midazolam, or pentobarbital, known as third-line agents. Use of these drugs to control SRSE has only been studied in small retrospective reviews or small prospective studies without controls ([Hocker, Britton et al. 2013](#)) therefore there is no agreement on which drug is optimal nor on an optimal dosing regimen for the treatments that are used.

The most common adverse effect of the third-line agents is hemodynamic instability; in addition, they are not universally effective, with breakthrough seizures and withdrawal seizures requiring dose adjustments and changes in third-line agent(s). The drug thought to be most effective in SRSE, pentobarbital, is also associated with the most toxic adverse effect profile, comprising

decreased blood pressure and cardiorespiratory collapse (Claassen, Hirsch et al. 2002). The ability to wean patients successfully off the third-line agents as quickly as possible is therefore paramount, and an adjunct to SRSE treatment that enhances the success of the third-line agents and supports their successful weaning in a short timeframe would be an important addition to the therapeutic armamentarium. Preliminary clinical data show that SAGE-547 has been a successful adjunct to third-line therapy in this regard.

### 3.4. SAGE-547 Injection

Allopregnanolone is an endogenous, naturally occurring neuroactive steroid formed in the corpus luteum of the ovary, adrenal cortex and central nervous system (CNS) (Holzbauer, Birmingham et al. 1985; Paul and Purdy 1992; Ottander, Poromaa et al. 2005). It is a metabolite of progesterone created by the actions of 5- $\alpha$  reductase and 3- $\alpha$  hydroxy-steroid dehydrogenase. Allopregnanolone is a potent positive allosteric modulator of both synaptic and extra-synaptic GABA<sub>A</sub> receptors.

SAGE-547 Injection (allopregnanolone aqueous formulation in Captisol<sup>®</sup>) is being developed for the treatment of patients in RSE who have not responded to standard treatment. SAGE-547 Injection is a solution of 5 mg/mL allopregnanolone in Sterile Water for Injection (SWFI), USP and 250 mg/mL betadex sulfobutyl-ether sodium, NF. It is further diluted with Sterile Water for Injection, USP (SWFI) in IV bags to achieve an allopregnanolone concentration of approximately 1.67 mg/mL in an approximately isotonic solution and will be administered intravenously.

#### 3.4.1. Scientific Rationale for SAGE-547 in SRSE

Ineffective recruitment of inhibitory neurotransmission, together with excessive neuronal excitation, likely plays a role in the initiation and propagation of the electrical disturbance occurring in SE. GABA ( $\gamma$ -aminobutyric acid), the major inhibitory neurotransmitter in the central nervous system (CNS), is released from GABAergic neurons and binds to several types of GABA receptors (GABA<sub>A</sub>, GABA<sub>B</sub>, and GABA<sub>C</sub>) on target neurons. GABA<sub>A</sub> receptors are macromolecular proteins that form a chloride ion channel complex and contain specific binding sites for GABA and a number of allosteric regulators, including barbiturates, benzodiazepines, and some anesthetic agents. GABA receptor-mediated inhibition contributes significantly to the normal termination of a seizure (Kapur and Macdonald 1997). SAGE-547 is a positive allosteric modulator of the GABA<sub>A</sub> receptor.

The importance of terminating seizure activity as soon as possible is underpinned by a growing body of evidence from research and clinical observation that SE becomes more difficult to control as its duration increases. It has been postulated that this occurs due to a mechanistic shift from inadequate GABAergic inhibitory receptor-mediated transmission to excessive N-methyl-D-aspartic acid (NMDA) excitatory receptor-mediated transmission (Kapur and Macdonald 1997). As prolonged epileptiform bursting results in a reduction of GABA<sub>A</sub>-mediated synaptic inhibition, antiepileptic treatments which rely on enhancing intrasynaptic GABA<sub>A</sub> neurotransmission become less effective the longer SE continues.

Furthermore, the constitutive process of synaptic GABA<sub>A</sub> receptor internalization is accelerated by the increased neuronal activity associated with seizures. These findings suggest that the rate of GABA<sub>A</sub> receptor internalization is regulated by neuronal activity, and its acceleration contributes to the reduction of inhibitory transmission observed during prolonged seizures (Kapur and Macdonald 1997). Of note is that SAGE-547 binds to extrasynaptic as well as intrasynaptic GABA<sub>A</sub> receptors;

extrasynaptic receptors remain active with ongoing seizure activity, resulting in a putative mode of action for SAGE-547 in SRSE.

Status epilepticus induces cerebral damage that includes neuronal cell necrosis, gliosis, and network reorganization. The major cause of cell death in cerebral damage is excitotoxicity, which is initiated by glutaminergic receptor over-activation, causing calcium to flood the cell, thereby leading to apoptosis and necrosis. This process is initiated within a few hours of the start of seizure activity, and provides the medical imperative to terminate SE as quickly as possible. To prevent the consequences of the excitotoxicity cascade, it is recommended that anesthesia be initiated within 1-2 hours of onset of seizures at doses designed to induce EEG burst suppression ([Shorvon and Ferlisi 2011](#)).

### **3.4.2. SAGE-547 Clinical Program in the Treatment of SRSE**

The current SAGE-547 development program includes:

- an ongoing Phase 2 open-label trial, Study 547-SSE-201;
- this proposed Phase 3 randomized, double-blind, placebo-controlled trial, Study 547-SSE-301;
- a planned open-label, expanded access protocol, Study 547-SSE-302;
- a number of EINDs for SAGE-547 in patients with SRSE.

The designs of these studies are all similar, with a five to six day infusion of SAGE-547 (or placebo), during which time attempts are made to wean the subject off all third-line agents. In the Phase 3 studies, those subjects who cannot be weaned off third-line agents while being administered SAGE-547 (or placebo) will be eligible for a second open-label infusion of SAGE-547 at a higher dose, which is also being employed for the latter patients being enrolled in the Phase 2 study. Follow up of subjects is for 21 – 30 days after the first infusion of study medication.

### **3.4.3. Data from the SAGE-547 Development Program**

The data from 30 subjects included in the on-going clinical evaluation of SAGE-547 for the treatment of adults and children with SRSE clearly offers preliminary evidence that SAGE-547 could provide substantial and clinically significant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate. These subjects comprise 20 from the ongoing Phase 2 trial (71% success rate in 12/17 evaluable subjects) and 10 subjects who received EIND treatments (78% success rate in 7/9 evaluable subjects).

Successful therapy of SRSE has been defined as “the SE is completely controlled by the therapy, without breakthrough of withdrawal seizures, or discontinuation due to side effects or death during therapy,” ([Ferlisi and Shorvon 2012](#)). By this definition, which is in accord with the efficacy assessments used in the overall clinical evaluation of SAGE-547, 19 of the 26 (73%) subjects with SRSE who completed the SAGE-547 infusion were treatment successes. As data collection is ongoing, this information is preliminary and subject to change upon further monitoring.

Published reports on RSE and SRSE have stated mortality rate ranges from 35% to 65%. The underlying etiologies of SE in the 547-SAGE-201 study and EINDs are heterogeneous, and each one conveys a different risk of mortality and longer term morbidity. However, the death rate in subjects who have received SAGE-547, 6 out of 30 (20%) subjects, appears to be lower than the published

rates. None of the deaths were considered related to SAGE-547: brain tumor, organophosphate toxicity, respiratory failure, respiratory arrest due to ventilator support withdrawal, and breast cancer.

In the Phase 2 study, 20 SAEs (15 non-fatal) have been reported in 13 (65%) subjects, and of these 3 events in 2 subjects (10%) were considered by the investigator to be related to SAGE-547: pulmonary emboli and tracheostomy dehiscence/infection. The Sponsor did not consider these events to be related to SAGE-547, rather to the underlying disease states. Four of the 20 subjects (20%) experienced AEs considered possibly related to SAGE-547 by the investigator, namely moderate myopathy and severe pulmonary emboli in 1 subject, moderate tracheostomy dehiscence and tracheostomy infection in 1 subject, moderate thrombocytosis in 1 subject and moderate BUN, ALT and AST elevation in 1 subject.

Review of the most current safety data from 547-SAGE-201 reveals that there were changes in serum chemistry, hematology, and urinalysis during the study, but that none of those changes were assessed as related to SAGE-547. There were also no SAGE-547-related changes to vital signs.

Despite the heterogeneity in the underlying causes of SE, the ages of the subject, comorbidities, which normally complicate the treatment of SE, and the fact that all subjects had failed current standard of care treatment, a large majority of subjects had a successful therapy outcome, with discontinuation of all third-line agents and resolution of SE.

Refer to the Investigational Brochure for further information on the pre-clinical and clinical data supporting the use of SAGE-547 in SRSE.

### **3.5. Study Rationale - SAGE-547 in SRSE**

#### **3.5.1. Justification for the Control Group**

Although SAGE-547 has demonstrated extremely promising activity in subjects with SRSE, both in the Phase 2 study and during the EINDs, these have been open-label investigations with no control data for comparison. Generally in the literature there are few data describing the success rates of wean attempts of third-line agents, and few comparative data on the effectiveness of the three main third-line agents, propofol, pentobarbital, and midazolam.

Several options for a control group in Study 547-SSE-301 were considered:

- No control group was thought to be unacceptable since there are no reliable published data on success rates in this population that could be used for broad comparisons;
- An active control was considered but found to be impractical since none of the third-line agents are approved for their use in SRSE, no standardized dosing regimens or treatment guidelines have been adopted for the management of SRSE, and clinicians were unlikely to agree which of the available third-line agents would be reserved for the active control arm;
- Historical controls were considered but abandoned because of the practical difficulties of obtaining high quality data, the lack of ability to prospectively match cases, and a suspicion that clinical practice in the standard of care of SRSE is evolving, mandating the use of prospective, concurrent control data;
- Comparison to standard of care alone was considered as a feasible design. However, in a field where no widely adopted treatment guidelines exist, there was a concern that knowledge of the treatment group (SAGE-547 plus standard of care versus standard of care

alone) would alter the behavior of the investigators such that they could be more aggressive with weaning in the SAGE-547 group;

- Placebo control is not without its challenges since the preliminary efficacy data for SAGE-547 show that the compound exerts central pharmacological effects and is associated with positive outcomes in around 70% of patients. There is therefore a potential ethical concern about administering placebo to desperately ill patients who have often exhausted all treatment options for SRSE. This concern has been addressed in two ways: firstly all patients receive current standard of care; secondly, all subjects who fail to be weaned from their third-line agents at the end of the blinded infusion of study drug will be administered open-label SAGE-547 without un-blinding their initial treatment allocation, so treatment with the investigational product is not denied, but delayed about a week in the setting of ongoing receipt of full current standard of care.

It was therefore decided that a blinded, placebo-controlled design was appropriate for Study 547-SSE-301.

### **3.5.2. Justification for the Dose Regimen**

The standard dose regimen has been studied in 19 subjects in the 547-SSE-201 Phase 2 trial; the average peak plasma concentration of SAGE-547 at the end of the loading dose was approximately 144 ng/ml. The average plasma concentration during the maintenance infusion was approximately 70 ng/ml. At these concentrations, there were no clear safety signals although two-thirds of subjects experienced an SAE and there were four deaths, all related to the underlying comorbid conditions. The standard dosing regimen was associated with an approximate 70% successful treatment outcome. For these reasons, the standard dosing regimen has been adopted for the initial SAGE-547 infusion to be compared in a blinded fashion to placebo.

In the 547-SSE-201 trial, three subjects have thus far received the higher dose regimen. This dose regimen has also been well tolerated. The average peak plasma concentrations at the end of the loading dose for both dosing regimens will be in the same range, as the loading dose is the same for both regimens. The average plasma concentrations observed during the higher maintenance dose are 102 ng/ml (n=2). The rationale for adopting the higher dose regimen as the open-label infusion of SAGE-547 for subjects who are retreated in this 547-SSE-301 trial is that those who fail on the standard SAGE-547 dose regimen are afforded the opportunity to have access to a higher dose. The justification to also administer the higher dose regimen to failures on placebo is that the regimen has thus far been well tolerated, and this methodology preserves the blind for the initial infusion.

A five-day dosing regimen with SAGE-547 was investigated in the Phase 2 study, 547-SSE-201. There were some cases when weaning off all third-line agents was not possible within 48 hours, but weaning was completed after the end of the infusion of SAGE-547. For this reason, the duration of dosing with SAGE-547 has been increased from 120 hours (five days) in Phase 2 to 144 hours (six days) in this Phase 3 study.

### **3.5.3. Rationale for Genetic Testing Sub-study**

Sage Therapeutics intends to perform genetic research in the SAGE-547 development program in order to explore how genetic variations may affect the metabolism and activity of SAGE-547. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials, and, possibly, to genetically-guided

treatment strategies for optimizing decision making with respect to individual benefit:risk. Participation of subjects in genetic research as part of the overall clinical study is optional.

### **3.6. Benefit-Risk Evaluation of the Present Study**

Previous reports of human administration of exogenous allopregnanolone indicate that for exposures in men and women up to 150 nM, the most commonly reported AEs were sedation (recorded as sleepiness or tiredness), feelings of intoxication (like alcohol), flushing, and mild headache (Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007). No SAEs were reported (Navarro, Kaddouz et al. 2003; Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007; Kask, Backstrom et al. 2008; Kask, Backstrom et al. 2009; Timby, Hedstrom et al. 2011a). In view of the reduced consciousness and sedation of study subjects at entry into this protocol, none of these previously-reported events are likely to impact subjects in this study.

To date, in the SAGE-547 Phase 2 study and the EIND subjects, a majority of subjects demonstrated a successful therapy outcome (>70%). The majority in the clinical trial (65%) have also experienced SAEs, but none has been considered related to SAGE-547 by the Sponsor (SAEs in 2 subjects (10%) were considered possibly related by Investigator). Five deaths have been reported in 30 subjects (20%), all related to the underlying cause of SRSE and not related to SAGE-547 – this is in the context of published mortality rates between 35% and 65%. These preliminary data suggest that SAGE-547 has the potential to provide clinically relevant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate.

The underlying etiologies of SE are heterogeneous, and each one conveys a different risk of mortality. Subjects who survive SRSE still have a high risk of severe morbidity (Neligan and Shorvon 2010). The subjects treated with SAGE-547 in Study 547-SSE-201, are heterogeneous in factors such as age and etiology of SE, factors that usually complicate treatment and can increase morbidity and mortality. Even with this heterogeneity, the preliminary efficacy and safety data for SAGE-547 are very encouraging, and the mortality rate suggests that the risk to benefit assessment of this treatment rests on the side of benefit.

## **4. ETHICS**

### **4.1. Institutional Review Board or Independent Ethics Committee**

This protocol will be reviewed and approved by the Institutional Review Board (IRB) where the study is conducted. The IRB will meet all FDA requirements governing IRBs (CFR, Title 21, Part 56).

### **4.2. Ethical Conduct of the Study**

The Sponsor, the Medical Monitor, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable ICH and GCP guidelines, and must also conduct the study in accordance with local regulations.

### **4.3. Subject Information and Informed Consent**

Subjects prospectively enrolled in this study will be unable to give consent. Therefore, consent will be given by proxy by a legally authorized representative (LAR). Written informed consent is required for each subject prior to any testing under this protocol not considered standard of care,

including screening tests and evaluations. Should a subject gain the ability to sufficiently comprehend the situation and consent during the course of the study, written informed consent or verbal assent will be documented as required or recommended by the institution's IRB.

The form of consent to be obtained will depend on the condition of the subject as determined by the Principal Investigator. The informed consent form (ICF), as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50.

It is the responsibility of the Investigator to obtain consent and to provide the subject's LAR with a copy of the signed and dated informed consent form. The informed consent form for subject participation must also be available as part of the subject file for review by the site's dedicated study monitor or any authorized auditor of the Sponsor or regulatory authorities.

All ICFs used in this study must be approved by the appropriate IRB and by the Sponsor. The ICF must not be altered without the prior agreement of the relevant IRB and the Sponsor.

#### **4.4. Ethical and Regulatory Considerations for Pharmacogenetic Sub-study**

##### **4.4.1. Informed Consent for Pharmacogenetics**

The genetic component of this study is optional and subjects may participate in other components of the main study without having to agree to participate in the genetic component. If subject chooses to participate in the genetic component of the study, the subject or LAR must sign and date a specific consent form for the genetic component of the study in addition to the main study consent form. The principal investigator(s) is responsible for ensuring that consent is freely given and that the subject understands that they may discontinue from the genetic aspect of the study independent of their decision to remain within or withdrawal from the main study.

##### **4.4.2. Subject Data Protection Relative to Pharmacogenomics**

Sage Therapeutics will not provide individual genotype results to subjects, their family members, their general physician, their employer or any insurance company unless required to do so by law. While extra precautions will be taken to preserve confidentiality and to prevent genetic data from being linked to an individual's identity outside of a restricted access site, in certain exceptional situations (e.g. in case of a medical emergency or as a consequence of a specific regulatory need), certain individuals may see both genetic data and the personal identifiers of a subject; however in all cases a subject's medical information and genetic files will remain physically separated.

## **5. STUDY OBJECTIVES**

### **5.1. Primary Objective**

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult and pediatric subjects with SRSE, and for the response to endure at least 24 hours after cessation of the SAGE-547 or placebo infusion (primary response).

## 5.2. Secondary Objectives

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in Clinical Global Impression Scale between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

## 5.3. Safety Objectives

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

## 5.4. Other Objectives

1. To evaluate the impact of retreatment with a higher dose of SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;



6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS) (age  $\geq 17$  years).

## **6. ENDPOINTS**

### **6.1. Primary Endpoint**

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### **6.2. Secondary Endpoints**

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) and to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### **6.3. Safety Endpoints**

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.

## 6.4. Other Endpoints

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who fail to respond to their randomized double blind treatment and are retreated with a higher dose of SAGE-547;
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS) (age  $\geq 17$  years).

## 7. INVESTIGATIONAL PLAN

### 7.1. Overview of Study Design

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE. Pediatric patients (those < 14 years of age) will be managed in a pediatric intensive care setting.

Figure 1 provides an overview of the study design and Figure 2 gives the details of treatment and follow-up on the active treatment arm. Patients will follow one of three paths to entry to the study. The first path is for patients who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst suppression with a third-line agent. These patients will be consented for the study after admission to the intensive care unit, but before any third-line agents are administered for burst suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their LAR. Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours. Once burst suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see Table 3). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of study drug.

The second path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst suppression pattern on the EEG. These patients may have had one or more previous unsuccessful weans and may be on more than one third-line agent.

Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of study drug.

The third path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These patients may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within six hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. Randomization will be stratified by concomitant pentobarbital use (yes or no) and number of previous third line agent wean attempts prior to randomization (one vs two or more).

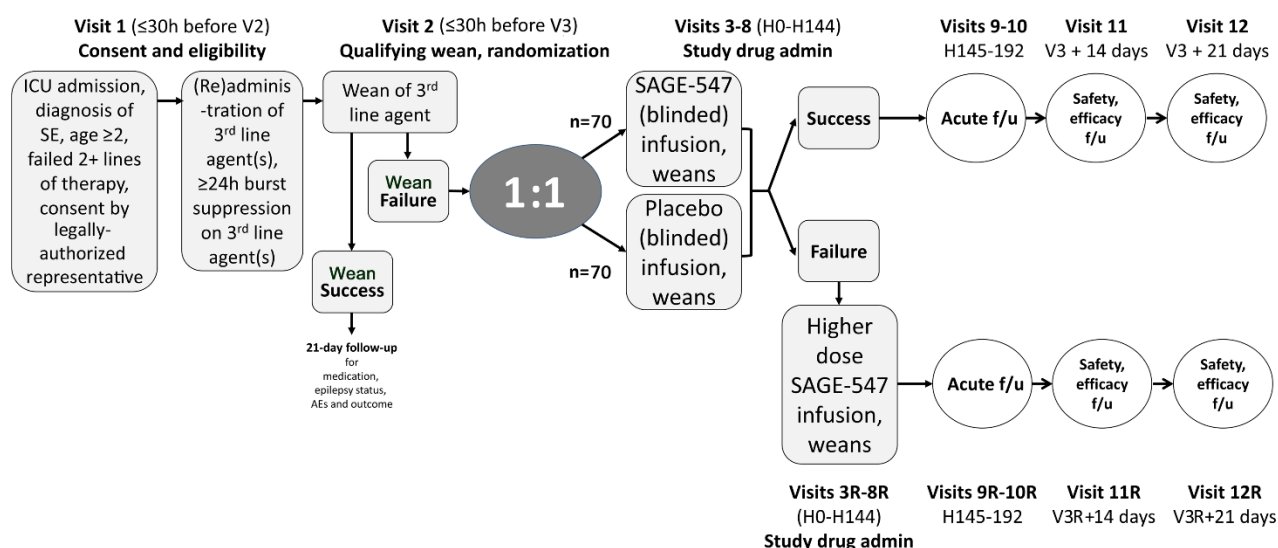
The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as the ability to wean the subject off all third-line agents before the end of the first infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication. Subjects must also have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) at the end of the primary endpoint assessment period as determined by EEG in order to be deemed a success. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#), [Table 2](#) and [Table 3](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. Eligibility for retreatment must be confirmed in writing by the medical monitor prior to the open-label infusion starting. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo will all subsequently be eligible to be administered SAGE-547 at the higher dose.

**Figure 1: Study Design**



## 7.2. Trial Conduct

This study will be conducted according to the principles of the World Medical Association Declaration of Helsinki and most recent amendment (2008), and in compliance with the protocol approved by the IRBs/Independent Ethics Committees (IECs), and in accordance with ICH Guidelines on GCP standards.

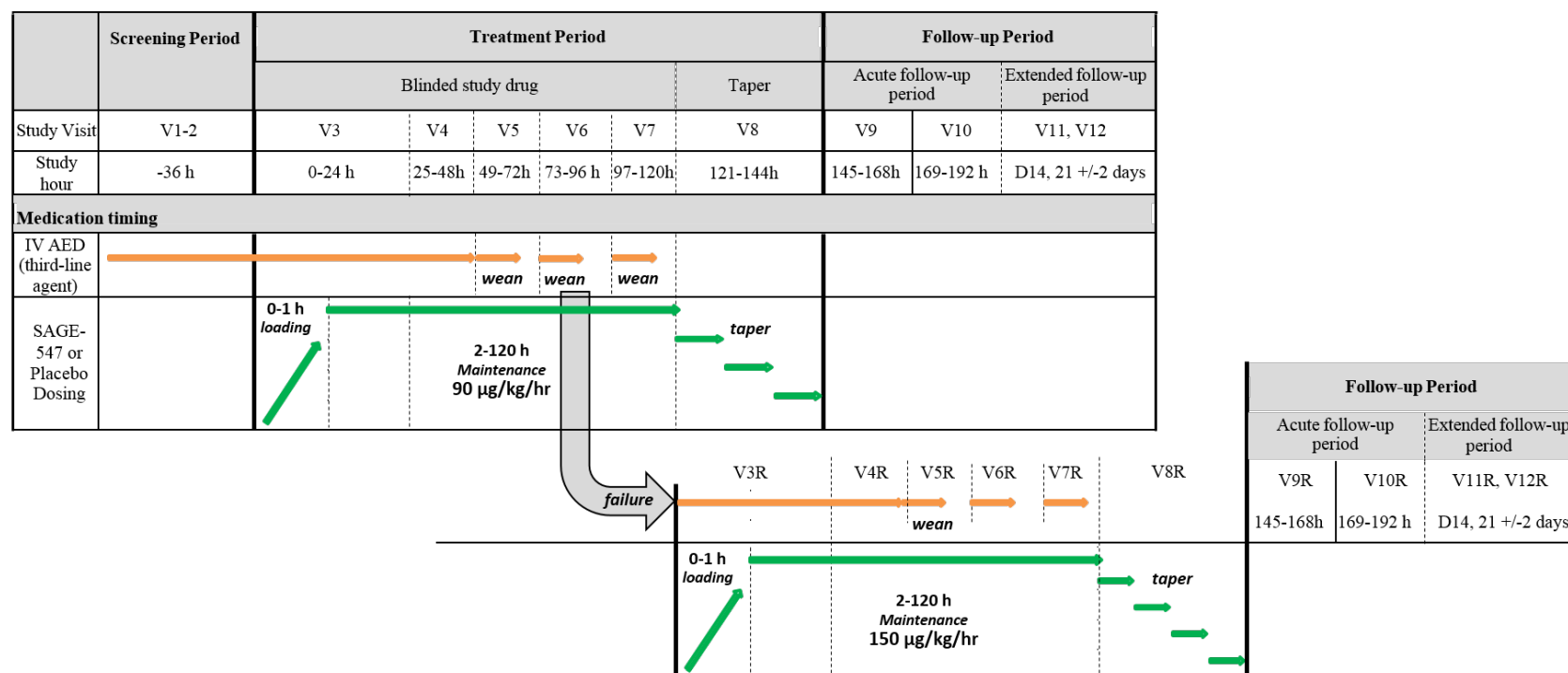
## 7.3. Blinding and Randomization

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo). Details of the dynamic randomization process will be included in the SAP.

The randomized portion of the study will be blinded, with the two treatment products (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

The second infusion of SAGE-547 will be administered on an open label basis to subjects who failed the primary endpoint wean.



**Figure 2: Details of Treatment Administration and Follow-up**

## 8. SELECTION AND WITHDRAWAL OF SUBJECTS

The study will randomize 140 patients at up to 150 sites. All subjects deemed eligible to enroll must have written Medical Monitor approval on a case-by-case basis prior to undertaking the qualifying wean.

### 8.1. Inclusion Criteria

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects two (2) years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; *or* who have previously failed one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst suppression pattern; *or* who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst suppression pattern.

### 8.2. Exclusion Criteria

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy.
4. Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing underlying neurological disorder.
5. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis but for whatever reason, dialysis is not planned or non-continuous dialysis planned (that would not adequately remove Captisol<sup>®</sup>);
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the experience of the investigator, is less than 30 days;
  - e. a do not resuscitate (DNR) order.

6. Subjects who are being administered more than three third-line agents concomitantly or for whom the qualifying wean cannot be completed within 24 hours or who are being administered a third-line agent for indications such as raised intra-cranial pressure that would preclude weaning according to this protocol.
7. Subjects with a living will that does not allow heroic measure.
8. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
9. Subjects who have been enrolled in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not withdraw or complete and then re-enroll).

### **8.3. Selection and Consent of Subjects for Pharmacogenetic Substudy**

All subjects will be asked to participate in pharmacogenetic research; however, participation in research is voluntary and a subject can decide to decline his/her participation without penalty or loss of benefit. Participation or lack thereof will not be a cause for exclusion from any aspect of the main study. In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **8.4. Subject Withdrawal / Study Termination**

#### **8.4.1. Withdrawal/Discontinuation of Individual Subjects**

The reasons for study drug discontinuation and/or subject withdrawal from the study must be recorded in the subject's electronic case report form (eCRF). The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject has been discontinued/withdrawn due to an AE.

##### **8.4.1.1. Withdrawal from the Study**

Subjects or their LAR may withdraw subjects from the study at any time for any reason without compromising the subject's medical care. The Investigator will also withdraw subjects upon the request of Sage Therapeutics or upon termination of the study.

Subjects who withdraw from the study prior to Visit 10 (or 10R) should complete the procedures scheduled for the day of study drug taper (hour 121-144; Visit8/8R) on the day of their withdrawal, including the SAGE-547 taper schedule, with the addition of the mortality assessment from Visit 12/12R. Subjects who withdraw from the study after Visit 10/10R should undergo study procedures as outlined for Visit 12/12R on the day of their withdrawal. In all cases, the reason for subject withdrawal will be recorded in the eCRF.

Withdrawal of subjects for any reason should be discussed with the Medical Monitor.

##### **8.4.1.2. Discontinuation of Study Drug**

If it is necessary to discontinue the study drug earlier than planned, subjects should continue to be followed per protocol to capture safety and efficacy assessments for the duration of the study period.



The investigator may withdraw the subject from the study drug for the following reasons:

- Upon subject's or LAR's request
- The subject or LAR is unwilling or unable to adhere to the protocol-specified visits
- The subject experiences an intolerable adverse event
- During the course of the study, the subject develops symptoms or conditions listed in the exclusion criteria.
- Other medical reason, at the discretion of the Investigator and/or the Medical Monitor

Subjects who discontinue the study due to an AE considered related to study drug should be followed until the event is resolved, considered stable, or the Investigator determines the event is no longer clinically significant. Study drug discontinuation due to AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

#### **8.4.2. Study Termination**

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of AEs or other findings suggesting unacceptable risk to subjects, administrative or operational reasons. In the event of study termination, Sage Therapeutics will provide written notification to the Investigator. Investigational sites must promptly notify their IRB and initiate withdrawal procedures for participating subjects.

## **9. INVESTIGATIONAL PRODUCT**

### **9.1. Identity of Investigational Product**

SAGE-547 Injection (allopregnanolone)

### **9.2. Clinical Supplies**

#### **9.2.1. SAGE-547**

Adequate supplies of SAGE-547 Injection and materials for intravenous administration will be provided to each site.

SAGE-547 Injection is a clear, colorless sterile solution of allopregnanolone intended for intravenous injection. SAGE-547 Injection is an aqueous solution of 5 mg/mL allopregnanolone in 250 mg/mL Captisol® (betadex sulfobutyl-ether sodium, NF). It is presented either un-buffered or buffered with 10 mM citrate at a pH of 6.0 in either 20 mL or 50 mL vials. SAGE-547 is further diluted according to the Pharmacy Manual to achieve an approximately isotonic solution and will be administered intravenously.

No preservatives are included in the drug product, which is intended to be used as a single-use vial. All inactive components (excipients) used in the formulation are compendial grade and conform to current USP/EP, and include sodium citrate, citric acid and betadex sulfobutyl-ether sodium (Captisol®).

**9.2.2. Placebo**

Placebo will be identical to SAGE-547 and presented in identical vials. Placebo will be manufactured in a similar way to SAGE-547 and comprises all excipients but no SAGE-547.

**9.2.3. Blinding**

The vials of SAGE-547 and placebo will be identical in every way so that they are indistinguishable by the pharmacist, investigator, anyone treating or managing the patient, the monitors, and the sponsor. In this way the first infusion of study drug administered to each patient will be double-blind.

For the blinded study drug infusions, subject-specific dosing kits will be provided. These dosing kits will be pre-labelled with kit number for the first blinded infusion. For the second-infusion, open-label kits will be provided, which will require subject assignment by the pharmacy for reconciliation purposes. The study kits must be stored under refrigerated conditions (2-8 °C). IV administration bags and lines may be provided for the blinded and open-label infusions. Refer to the Pharmacy Manual for additional details.

The label for the SAGE-547 Injection vials will include standard product identification information according to the Code of Federal Regulations, 21CFR 312.6. All study labels will also contain the following statement:

Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use.

**9.3. Preparation of SAGE-547 or Placebo Injection for Dosing**

The Pharmacy will be responsible for preparing the blinded and open-label study drug for subject dosing. The prepared admixture will be assigned a room temperature (20-25 °C) storage shelf life of 30 hours from time of compounding.

SAGE-547, which is hypertonic, will require dilution with SWFI to achieve an approximately isotonic solution according to the instructions provided in the Pharmacy Manual. Exactly the same procedures will be used to prepare the placebo admixture, so that all site staff remain blinded as to treatment allocation for the first infusion of study drug. SAGE-547 Injection is not intended to be administered to patients undiluted.

Refer to the Pharmacy Manual for specific instructions regarding infusion preparation.

**9.4. Administration and Accountability**

The Pharmacy will maintain accurate records of all investigational product supplies. Accurate records will be kept regarding the volume of SAGE-547 Injection or placebo used for each IV preparation, as well as the required infusion rate or rates, and the date and time of preparation. Reasons for departure from the expected dosing regimen must also be recorded. To satisfy regulatory requirements regarding drug accountability, all study medication will be reconciled in full. Refer to the Pharmacy Manual for additional details.

## 10. TREATMENT OF SUBJECTS

### 10.1. Dosing Schedule (Blinded Infusions)

SAGE-547 Injection or placebo will be administered according to the dosing schedules in [Table 5](#). The infusion rates to accomplish these  $\mu\text{g/kg/h}$  doses will be calculated according to the weight of the subject. The infusion rates will be applied to blinded study drug for the first infusion of study medication.

**Table 5: SAGE-547 or Placebo Dosing Schedule**

Hour	Type and Duration of Study Drug Infusion	Description
H1	One hour loading Infusion	300 $\mu\text{g/kg/h}$
H2 – H120	119 hour maintenance infusion	90 $\mu\text{g/kg/h}$
H121 – H128	8 hour taper	65 $\mu\text{g/kg/h}$
H129 – H136	8 hour taper	45 $\mu\text{g/kg/h}$
H137 – H144	8 hour taper	25 $\mu\text{g/kg/h}$

### 10.2. Dosing Schedule (Open-Label Infusions)

If a subject fails wean from third-line agent(s) or requires re-instatement of third-line therapy within 24 hours of discontinuing the initial infusion of study drug, SAGE-547 Injection will be re-administered according to the dosing schedule in [Table 6](#). The infusion rates to accomplish these  $\mu\text{g/kg/h}$  doses will be calculated according to the weight of the subject. These infusion rates will be applied to SAGE-547 re-treatment for the open-label second infusions of study medication.

**Table 6: SAGE-547 Open Label Dosing Schedule**

Hour	Type and Duration of SAGE-547 Infusion	Description
H1	One hour loading Infusion	300 $\mu\text{g/kg/h}$
H2 – H120	119 hour maintenance infusion	150 $\mu\text{g/kg/h}$
H121 – H126	6 hour taper	125 $\mu\text{g/kg/h}$
H127 – H132	6 hour taper	95 $\mu\text{g/kg/h}$
H133 – H138	6 hour taper	65 $\mu\text{g/kg/h}$
H139 – H144	6 hour taper	35 $\mu\text{g/kg/h}$

### 10.3. Route of Administration

SAGE-547 Injection is intended for IV administration only. The compatibility of SAGE-547 with other drugs is unknown, and the product should be administered via a dedicated peripheral IV line using any Sage-supplied study-specific IV administration bags and lines. In order to preserve blinding, these instructions also apply to the blinded placebo infusions.

### 10.4. Treatment Period

The treatment period with double-blind SAGE-547 or placebo is six 24-hour periods (144 hours), which may encompass 6-7 calendar days. The retreatment period is of identical duration.

## **10.5. Concomitant Medications, Procedures and Treatments**

Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. All concomitant medications, procedures, and treatments should be documented throughout the study from Screening through Visit 12/12R and recorded on the eCRF.

SAGE-547 has demonstrated inhibitory effects on cytochrome P450 isoenzyme 2C9 (CYP2C9). Therefore, AEDs such as phenytoin and phenobarbital that are primarily metabolized by CYP2C9 should be closely monitored during SAGE-547 administration to ensure target exposures are maintained.

### **10.5.1. Concomitant AEDs**

Subjects may enter the study on AEDs, and be administered AEDs during the study. All of these must be recorded on the eCRF with details including date and time of starting and stopping each AED, the route of administration, changes in doses, and frequency of administration. In addition, details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the eCRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.

### **10.5.2. Concomitant Third-Line Agents**

All third-line agents (as defined in [Section 8](#)) administered since the diagnosis of SE will be recorded on the eCRF, whatever path the patient took for entry into the study. Details will include the name of the drug, the start and stop dates and times, and, after consent, the doses with start and stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

In addition, those changes in dose that constitute a wean attempt will be marked as such on the eCRF. In this way the start and stop dates and times of all wean attempts (see [Section 11](#) for definitions) will be recorded, as will the type of wean (QW, OW, or TW) and the outcome of the wean attempt (successful, failed and dose of this third-line agent increased or failed and this third-line agent stopped and another third-line agent started). Those wean attempts that occur after the TW up to and including Visit 12/12R will be marked “AW”.

Some third-line agents (such as propofol) are also used to induce sedation to facilitate a subject’s ability to tolerate the ventilator. For subjects requiring such sedation, propofol is the preferred agent unless there are contraindications. The eCRF will make clear from the indication for the third-line agent when it is being used for burst or seizure suppression and when it is being used as ventilator support or for another purpose. The investigator will add a note to the eCRF to justify that the doses used are appropriate for sedation and not for seizure or burst suppression. The doses used for ventilator support and other similar uses are usually much lower than those used for seizure or burst suppression, and use of these third-line agents for these other purposes does not constitute a wean failure under this protocol.

### **10.5.3. Concomitant Pressors**

The start and stop dates and times of all pressors will be recorded as well as the start and stop dates and times of all dose changes.

#### **10.5.4. Other Concomitant Medications**

All other concomitant medications must be recorded on the eCRF with details including date and time of starting and stopping, the route of administration, dose, and frequency of administration.

### **11. STUDY ASSESSMENTS**

#### **11.1. Efficacy Assessments**

##### **11.1.1. Primary Efficacy**

Success or failure will be determined, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo infusion and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the blinded (first) infusion of SAGE-547 or placebo. In addition, subjects must have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) to be deemed to be successes. All subjects who fail to complete their infusion of randomized treatment or do not have at least one attempt during study treatment to wean off all third-line agents will be considered as “failures” for the primary endpoint.

##### **11.1.1.1. Weaning**

Third-line agents are anesthetic agents that are administered in order to reach a seizure or burst suppression EEG pattern. For the purposes of this study, third-line agents are defined as continuous intravenous infusions of pentobarbital, midazolam, propofol, and ketamine at maintenance doses alone or in combination sufficient to produce a burst suppression pattern on the EEG. The following are considered to be minimum maintenance doses of these agents that may be expected alone or in combination to achieve EEG burst suppression. If subjects are on lower doses than these and are not in EEG burst suppression for the 24 hours prior to the QW or the first 12 hours of the blinded study drug infusion, they will be considered to be screen failures/protocol violators and will exit the study.

- Pentobarbital: 1 mg/kg/hour
- Midazolam: 0.1 mg/kg/hour
- Propofol: 3 mg/kg/hour
- Ketamine 1.2 mg/kg/hour

The timing and nature of the third-line agent weans will be guided by the Clinical Standardization Guidelines for the study, and the clinical judgment of the investigator, and will always be primarily done in the best medical interests of the subject. Advice about weaning may be sought from the Clinical Standardization Team, a group of fellow investigators with experience of performing clinical trials in subjects with SRSE. The Clinical Standardization Team will be able to review EEGs in real time related to key study timepoints (qualifying wean, terminal wean, and the period after the end of the blinded study drug infusion) in order to provide advice about compliance with the Clinical Standardization Guidelines.

The following guidance for weaning applies to all weans of third-line agents undertaken during the study. These weans include the qualifying wean (QW); the terminal wean (TW), which is the wean

of the third-line agent if the subject is on only one third-line agent or the wean of the last third-line agent if the subject is on more than one third-line agent; the other weans (OW), which are the weans of the third-line agents other than the TW if the subject is on more than one third-line agent. The guidance also applies to additional weans (AW), which are the weans from third line agents that take place after the TW for the first blinded study drug infusion or the second open-label study drug infusion.

### **QW Guidance**

- Wean to be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace that third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Investigators should allow 24 hours to lapse after the end of a “successful” qualifying wean before finally declaring the QW a success. If a third-line agent needs to be re-instituted within that 24 hours, the QW is a failure, and the subject may then be randomized in the study.

### **OW Guidance**

- First OW should not begin before H49 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- If the subject is on two third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the TW. However the OW may be completed over a shorter or longer time period and may overlap if clinically indicated with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- If the subject is on three third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the wean of the second agent. The second agent should be weaned over 24 hours and that wean completed before starting the TW. However the OWs may be completed over a shorter or longer time period and may overlap if clinically indicated with each other and with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- All OWs should be completed before H96 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **TW Guidance**

- The TW is defined as the wean of the last third-line agent.

- If the subject is on one third-line agent, the TW should not begin before H49 and should begin no later than H97 after starting administration of study drug or starting the open-label infusion of SAGE-547. If the subject has had one or more OWs, the TW should ideally begin as soon as the last OW is complete but in any case not later than H97 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- The TW must be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace this third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Every effort must be made to complete the TW before H120 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547, but the TW must be complete before H144 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **AW Guidance**

- AWs will take place when medically indicated in the opinion of the investigator.
- Ideally the AW should take place over 24 hours, but completion may be over a shorter or longer time period than this. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.

### **11.1.1.2. EEG**

Electroencephalographs (EEGs) that are representative of the intermittent or continuous EEG being used to support key investigator decisions will be collected at the following time points:

- A six-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst suppression for the second path to eligibility, and a variable pattern for the third path to eligibility.
- EEG will be performed to cover the qualifying wean (QWEEG). EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for the one hour after the end of the QW. The duration of the QWEEG will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s) or the decision to re-institute a third-line agent(s) at doses intended to induce burst suppression.
- EEG will be performed from three hours prior to the start of the blinded infusion to five hours after the start of the blinded infusion. This will be called the BIEEG. The intent of this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG.

- EEG will be performed to cover the final or terminal wean of third-line agent (TWEEG). The TW is the wean of the final third-line agent during the blinded administration of study drug or the open-label infusion of SAGE-547; if the subject was on one third-line agent, the TW is the wean of that agent. If the subject was on three third-line agents, the TW is the wean of the third and final agent. EEG recording will start 30 minutes prior to the start of the TW, continue for up to 24 hours during the TW, and then continue for the one hour after the end of the TW. The duration of the TWEEG will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the final third-line agent or the decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity could not be managed using intermittent bolus doses of AEDs.
- EEG will be performed during the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 (TAEED). The TAEED is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the start of the taper (at Hour 119.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours during the taper, and then continue for the one hour after the end of the taper (to Hour 145 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547). The duration of the TAEED will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity seen during the taper could not be managed using intermittent bolus doses of AEDs.
- EEG will be obtained to cover the end of the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 and the ensuing 24-hour period, during which the primary endpoint is assessed (PAEED). The PAEED is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the end of taper (at Hour 143.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours after the end of the blinded administration of study treatment or the open-label infusion of SAGE-547, and then continue for the one hour after the end of the 24-hour assessment period (to Hour 169 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547). The duration of the PAEED will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity seen in the 24 hours following the end of the blinded administration of study treatment or the open-label infusion of SAGE-547 that could not be managed using intermittent bolus doses of AEDs.

In practice, most subjects are on continuous EEG monitoring or long periods of intermittent EEG monitoring. However, this protocol does not mandate continuous EEG monitoring and breaks from EEG monitoring to provide relief to the scalp from the irritating effects of the electrodes are advised, particularly in children, according to local practice. If a break in EEG monitoring is mandated by local practice guidelines at a time when one of the protocolled EEG segments is to be collected, the break in EEG monitoring will take precedence, with the reason for missing the EEG reading noted on the eCRF. The EEGs obtained for the study are therefore part of the existing EEG record rather than being obtained de-novo at each timepoint. For timepoints where there might be some



ambiguity, such as the TWEEN, the final EEG record is that of the final attempt to wean the last third-line agent, even if earlier attempts to wean that agent took place. In some cases (the TAE, QWEE, BIE, TWE, TAE, and PAEE), the EEG records will overlap, but different cuts are taken to service the different EEG record requirements.

The electronic EEG file will be de-identified, the date and time of the start and stop of the EEG and the subject number will be attached to the file, and the study time point will be indicated (CEE, QWEE, BIE, TWE, TAE, and PAEE). The PI will indicate on the eCRF what the EEG shows, as follows:

- For the CEE, the PI will describe the EEG pattern that determined which path to eligibility the subject was on.
- For the QWEE, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure on the qualifying wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the qualifying wean).
- For the BIE, the PI will note the date and time of the start of the EEG and the pattern seen on the EEG.
- For the TWE, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure on the terminal wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the terminal wean).
- For the TAE, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst suppression before the end of the SAGE-547 infusion).
- For the PAEE, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst suppression in the 24 hours following the end of the SAGE-547 infusion).

A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm the PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period (average EEG power at the end of Visit 9 of more than two microvolts).

- All subjects will have the CEE and QWEE collected and stored, and the QWEE read;
- Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;
- Those subjects randomized who are not retreated will have the BIE, TWE, TAE and PAEE related to the blinded study drug infusion collected and stored, and the QWEE, TWE, and PAEE related to the blinded study drug infusion read;

- Those subjects randomized who are retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion and the TWEEG, TAEED, and PAEEG related to the open-label study drug infusion collected and stored, and the QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read.

All EEG records may be subject to quantitative EEG analysis.

### **11.1.2. Secondary Efficacy**

#### **11.1.2.1. Clinical Global Impression Scale (CGI)**

The clinical global impression scales are often utilized in clinical trials to allow clinicians to integrate several sources of information into a single rating of the subject's condition. Both the CGI-Severity (Question 1, CGI-S) and the CGI-Improvement (Question 2, CGI-I) employ a 7-point Likert scale measuring severity of the disease state in the subject and improvement, respectively. All severity assessments after initiation of SAGE-547 treatment should consider the general state of the subject over the preceding week. The third question on the scale will not be employed in this trial, and where the scale states "mental illness", this means "physical illness" in this trial.

The CGI-S will be evaluated at Visit 1 and at the last visit, Visit 12 or 12R. The CGI-I will be evaluated at Visit 12 or 12R.

#### **11.1.2.2. Epilepsy Status**

At Visit 1, the diagnosis of epilepsy will be documented as a no/yes question. If there was a previous diagnosis of epilepsy, further details will be documented, including:

- Date of diagnosis;
- Details of anti-epileptic drugs currently being taken;
- Type of epilepsy;
- Seizure frequency in the past month.

Information about the current (index) episode of status epilepticus will be obtained at Visit 1:

- Date of onset
- Date of failure to respond to first line agent(s) and the name(s) of the agent(s)
- Date of failure to respond to second line agent(s) and the name(s) of the agent(s)
- Any previous treatment with third line agents and the response to those agents (details of the third line agent drugs and previous wean attempts will be recorded on the Third Line Agent Medication CRF)
- The cause of the index episode of status epilepticus
- If the subject was transferred from another hospital or from within the hospital, the reason for the transfer will be recorded (such as for study enrollment, due to lack of medical options at original hospital or unit, due to lack of beds at the original hospital or unit, family request, other)

Previous (non-index) diagnosis of status epilepticus will be documented as a no/yes question. If SE did occur in the past, further information will be gathered, including:

- SE, RSE, or SRSE diagnosis, whichever was the most severe diagnosis for each episode;
- Cause;
- Treatment, including experimental treatments and need for intubation/ventilation;
- Dates of onset and duration if the episode of status epilepticus occurred in the past 12 months.

At Visit 12 or Visit 12R, the following information will be gathered:

- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of SE up to and including Visit 12 or Visit 12R;
- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of seizures (convulsive and non-convulsive) up to and including Visit 12 or Visit 12R;
- Number of separate episodes of SE after H144 at the end of Visit 8 or Visit 8R (no/yes); if yes,
  - SE, RSE, or SRSE diagnosis;
  - Cause;
  - Treatment, including experimental treatments and need for intubation/ventilation;
  - Dates of onset and duration.

Note that a separate episode of SE is defined as an episode of SE separated from other periods of status epilepticus by at least 24 hours.

- Diagnosis of epilepsy since Visit 11 or Visit 11R will be documented as a no/yes question. If a diagnosis of epilepsy has been made, further details will be documented, including:
  - Status as ongoing or new epilepsy since Visit 11 or Visit 11R after initiation of SAGE-547 treatment;
  - Details of anti-epileptic drugs currently being taken;
  - Type of epilepsy and seizure frequency in the past week.

## **11.2. Safety Assessments**

The safety and tolerability of SAGE-547 will be assessed using adverse events, clinical laboratory measures, vital signs, ECG intervals and morphology, and mortality. All safety assessments should be performed per hospital standard of care and will be collected periodically throughout the study according to [Table 1](#), [Table 2](#), and [Table 3](#) (Schedules of Assessments).

### **11.2.1. Adverse Events**

AEs will be collected after informed consent has been signed and prior to study-specific screening procedures not considered standard of care, during subject preparation for SAGE-547 administration and through Visit 12 or Visit 12R. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™) coding system (current version). See [Section 14](#) for additional details.

### **11.2.2. Clinical Laboratory Tests**

Blood samples will be taken for hematology, and serum chemistry and GFR will be calculated at:

- Visit 1 and then at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.
- Blood samples will be taken at Visit 11 or Visit 11R for serum chemistry (renal panel only).

Urine samples (20 ml) will be taken for urinalysis and urine NAG analysis at:

- Visit 1 and at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.

These samples will be analyzed at a central laboratory; hour-to-hour medical decisions will be based on sampling for laboratory testing done outside the protocol as part of normal standard of care. GFR will be calculated using values from local laboratory tests.

Any out-of-range values will be flagged by the laboratory; the investigator will add a comment about whether the abnormality is clinically significant. Clinical significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

#### **11.2.2.1. Hematology and Serum Chemistry**

Hematology will include complete blood count (CBC) white blood cell count with differential, platelet count and red blood cell (RBC) count, hemoglobin and hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose.

#### **11.2.2.2. Pregnancy Test**

Females of child-bearing potential will be tested for pregnancy by serum pregnancy test at Visit 1. In this study, since an accurate history of menstruation in girls and menopause in older women may not be available at Visit 1, “child-bearing potential” is taken to mean any female aged 10 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy. Female subjects with a positive pregnancy test will be ineligible for study participation.

#### **11.2.2.3. Urinalysis**

Urinalysis will include assessment of protein, blood, leukocytes, glucose, ketones, urobilinogen, pH, and specific gravity.

### **11.2.3. Vital Signs**

Blood pressure, heart rate, and temperature will be recorded at the following time points relative to the first infusion of study drug, and to the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547:

- Visit 1;
- At 0, +30, +60 minutes (+/-15 minutes) and +2, +4 and +8 hours (+/- 30 minutes) after the start of the infusion;
- At +24, +48, +72, +96, +120, +144, +168, and +192 hours (+/- 2 hours) after the start of the infusion.

#### **11.2.4. Weight and Height**

Weight and height will be measured at Visit 1 and weight will also be measured once during each 24 hour period of the first infusion of study drug, and of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547. These daily weights will be used to modify the dose of SAGE-547 if required.

#### **11.2.5. ECG**

12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours; at other times the allowed time window for ECGs is +/- 2 hours:

- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +128, +136, +144, +152, +160, and +192 hours after the start of the blinded (first) study drug infusion
- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +126, +132, +138, +144, +152, +160, and +192 hours after the start of the open-label (second) study drug

The heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm.

#### **11.2.6. Mortality**

Mortality will be recorded on the Visit 12 or Visit 12R case report form. If the subject has died, the following information will be collected:

- Date of death;
- Cause of death.

As accurate as possible cause of death will be collected, which will be further categorized as due to one of the following causes:

- SE;
- complications of long term intubation and third-line agent infusions;
- underlying cause of qualifying SE;
- co-morbidity existing at the time of the qualifying SE;
- new co-morbidity or trauma;
- study drug;
- other (specify).

### 11.2.7. Pharmacogenetic Samples

If a subject's LAR consents to pharmacogenetic sampling, a blood sample for genetic research will be collected at Visit 1 in order to avoid the possible introduction of bias through the exclusion of patients who may withdraw from study due to an AE (a subject population that may be of specific interest for subsequent genetic analysis). If for any reason a sample cannot be taken prior to treatment, a sample can be drawn at any point prior to completion with the restriction that no more than one genetic sample be taken per subject.

The objective of this research is to collect and store blood samples for possible DNA extraction and exploratory research into how genes or specific genetic variation may influence response (i.e. distribution, safety, tolerability, and efficacy) to SAGE-547. Specific genetic variations of interest include but are not limited to: classes of metabolizing enzymes (e.g. Cytochrome P450 supra-family genes), genes encoding enzymes involved in the production and metabolism of allopregnanolone (e.g. AKR1C4 (3 $\alpha$ -hydroxysteroid dehydrogenase)), genes associated with the GABA receptor (e.g. GABRA1-A6, GABRB1-B3, GABRD, GABRE, GABRG1-3) and genes associated with the production and degradation of GABA.

Future research may suggest other genes or gene categories as candidates for influencing not only response to SAGE-547 but also susceptibility to disorders for which SAGE-547 is being evaluated. Thus, the genetic research may involve study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.

#### 11.2.7.1. Biological Sampling and Coding Procedures (Pharmacogenetics)

To ensure patient confidentiality, utmost care will be taken in the coding and storage of pharmacogenetic samples.

*Extraction and coding:* DNA will be extracted from the blood sample and the DNA sample will be assigned a unique number replacing information from sampling tube. The assigned DNA number will be used to identify the sample and its corresponding information within Sage Therapeutics or at any designated contract laboratory for the purpose of sequencing of other DNA specific analysis. No personal details sufficient for individual identification will be available to any person (internal or external to Sage Therapeutics) working with the DNA.

*Genotype/Phenotype Analysis:* Samples and data from genetic analysis will be coded. The link between subject enrollment / randomization code and DNA number will be maintained and stored in a secure environment with restricted access. The established link will be used to identify relevant DNA samples for analysis, facilitated correlation of genotype results with clinical data, allow regulatory audit, and to trace samples for destruction in case of withdrawal of consent.

#### 11.2.7.2. Retention of Biological Samples for Pharmacogenetic Analysis

Extracted DNA is a finite research that is destroyed in the process of being analyzed. Primary blood samples from which DNA can be extracted will be stored and used until no further analyses are possible, a maximum storage period of 25 years from time of last subject last visit has been reached, or an individual or LAR withdraws his/her or their consent.

## 11.2.8. Other Outcomes

### 11.2.8.1. Pharmacokinetic Data

Formal plasma and urine analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS)). In addition, all samples will be analyzed for important SAGE-547 metabolites (if and when these are identified) and Captisol® concentrations.

#### Plasma Analysis

Plasma will be collected to assay for SAGE-547 concentrations at the following time points relative to the start of each infusion of study drug:

- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion.
- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open label SAGE-547 study drug infusion.
- All samples will also be analyzed for plasma concentrations of important metabolites of SAGE-547 if and when these are identified.
- All samples will also be analyzed for plasma concentrations of Captisol®.

The plasma samples will be drawn from the arm contralateral to that used for drug administration. Drawing samples from peripheral arterial or venous lines or from a central line is permissible. PK collection times should be adhered to as strictly as possible. The allowed time window for all samples is: pre-dose in the two hours prior to starting the infusion of study drug; samples up to and including 1h, +/- 5 minutes; subsequent samples, +/- 15 minutes. Subject-specific PK kits for sampling including instructions on collection and processing methods, and storage and shipping conditions, will be provided separately. To maintain the blind, all subjects will have samples taken as outlined above: subjects receiving SAGE-547 will have all samples analyzed for all analytes. Subjects on placebo may have samples analyzed to investigate endogenous allopregnanolone and metabolite concentrations, as well as Captisol® concentrations; experience with the plasma concentration data will determine if and which placebo samples are analyzed.

Each blood sample will be 3 ml in volume for adults and children weighing 30 kg or more, and 2 ml in volume for children weighing less than 30 kg. Separate aliquots will be obtained from each sample to service the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum blood draw for PK analysis for a subject having two infusions of study drug will be 99 ml (66 ml for children weighing less than 30 kg).

Plasma PK parameters for SAGE-547 will be calculated where appropriate (e.g.,  $C_{max}$ ,  $C_{min}$ ,  $t_{max}$ ,  $AUC_{last}$ ,  $AUC_{\infty}$ ,  $CL_s$ ). In addition, similar PK parameters will be calculated for Captisol®. PK parameters for important metabolites of SAGE-547 may be calculated. An evaluation will be made

of the feasibility of adopting a population-PK approach to assess drug-drug-interactions with SAGE-547 as victim of AEDs.

In addition, the Visit 9 sample may be analyzed for plasma concentrations of third-line agents.

#### Other Analysis

If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations.

Full details of all pharmacokinetic analyses will be described in the Pharmacokinetic Analysis Plan.

#### **11.2.8.2. Correlation of QT/QTc Changes and Plasma Concentrations of SAGE-547**

An analysis will be performed to determine whether there is any correlation between changes in QT/QTc interval and plasma concentrations of SAGE-547, in order to investigate any effect that SAGE-547 may have on QT/QTc interval.

#### **11.2.8.3. Pharmacoeconomic Data**

At Visit 12 or Visit 12R, the following information will be collected: number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital. If the subject dies before Visit 12 or Visit 12R, data will be collected up to the date of death. The definition of “hospital” is the institution that the subject was initially treated in. If the subject is transferred to another hospital, that hospital would be the “discharge destination from the hospital” and the “number of days in hospital” would be the number of days in the initial treating hospital.

For those subjects discharged from hospital before Visit 12/12R, the following questions will be asked:

- On what study day was the subject discharged from hospital?
- What type of facility was the subject discharged to (another hospital, a rehabilitation center, a supported care facility, home, other)?
- How many days did the subject stay in this facility?

The following questions will be answered regarding the stay in the ICU and hospital:

- Was the subject still in the ICU at the end of Visit 10/10R?
- If the FOUR Score was  $\geq 12$  at Visit 10/10R and the subject was in the ICU at Visit 10/10R, what was the reason for the subject not being discharged from the ICU (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, other)?
- Was the subject still an in-patient in the hospital at the end of Visit 12/12R?
- If the FOUR Score was  $\geq 15$  at Visit 12/12R and the subject was in the hospital at Visit 12/12R, what was the reason for the subject not being discharged from the hospital (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, unsuitable home circumstances, other)?



#### **11.2.8.4. STESS**

The STESS will be assessed during Visit 1 in order to assess the severity of the status epilepticus.

#### **11.2.8.5. FOUR Score**

The Full Outline of UnResponsiveness or FOUR Score is designed to assess conscious level and unlike other scores, is suitable for subjects who are intubated. It assesses four domains of neurological function (eye responses, motor responses, brainstem reflexes, and breathing pattern).

The FOUR Score will be collected at the following time points relative to each infusion of study drug (the initial blinded infusion and the second open-label infusion if this is administered):

- baseline, +24, +48, +72, +96, +120, +144, +168, and +192 hours (all +/- 2 hours) after the start of the infusion, and at Visit 11/11R and Visit 12/12R.

#### **11.2.8.6. Glasgow Outcome Scale (GOS)**

The GOS is a relatively common assessment scale used to standardize descriptions of the objective degree of recovery from brain injury such as cerebral trauma, or in this case SRSE. It was first used in 1975 ([Jennett and Bond 1975](#)) and allows a prediction of the long-term course of rehabilitation to return to work and everyday life. The scale classifies subjects into 5 groups:

- Death
- Persistent vegetative state
- Severe disability
- Moderate disability
- Good recovery

The GOS will be assessed at Visit 12 or Visit 12R.

#### **11.2.8.7. Supervision Rating Scale (SRS)**

The Supervision Rating (SRS) measures the level of supervision that a patient/subject receives from caregivers. The SRS rates level of supervision on a 13-point ordinal scale that can optionally be grouped into five ranked categories (Independent, Overnight Supervision, Part-Time Supervision, Full-Time Indirect Supervision, and Full-Time Direct Supervision). The SRS was designed to be rated by a clinician based on interviews with the subject and an informant who has observed at first hand the level of supervision received by the subject ([Boake 2000](#)). Scoring is a one-step procedure in which the clinician assigns the rating that is closest to the subject's level. Ratings are based on the level of supervision received, not on how much supervision a subject is judged or predicted to need.

The SRS will be assessed at Visit 1 and Visit 12 or Visit 12R. The Visit 1 assessment will be a retrospective assessment of the supervision required by the subject immediately prior to the admission that included the index episode of status epilepticus.

#### **11.2.8.8. Modified Rankin Scale – 9Q (mRS-9Q)**

The Modified Rankin Scale (mRS) is a commonly used scale to determine disability and functional dependence due to neurological insult such as stroke in adults. The 7-point scale (0 – 6) denotes functional capacity from no symptoms (0) to severe disability (5) and death (6). The Modified

Rankin Scale – 9Q is a shortened version consisting of 9 questions that reliably determines the mRS score and was developed to both simplify the assessment and expand the rater base to non- medically trained personnel (Patel, Rao et al. 2012). The assessment is a web-based tool in the public domain with automatic score calculation and error checking found at [www.modifiedrankin.com](http://www.modifiedrankin.com).

The mRS will be assessed at Visit 1 and at Visit 12 or Visit 12R in subjects  $\geq 17$  years of age. The baseline assessment will be a retrospective assessment of the disability and dependence of the subject immediately prior to the admission that included the index episode of status epilepticus.

## 12. STUDY PROCEDURES

The study procedures listed below by study day reflect the required data collection times for this protocol. When a time window is necessary, this is specified below. If no time window is specified, the test may be performed at any time within the specified 24-hour period.

### 12.1. Visit 1 (V2-≤30h)

The baseline period will be up to approximately 84 hours prior to starting blinded study treatment and should include the assessments/procedures listed below and summarized in [Table 1 and Table 2 \(for retreatment\)](#), the Schedules of Events.

- Informed consent
- Eligibility checklist
- Verification of inclusion/exclusion criteria.
- Demographic information and medical history obtained by proxy and confirmed by the subject when possible.
- SE and wean history
- Blood will be collected from female subjects 10 years to 55 years for a serum pregnancy test unless they are known to be pre-menstrual or post-menopausal or to have had a hysterectomy.
- Blood and urine samples collected for clinical laboratory testing.
- Pharmacogenetic sample will be collected from consenting/eligible subjects.
- Vital signs
- Height
- Weight
- An ECG reading taken.
- Administration of the STESS.
- Administration of the FOUR Score.
- Administration of SRS.
- Administration of the mRS-9Q assessment.
- Assessment of the CGI scale.
- Evaluation of epilepsy status.
- Administration of continuous IV third-line agents.
- Perform EEG.
- Recording of adverse events.
- Recording of previous and concomitant anti-epileptic drugs.
- Recording of previous and concomitant third-line agents.
- Recording of concomitant pressors.

- Recording of other concomitant medications, procedures, and treatments.

## **12.2. Visit 2 (V3-≤54h)**

- Recording of adverse events.
- Recording of concomitant anti-epileptic drugs.
- Recording of concomitant third-line agents.
- Recording of concomitant pressors.
- Recording of other concomitant medications, procedures, and treatments.
- Wean of continuous third-line agent:
  - If wean is successful, subject is followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (these subjects are Qualifying Wean Success subjects or QWS subjects);
  - If wean is not successful, there is ongoing intravenous administration of at least one continuous IV third-line agent and EEG is performed and the subject is randomized.

## **12.3. SAGE-547 Treatment Period**

### **12.3.1. Visit 3/3R (0-24 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs will be recorded at:
  - 0, +30, +60 minutes (+/-15 minutes) and +2, +4, +8 (+/- 30 minutes) and +24 hours (+/- 2 hours) after the start of the infusion
- ECG readings will be recorded immediately after PK sampling at:
  - 0 (pre-dose) and at +0.5, +1, +3, +6, +12, and +24 hours after the start of the blinded study drug infusion.
- A blood sample for PK analysis should be collected at the following time points (all +/- 15 minutes except where otherwise stated):
  - 0 (pre-dose, within two hours of the start of the infusion) and at +0.5, +1 (+/- 5 minutes), +3, +6, +12, and +24 hours after the start of the blinded study drug infusion.
- Completion of the FOUR Score
  - +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the end of the QW)
- Ongoing intravenous administration of a continuous IV third-line agent.
- Study drug administration in loading (Hour 0-1) and maintenance infusions (at completion of Hour 1).

- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.2. Visit 4/4R (25-48 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +48 hours (+/- 2 hours) after the start of the infusion
- An ECG reading taken immediately after PK sampling:
  - +48 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +48 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +48 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent.
- Ongoing study drug maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.3. Visit 5/5R (49-72 hours)**

- Weight
- Vital signs should be recorded at:
  - +72 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +72 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +72 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +72 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:

- initiate weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.4. Visit 6/6R (73-96 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +96 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +96 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +96 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +96 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Perform EEG.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.5. Visit 7/7R (97-120 hours)**

- Weight
- Vital signs should be recorded at:
  - +120 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +120 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:

- +120 hours (+/- 15 minutes) after the start of study drug infusion, immediately prior to the end of the maintenance infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +120 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled. Complete wean by 120 hours if at all possible.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## **12.4. SAGE-547 Taper Period**

### **12.4.1. Visit 8/8R (121-144 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +144 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after each PK sampling:
  - +128, +136 hours and +144 hours after the start of the study drug infusion
  - During the open-label retreatment phase of the study ECG readings at: +126, +132, +138 hours and +144 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected (+/- 15 minutes unless otherwise stated):
  - +128 (immediately prior to the end of the first taper step), +136 hours (+/- 5 minutes, immediately prior to the end of the second taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of study drug infusion.
  - During the open-label retreatment phase of the study PK blood draws at: +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 hours (+/- 5 minutes, immediately prior to the end of the third taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of the study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +144 hours (+/- 2 hours) after the start of the infusion
- Complete wean of third line agents by H144 if not completed by H120.

- Perform EEG.
- Taper of SAGE-547 infusion begins at hour 121.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## **12.5. Follow-up Period**

### **12.5.1. Visit 9/9R (145-168 hours)**

- Vital signs should be recorded at:
  - +168 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +152, +160 hours (+/- 2 hours) after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +152 and +160 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +168 hours (+/- 2 hours) after the start of the infusion
- Perform EEG.
- Assessment of the presence of physiologic brain activity using EEG.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.5.2. Visit 10/10R (169-192 hours)**

- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +192 hours (+/- 2 hours) after the start of the infusion
- At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine retreatment with higher dose of study drug. All patients for retreatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.



- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.3. Visit 11/11R (Visit 3/3R + 14d ( $\pm 2$ ))**

- Blood samples collected for clinical laboratory testing (renal panel only).
- Completion of the FOUR Score (QWS subjects also).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.4. Visit 12/12R (Visit 3/3R + 21d ( $\pm 2$ ))**

All assessments also performed for QWS subjects.

- Completion of the FOUR Score.
- Administration of the GOS.
- Administration of the SRS.
- Administration of the mRS-9Q assessment.
- Evaluation of epilepsy status (see [Section 11.1.2.2](#) for details).
- Assessment of the CGI Scale.
- Recording of adverse events.
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications.
- Collection of pharmacoeconomic data.
- Mortality will be assessed throughout the study period.

## **13. STATISTICS**

### **13.1. Statistical Plan**

Complete details for the analysis and reporting of data from this study will be contained in the Statistical Analysis Plan (SAP).

#### **13.1.1. Interim Analysis**

When approximately 50% of subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### 13.1.2. Study Populations

The **Safety Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to actual treatment. This analysis population will be used for all safety analyses.

The **Intent to Treat Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to randomized treatment. This analysis population will be used for all efficacy analyses.

The **Modified Intent to Treat Population** is defined as all subjects who:

1. complete their initial course of blinded SAGE-547 or placebo treatment unless the non-completion was due a drug-related adverse event; and
2. have at least one attempt to wean from third-line agents prior to the end of blinded study treatment infusion unless the failure to wean was because seizures were not controlled.

Subjects will be classified according to randomized treatment. This analysis population will be used for sensitivity analyses of the primary endpoint and select secondary efficacy endpoints.

Narratives will be prepared for all subjects who do not complete the infusion of blinded study medication or were not subjected to any wean attempts. Narratives will include details of the cause of SE, the comorbid conditions, the adverse event(s), and reasons for non-completion of the infusion or failure to attempt weaning. This blinded narrative will be reviewed by the medical monitors and the patient adjudicated as MITT eligible or ineligible. Acceptable reasons for defining a subject as MITT ineligible include death or withdrawal of consent due to progression of the underlying cause of SE or comorbid conditions, unless the cause of death or progression of disease were thought by the investigator, sponsor, or DSMB to be related to study drug.

The **Per-Protocol (PP) Population** is defined as a subset of the MITT population but will exclude data from all subjects with significant protocol violations or deviations. Subjects will be classified according to actual treatment received. This data set will be used for sensitivity analyses to examine the robustness of results for the primary and key secondary efficacy endpoints.

The **Pharmacokinetics Population** is defined as all subjects who at least had an infusion of blinded SAGE-547 initiated and have at least one pharmacokinetic sample collected.

The **Pharmacogenetic Population** is defined all subjects who consent to being included in the pharmacogenetic assessment and provide a pharmacogenetic sample.

Summary statistics of all data collected will be presented for subjects who were QW successes.

### 13.1.3. General Aspects

Tabular displays of descriptive statistics will be provided for all variables. Summary tables will include n, mean, mean, standard deviation, minimum and maximum for continuous variable and frequency and percentage for categorical variables.

### 13.1.4. Analysis of Primary Endpoint

The analysis of response to treatment (see Section 11.1.1 for definition of primary endpoint) between SAGE-547 treated subjects and placebo treated subjects will be performed on the ITT population using a Cochran-Mantel-Haenszel (CMH) test with variables for treatment, concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to

randomization (one vs two or more). The CMH general association statistic and its associated p-value will be presented. The comparison of treatment response rates will be conducted at the 5% level of significance. To confirm the CMH results, a permutation test will also be conducted.

An additional analysis of the primary endpoint will also be performed on the MITT population. In addition sensitivity analyses of the primary endpoint will be performed using the ITT population based on:

- the number of third-line agents (one, two, or three) subjects were administered post-randomization; and
- which third line agent was the subject of the first TW.

### **13.1.5. Analysis of Secondary Efficacy Endpoints**

Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section (Section 6). Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. The analysis of the secondary endpoints will also be performed on the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

### **13.1.6. Analysis of Other Endpoints**

Safety and “Other” endpoints will only be summarized by treatment group.

Summaries of safety endpoints will be based on the overall Safety Population.

### **13.1.7. Epilepsy and SRSE Status**

Diagnosis of epilepsy and recurrence of RSE or SRSE will be documented as the percentage of subjects by time point and overall. Kaplan-Meier curves may be plotted if sufficient data are available.

Utilization of AEDs during follow-up and during recurrence will be summarized.

### **13.1.8. Questionnaires**

The data collected from each questionnaire will be interpreted according to the standard methodology for that questionnaire. There will be no adjustment for missing values.

### **13.1.9. Pharmacokinetic Data Analysis**

Details of the pharmacokinetic data analysis will be described in detail in a separate Pharmacokinetic Analysis Plan.

### **13.1.10. Pharmacogenetic Data Analysis**

Any genotype data generated in this study will be stored within a secured database within Sage Therapeutics and / or a third party contracted to work with Sage Therapeutics to analyze the samples. Because the number of subjects agreeing to participate in the genetic research component of the study is unknown, it is not possible to establish, a priori, whether sufficient samples will be obtained to support formal statistical evaluation of data. As a consequence a Pharmacogenetic Analysis Plan will only be prepared where appropriate and the results obtained from any genetic research will be reported in a report separate from the main study CSR.

### **13.1.11. Retreated Subjects**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are retreated with SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo.

### **13.1.12. EEG-Responders**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who are classified as EEG-responders/non-responders based on the independent assessment of the PAEEG. Summaries will be derived for the two randomized treatment groups.

### **13.1.13. QT/QTc Assessment**

An analysis of the correlation between changes in QT/QTc intervals and SAGE-547 plasma levels will be performed to investigate if there is a potential effect that SAGE-547 may have on QT/QTc interval. A detailed description of the QT/QTc assessment will be included in the SAP.

### **13.1.14. Quantitative EEG**

The six EEG records for each subject may be subjected to exploratory quantitative EEG analysis, the details of which will be included in the EEG Analysis Plan. In summary the following comparisons may be made, SAGE-547 versus placebo: the QWEEG versus the TWEEG (main analysis); the CEEG versus PAEEG (subsidiary analysis); and TAEEG versus PAEEG (exploratory analysis).

## **13.2. Determination of Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between treatment groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

### **13.3. Statistical Analysis Plan**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

## **14. ADVERSE EVENTS**

The safety procedures in this study will be detailed in a Safety Management Plan, which will be agreed and signed before the first subject is randomized in the study. [Section 14.1](#) summarizes Investigator responsibilities regarding the identification and documentation of AEs, the classification of AEs for relationship to study drug and severity, and the reporting of AE information to the Sponsor and the IRB.

[Section 14.2](#) summarizes Sponsor/Medical Monitor Responsibilities regarding monitoring of AE data and reporting relevant safety information to FDA.

[Section 14.3](#) lists important AE definitions.

### **14.1. Investigator Responsibilities**

#### **14.1.1. Identification and Documentation of Adverse Events by Investigator**

Subjects will be evaluated and questioned generally (if possible) to identify AEs during the course of the study. AEs will be collected from the signature of the consent form through Visit 12/12R. Adverse events that occur prior to completion of screening will be captured on the Medical History eCRF. Adverse events that occur after completion of screening will be recorded on the Adverse Event eCRF.

All AEs revealed by observation, other diagnostic procedures, or spontaneously reported by the subject and/or in response to an open question from study personnel will be recorded on the Adverse Event Form. Any clinically significant deterioration in laboratory assessments or other clinical findings are considered an AE and must be recorded on the Adverse Event Form, unless otherwise stated. AE information recorded will be entered into the database on an ongoing basis.

AEs with a relationship considered related to study drug (probable, possible) should be followed until the event is resolved or the Investigator determines the event is stable or no longer clinically significant. AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

For SAEs, an electronic Serious Adverse Event eCRF must be completed with as much information as possible and submitted in the time frame described below in [Section 14.1.3](#). When new significant information is obtained as well as when the outcome of an event is known, the electronic SAE eCRF should be updated within 24 hours. If the subject was an outpatient at the time of the SAE and was re-hospitalized due to the SAE, a copy of relevant hospital records (e.g., admission report, laboratory test results, discharge summary, etc.) may be requested to be included as part of the subject medical file.

All SAEs will be followed until resolved or until a stable status has been achieved.

**14.1.2. Adverse Event Classification****14.1.2.1. Relationship to Investigational Drug**

None:	No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state.
Possible:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject, but this is not known for sure.
Probable:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

**14.1.2.2. Severity**

Mild	Discomfort noticed, but no disruption to daily activity.  For subjects that are unconscious, this may be a slight or minor change in a lab result or clinical sign or symptom that does not require immediate corrective action.
Moderate	Discomfort sufficient to reduce or affect normal daily activity, but is not hazardous to health; prescription drug therapy may be employed to treat the AE.  For subjects that are unconscious, this may be a clinically meaningful change that may require immediate corrective action.
Severe	Inability to work or perform normal daily activity and represented a definite hazard to health; prescription drug therapy and/or hospitalization may be employed to treat the AE.  For unconscious subjects, this may be a significant clinical change that requires immediate corrective action.

**14.1.2.3. Action Taken with Investigational Drug**

None	Study medication was continued without change.
Discontinued	Study medication was terminated.
Dose adjusted	Study medication dose/infusion rate was changed and then continued per protocol.
Interrupted	Study medication was interrupted and then continued per protocol.
Unknown	The action taken with regard to study medication is unknown.
Not applicable	Administration of study medication was not ongoing.

**14.1.2.4. Assessment of Outcome**

Ongoing	At the end of the study, the event has not resolved or stabilized.
Ongoing and stable	The event is ongoing but has stabilized and is unlikely to change
Resolved	The event has resolved or the subject recovered without sequelae.
Resolved with sequelae	The event has at least one secondary outcome that may result in permanent disability and/or functional limitation.
Unknown	The status of the event is unknown.
Death	The subject has expired.

**14.1.3. Investigator Reporting to Sponsor and Sponsor Emergency Contact**

All new SAEs that come to the Investigator and/or Sponsor's notice during the course of the study (up to and including the last study visit) must be reported by the Investigator on the designated electronic report form within 24 hours of the point in time when the Investigator becomes aware of the SAE. As additional information becomes available, the designated electronic report form must be updated within 24 hours.

Investigators must report any SAE, whether or not considered drug related. The report must include an assessment of whether there is a reasonable possibility that the drug caused the event.

In a medical emergency (ie, an event that requires immediate attention regarding the treatment of a subject, operation of the clinical study, and/or the use of investigational drug), study site staff will apply appropriate medical intervention according to current standards of care, and contact the Medical Monitor.

**14.1.4. Medical Monitor and Emergency Contact Information**

[REDACTED], MD  
[REDACTED]

**14.1.5. SAE Reporting Contact Information**

Contact information and reporting instructions are provided in the Safety Management Plan.

**14.1.6. Reporting to Institutional Review Boards (IRBs)**

It is the responsibility of the Investigator to promptly notify the institution's IRB of all serious and unexpected suspected adverse reactions (see [Section 14.3](#) for definitions).



## **14.2. Sponsor/Medical Monitor Responsibilities**

### **14.2.1. Monitoring of Adverse Event Data**

The Medical Monitor will review any newly reported adverse events in an ongoing basis. If the aggregate assessment indicates that an event is occurring more frequently than would normally be expected in this population, or as previously observed, and the sponsor believes that the events are causally related to the administration of SAGE-547, the Sponsor will then report that information in an IND safety report.

### **14.2.2. Data Safety Monitoring Board**

An independent DSMB will monitor the clinical, PK and PD data for safety signals throughout the study and will be asked to assess the placebo response rate at the time of the interim analysis to determine final sample size. In order to perform their monitoring function the DSMB will have access to un-blinded safety data as necessary.

The composition and procedures for the board will be described in a separate DSMB Charter.

### **14.2.3. Reporting to FDA**

The Sponsor must report in an IND safety report any suspected adverse reaction to study treatment that is both serious and unexpected (21 CFR 312.32(c)(1)(i)). Before submitting an IND safety report, the Sponsor will ensure the event meets all three of the definitions: (1) suspected adverse reaction, (2) serious, (3) unexpected. If the AE does not meet all three of the definitions, it should not be submitted as an IND safety report. The Sponsor should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the adverse event and, therefore, that the event meets the definition of a suspected adverse reaction.

If there is a serious and unexpected suspected adverse reaction, the Sponsor will notify the appropriate regulatory agency(ies) and all appropriate parties on an expedited basis. In addition, Sponsors must submit expedited reports of an increased rate of occurrence or severity of serious suspected adverse reactions over that listed in the protocol or Investigational Brochure.

SUSARs will be unblinded prior to reporting to FDA. Unless it is necessary to unblind for the safety of the patient, the investigator will not be informed of the unblinding of the subject.

Under 21 CFR 312.32, Sponsors should identify in the protocol SAEs that it does not plan to report individually in an expedited manner, because they are known consequences of the disease or otherwise common in the study population. Given the grave condition and prognosis of SRSE being studied, individual occurrences of seizures or seizure activity will not be reported expeditiously in this study. Regardless of which events are reported in an expedited manner, all adverse events will be closely monitored throughout the study.

## **14.3. Adverse Event Definitions**

### **14.3.1. Adverse Event**

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

### **14.3.2. Suspected Adverse Reaction**

Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

### **14.3.3. Life-Threatening**

An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

### **14.3.4. Serious**

An AE or suspected adverse reaction is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE – see definition above
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disability
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

### **14.3.5. Unexpected**

An AE or suspected adverse reaction is considered “unexpected”:

- If it is not listed in the Investigational Brochure or is not listed at the specificity or severity that has been observed, or
- If an Investigational Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigational Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigational Brochure listed only cerebral vascular accidents.

“Unexpected,” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigational Brochure as occurring with a class of drugs or as anticipated from

the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

#### **14.4. Emergency Identification of Study Medication**

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject's treatment in the study via the IVRS; this normally requires prior approval by the medical monitor. However, if the subject is at immediate risk and the Investigator believes that immediate knowledge of the study treatment will alter medical management, discussion with the medical monitor may take place after unblinding. The Investigator will not unblind the medical monitor during that discussion. The process of unblinding will ensure that only the investigator is unblinded; the medical monitor, study management team, and data management team will not be made aware of the treatment allocation of an individual subject. All cases of emergency unblinding will be fully documented in a way that does not unblind the medical monitor, study management team, and data management team.

### **15. STUDY ADMINISTRATIVE CONSIDERATIONS**

#### **15.1. Quality Control and Quality Assurance**

The Investigators and institutions will permit trial related monitoring, audits, IRB review, and regulatory inspections as requested by FDA, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed informed consent forms, etc.) in addition to case report forms.

Quality assurance and quality control systems with written standard operating procedures (SOPs) will be followed to ensure this trial will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The site's dedicated study monitor will arrange to visit the Investigator at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be identified and resolved. The study monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality assurance officers named by Sage Therapeutics or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements, made by the Sponsor with the Investigator/institution and any other parties involved with the clinical trial, will be in writing in a separate agreement.

## **15.2. Data Handling and Recordkeeping**

### **15.2.1. Data Handling**

Procedures for data handling (including electronic data) used in this protocol will be documented in a Data Management Plan.

### **15.2.2. Case Report Form Completion**

eCRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of demographics, study drug administration, study procedures, AEs, questionnaire completion, efficacy assessments and subject status, including survival.

The Investigator will maintain copies of the eCRFs at the study site. For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate eCRF.

### **15.2.3. Retention of Study Records**

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval and until there are no pending or contemplated marketing applications or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to an appropriate person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

## **15.3. Confidentiality**

To maintain subject privacy, all eCRFs, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available trial registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by Sage Therapeutics to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

#### **15.4. Publication Policy**

All information concerning SAGE-547 is considered confidential and shall remain the sole property of Sage Therapeutics. The Investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval from Sage Therapeutics. No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between Sage Therapeutics and the Investigator.

#### **15.5. Protocol Amendments**

Changes to the conduct of the study should be prepared as a protocol amendment by the Sponsor. Protocol amendments should receive written IRB/IEC approval prior to implementation at the investigative site, except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the trial (eg, change of monitor, telephone numbers). In this case, Sage Therapeutics will amend and implement the protocol change and subsequently notify the regulatory authorities and the Investigative sites who will notify the respective IRB, as appropriate.

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**APPENDIX 1. APPENDIX 1: FOUR SCORE****FOUR score****Full Outline of UnResponsiveness****Eye response**

- E4: eyelids open or opened, tracking, or blinking to command
- E3: eyelids open but not tracking
- E2: eyelids closed but open to loud voice
- E1: eyelids closed but open to pain
- E0: eyelids remain closed with pain

**Motor response**

- M4: thumbs-up, fist or peace sign
- M3: localizing to pain
- M2: flexion response to pain
- M1: extension response to pain
- M0: no response to pain or generalized myoclonus status

**Brainstem reflexes**

- B4: pupil and corneal reflexes present
- B3: one pupil wide and fixed
- B2: pupil or corneal reflexes absent
- B1: pupil and corneal reflexes absent
- B0: absent pupil, corneal and cough reflex

**Respiration pattern**

- R4: not intubated, regular breathing pattern
- R3: not intubated, Cheyne-Stokes breathing pattern
- R2: not intubated, irregular breathing
- R1: breathes above ventilatory rate
- R0: breathes at ventilator rate or apnea

Reference ([Iyer, Hoel et al. 2009](#)).



**APPENDIX 2. GLASGOW OUTCOME SCALE (GOS)****GLASGOW  
OUTCOME  
SCALE**

Patient Name: \_\_\_\_\_  
 Rater Name: \_\_\_\_\_  
 Date: \_\_\_\_\_

*Note:* The scale presented here is based on the original article by Jennett and Bond. It has become common practice in clinical trial administration, however, to use a modified version that places the scores in reverse order (i.e., "good recovery" = 1, "moderate disability" =2, etc.).

Score	Description
1	DEATH
2	PERSISTENT VEGETATIVE STATE Patient exhibits no <i>obvious cortical</i> function.
3	SEVERE DISABILITY (Conscious but disabled). Patient depends upon others for daily support due to mental or physical disability or both.
4	MODERATE DISABILITY (Disabled but independent). Patient is independent as far as daily life is concerned. The disabilities found include varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes.
5	GOOD RECOVERY Resumption of normal activities even though there may be minor neurological or psychological deficits.

**TOTAL (1-5):** \_\_\_\_\_

Reference ([Jennett and Bond 1975](#)).

## APPENDIX 3. SUPERVISION RATING SCALE (SRS)

### SUPERVISION RATING SCALE (SRS)

**Instructions:** Circle the rating that is closest to the amount of supervision that the patient *actually receives*. "Supervision" means that someone is responsible for being with the patient.

<u>Rating</u>	<u>Description</u>
<b>Level 1: INDEPENDENT</b>	
1	The patient lives alone or independently. Other persons can live with the patient, but they cannot take responsibility for supervision (for example, a child or elderly person).
2	The patient is unsupervised overnight. The patient lives with one or more persons who <i>could</i> be responsible for supervision (for example, a spouse or roommate), but they are <i>all</i> sometimes absent overnight.
<b>Level 2: OVERNIGHT SUPERVISION</b>	
3	The patient is only supervised overnight. One or more supervising persons are always present overnight but they are <i>all</i> sometimes absent for the rest of the day.
<b>Level 3: PART-TIME SUPERVISION</b>	
4	The patient is supervised overnight and part-time during waking hours, but is allowed on independent outings. One or more supervising persons are always present overnight and are also present during part of waking hours every day. However, the patient is sometimes allowed to leave the residence without being accompanied by someone who is responsible for supervision.
5	The patient is supervised overnight and part-time during waking hours, but is unsupervised during working hours. Supervising persons are <i>all</i> sometimes absent for enough time for them to work full-time outside the home.
6	The patient is supervised overnight and during most waking hours. Supervising persons are <i>all</i> sometimes absent for periods longer than one hour, but less than the time needed to hold a full-time job away from home.
7	The patient is supervised overnight and during almost all waking hours. Supervising persons are <i>all</i> sometimes absent for periods shorter than one hour.
<b>Level 4: FULL-TIME INDIRECT SUPERVISION</b>	
8	The patient is under full-time indirect supervision. At least one supervising person is <i>always</i> present, but the supervising person does not check on the patient more than once every 30 minutes.
9	Same as #8 plus requires overnight safety precautions (for example, a deadbolt on outside door).
<b>Level 5: FULL-TIME DIRECT SUPERVISION</b>	
10	The patient is under full-time direct supervision. At least one supervising person is always present and the supervising person checks on the patient more than once every thirty minutes.
11	The patient lives in a setting in which the exits are physically controlled by others (for example, a locked ward).
12	Same as #11 plus a supervising person is designated to provide full-time line-of-sight supervision (for example, an escape watch or suicide watch).
13	The patient is in physical restraints.

3/12/93

Corwin Boake, Ph.D., TIRR, 1333 Moursund, Houston, TX 77030-3405, 713/799-6990

## APPENDIX 4. MODIFIED RANKIN SCALE – LEVEL OF FUNCTION SURVEY (mRS-9Q)

1. Do you have any symptoms that are bothering you? (For example, trouble with reading or writing, trouble speaking, problems with vision, numbness, weakness, balance trouble, or problems with swallowing?)	YES <input type="radio"/>	NO <input type="radio"/>
2. Are you able to do the same work as before?	YES <input type="radio"/>	NO <input type="radio"/>
3. Are you able to keep up with your hobbies?	YES <input type="radio"/>	NO <input type="radio"/>
4. Have you maintained your ties to friends and family?	YES <input type="radio"/>	NO <input type="radio"/>
5. Do you need help making a simple meal, doing household chores, or balancing a checkbook?	YES <input type="radio"/>	NO <input type="radio"/>
6. Do you need help with shopping or traveling close to home?	YES <input type="radio"/>	NO <input type="radio"/>
7. Do you need another person to help you walk?	YES <input type="radio"/>	NO <input type="radio"/>
8. Do you need help with eating, going to the toilet, or bathing?	YES <input type="radio"/>	NO <input type="radio"/>
9. Do you stay in bed most of the day and need constant nursing care?	YES <input type="radio"/>	NO <input type="radio"/>

## APPENDIX 5. CLINICAL GLOBAL IMPRESSION (CGI)

### Clinical Global Impression (CGI)

#### 1. Severity of illness

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- |                             |   |
|-----------------------------|---|
| 0 = Not assessed            | 4 = Moderately ill                        |
| 1 = Normal, not at all ill  | 5 = Markedly ill                          |
| 2 = Borderline mentally ill | 6 = Severely ill                          |
| 3 = Mildly ill              | 7 = Among the most extremely ill patients |

#### 2. Global improvement: Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.

Compared to his condition at admission to the project, how much has he changed?

- |                        |                     |
|------------------------|---------------------|
| 0 = Not assessed       | 4 = No change       |
| 1 = Very much improved | 5 = Minimally worse |
| 2 = Much improved      | 6 = Much worse      |
| 3 = Minimally improved | 7 = Very much worse |

#### 3. Efficacy index: Rate this item on the basis of drug effect only.

Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.

EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect		Side effects			
		None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
<b>Marked</b>	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
<b>Moderate</b>	Decided improvement. Partial remission of symptoms	05	06	07	08
<b>Minimal</b>	Slight improvement which doesn't alter status of care of patient	09	10	11	12
<b>Unchanged or worse</b>		13	14	15	16
Not assessed = 00					

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

**APPENDIX 6. STATUS EPILEPTICUS SEVERITY SCORE (STESS)**

Outcome Predictor	Feature	Score
Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type (prior to first treatment)	Simple-partial, complex-parial, absence, myoclonic (complicating idiopathic generalized epilepsy)	0
	Generalized-convulsive	1
	Nonconvulsive status epilepticus in coma	2
Age	< 65 years	0
	≥ 65 years	2
History of previous seizures	Yes	0
	No or unknown	1
Summed Total		

**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY  
TO EVALUATE THE EFFICACY AND SAFETY OF SAGE-547 INJECTION  
IN THE TREATMENT OF SUBJECTS WITH SUPER-REFRACTORY  
STATUS EPILEPTICUS**

**PROTOCOL NUMBER: 547-SSE-301**

**IND NUMBER: 117901**

**EudraCT Number: 2015-002142-31**

Product: SAGE-547 Injection (allopregnanolone)

Sponsor Contact: [REDACTED], MD

[REDACTED]  
Sage Therapeutics  
215 First Street  
Cambridge, MA 02142

Medical Monitor: [REDACTED], MD

Date of Protocol: 09 March 2015

Date of Amendment One 27 May 2015

Date of Amendment One 01 March 2016  
(Denmark Specific)

**Confidentiality Statement**

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

**PROTOCOL NUMBER: 547-SSE-301**

Sponsor [REDACTED]:

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]:

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

CRO [REDACTED]:

[REDACTED]

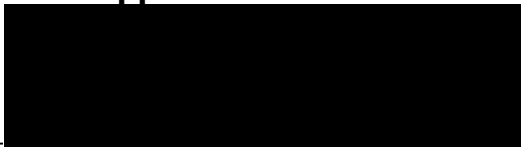
## 1. SIGNATURE PAGE

Title of Protocol:

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus

Protocol No: 547-SSE-301


### Sponsor Approval



01 March 2016

, MD

\_\_\_\_\_  
Date (dd/mmm/yyyy)

  
Sage Therapeutics

### Investigator Agreement

By signing this page I attest that I have read and understand the contents of Clinical Protocol 547-SSE-301 and any current amendments. I agree to adhere to the design, conduct, and reporting requirements of the study as stated in the clinical protocol and to my obligations to the Sponsor as described in the protocol and executed contracts between myself, my Institution, and the Sponsor. I also agree to adhere to any subsequent amendments to the clinical protocol.

Investigator's Signature: \_\_\_\_\_

Investigator's Name: \_\_\_\_\_

Institution: \_\_\_\_\_

Date: \_\_\_\_\_



## 2. SYNOPSIS

<b>Name of Sponsor:</b> Sage Therapeutics 215 First Street Cambridge, MA 02142		
<b>Protocol No.</b> 547-SSE-301	<b>Phase:</b> 3	
<b>Name of Investigational Product:</b> SAGE-547 Injection		
<b>Name of Active Ingredient:</b> Allopregnanolone		
<b>Title of the Protocol:</b> A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus		
<b>Dosing Regimen: SAGE-547 or Placebo Dosing Schedule</b>		
<b>Hour</b>	<b>Type and Duration of SAGE-547 Infusions</b>	<b>Dose</b>
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	90 µg/kg/h
H121 – H128	8 hour taper	65 µg/kg/h
H129 – H136	8 hour taper	45 µg/kg/h
H137 – H144	8 hour taper	25 µg/kg/h
<b>Dosing Regimen: SAGE-547 Open Label Dosing Schedule</b>		
<b>Hour</b>	<b>Type and Duration of SAGE-547 Infusion</b>	<b>Dose</b>
H1	One hour loading infusion	300 µg/kg/h
H2 –H120	119 hour maintenance infusion	150 µg/kg/h
H121 – H126	6 hour taper	125 µg/kg/h
H127 – H132	6 hour taper	95 µg/kg/h
H133 – H138	6 hour taper	65 µg/kg/h
H139 – H144	6 hour taper	35 µg/kg/h
<b>Study Sites</b> Up to 150 sites in the USA, Europe, and Canada.		
<b>Number of Subjects</b>		

The study will randomize 140 subjects at up to 150 sites.
<b>Study Population</b> <p>Subjects will be aged two years or more, in SRSE<sup>1</sup> (as defined in the Inclusion Criteria <a href="#">Section 8.1</a>), and being managed in an intensive care setting.</p>
<b>Duration of Subject Involvement</b> <p>Individual subject participation will be up to 30 days.</p>
<b>Study Design</b> <p>This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.</p> <p>Patients will follow one of three paths to entry to the study. The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst suppression with a third-line agent. These subjects will be consented for the study after admission to the intensive care unit, but before any third-line agents are administered for burst suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their legally authorized representative (LAR). Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours. Once burst suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of study drug.</p> <p>The second path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst suppression pattern on the EEG. These subjects may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of study drug.</p> <p>The third path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst</p>

<sup>1</sup> In this study, the term Super-Refractory Status Epilepticus or SRSE is equivalent to “Refractory Status Epilepticus (RSE) that has failed standard treatment” and the two terms are used interchangeably.

suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These subjects may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 treatment or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within six hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo).

The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that subjects, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as both the ability to wean the subject off all third-line agents before the end of the infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication infusion, and concurrent signs of physiologic brain activity as determined by EEG. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#) and [Error! Not a valid result for table.](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo will all subsequently be eligible to be administered SAGE-547 at the higher dose.

### Visit Schedule

The visit schedule and an overview of events at each visit is provided in [Table 1](#), [Error! Not a valid result for table.](#) and [Table 3](#) Schedule of Assessments.

**Study Objectives*****Primary objective:***

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult and pediatric subjects with SRSE, and for the response to endure at least 24 hours after the end of the SAGE-547 or placebo infusion (primary response).

***Secondary objectives:***

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in the Clinical Global Impression scale (CGI) between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

***Safety objectives:***

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

***Other objectives:***

1. To evaluate the impact of retreatment with a higher dose SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;

3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;
6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS) (age  $\geq 17$  years).

## Endpoints

### *Primary endpoint:*

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### *Secondary endpoints:*

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### *Safety endpoints:*

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.

**Other endpoints:**

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who fail to respond to their randomized double blind treatment and are retreated with a higher dose of SAGE-547.
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS) (age  $\geq 17$  years).

**Inclusion Criteria**

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects two (2) years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst suppression pattern; or who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst suppression pattern.

**Exclusion Criteria**

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone or any excipients in SAGE-547.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy.

4. Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing underlying neurological disorder.
5. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis for whatever reason, but dialysis is not planned or non-continuous dialysis is planned (that would not adequately remove Captisol®);
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the opinion of the investigator, of less than 30 days;
  - e. a do not resuscitate (DNR) order.
6. Subjects who are being administered more than three third-line agents concomitantly or in whom the qualifying wean cannot be completed within 24 hours, or who are being administered a third-line agent for other indications such as management of raised intra-cranial pressure that would preclude weaning according to this protocol.
7. Subjects with a living will that does not allow heroic measures.
8. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
9. Subjects who have been enrolled in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not withdraw or complete and then re-enroll).

### **Pharmacogenetic Research**

In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **Statistical Analysis**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

### **Interim Analysis**

When approximately 50% of the subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### **Analysis of Primary Endpoint**

The analysis of response to treatment between SAGE-547 treated subjects and placebo treated subjects will be performed using a Cochran-Mantel-Haenszel test with variables for treatment, concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). In this analysis, a treatment responder is a subject who is successfully weaned off all third-line agents and blinded study medication prior to the end of study treatment infusion and remains off third-line agents for at least 24 hours following cessation of the blinded study medication, and who has concurrent signs of physiologic brain activity as determined by EEG. The analysis will be based on the ITT Population. The comparison of treatment response rates will be conducted at the 5% level of significance.

### **Analysis of Secondary Efficacy Endpoints**

The primary analysis will be repeated for the MITT population. Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section. Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. Secondary analyses will be repeated for the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from Baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third-line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

Summaries of safety endpoints will be based on the overall Safety Population which is defined as all subjects who at least initiated the infusion with blinded study treatment.

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are retreated with SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo. Summary statistics will be presented for subjects who were QW successes.

### **Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).



**Table 1: Schedule of Assessments for Protocol 547-SSE-301: One Infusion of Study Drug (blinded)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical/SE/Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X		X	X	X	X	X	X				
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X		X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X		X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X		X	X		X		X		X		
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X			
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>o</sup>											X
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV 3rd-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>p</sup>				
EEG	X	X				X		X	X			
Randomization		X										
Study Drug Administration <sup>q</sup>			X	X	X	X	X	X				
TW Outcome & Retreat Decision										X <sup>r</sup>		
Physiologic Brain Activity									X			
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

**Table 2: Schedule of Assessments for Protocol 547-SSE-301: Two Infusions of Study Drug (one blinded, one open-label)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V3R
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	0-24h
Eligibility Checklist	X										S
Informed Consent <sup>a</sup>	X										E
Inclusion/Exclusion Criteria	X										E
Demography <sup>b</sup>	X										
Medical and SE and Wean History <sup>c</sup>	X										T
Height	X										A
Weight <sup>d</sup>	X		X	X	X	X	X	X			B
Serum Pregnancy Test <sup>e</sup>	X										L
Hematology <sup>f</sup>	X		X	X		X		X		X <sup>g</sup>	E
Serum Chemistry and GFR	X		X	X		X		X		X	
Urinalysis <sup>h</sup>	X		X	X		X		X		X	E
Pharmacogenetic sample	X										X
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X	T
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X	E
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X		N
STESS	X										I
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	O
Glasgow Outcome Score (GOS)											N
Supervision Rating Scale (SRS)	X <sup>o</sup>										
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>										
Epilepsy Status	X										N
Clinical Global Impression (CGI)	X										E
Continuous IV Third-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>p</sup>			X
EEG	X	X				X		X	X		T
Randomization		X									
Study Drug Administration <sup>q</sup>			X	X	X	X	X	X			
TW Outcome and Retreat Decision										X <sup>r</sup>	P
Physiologic Brain Activity									X		
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	A
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	G
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	E
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X	
Pharmacoeconomic Data											
Mortality											

Table 2 continued

	V3R	V4R	V5R	V6R	V7R	V8R	V9R	V10R	V11R	V12R
	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3R+14d (±2d)	V3R+21d (±2d)
Weight <sup>d</sup>	X	X	X	X	X	X				
Serum Pregnancy Test <sup>e</sup>										
Hematology <sup>f</sup>	X	X		X		X		X <sup>g</sup>		
Serum Chemistry and GFR	X	X		X		X		X	X	
Urinalysis <sup>h</sup>	X	X		X		X		X		
Vital Signs <sup>i</sup>	X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>	X	X	X	X	X	X	X			
STESS										
FOUR Score <sup>m</sup>	X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)										X
Supervision Rating Scale (SRS)										X
Modified Rankin Score (mRS) <sup>n</sup>										X
Epilepsy Status										X
Clinical Global Impression Scale (CGI)										X
Continuous IV Third-Line Agent(s)	X	X	Wean	Wean	Wean	Wean <sup>p</sup>				
EEG			X			X	X			
Randomization										
Study Drug Administration <sup>q</sup>	X	X	X	X	X	X				
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data										X
Mortality										X

**Table 3: Schedule of Assessments for Protocol 547-SSE-301: Qualifying Wean Successes**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical and SE and Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X											
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X											
Serum Chemistry and GFR <sup>f</sup>	X											
Urinalysis <sup>h</sup>	X											
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X											
ECG <sup>j</sup>	X											
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>o</sup>											X
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV Third-Line Agent(s)	X	Wean										
EEG	X	X										
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

<sup>a</sup> Written informed consent by proxy (LAR) will be obtained prior to starting any study-related procedures not considered standard of care.

<sup>b</sup> Demographic information will be obtained by proxy and confirmed by the subject when possible.

<sup>c</sup> Medical history will be obtained by proxy and confirmed by the subject when possible. All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Dosing changes with the third-line agent(s) that constitute a wean attempt will be marked as such on the CRF, and the start/stop dates and times of all wean attempts prior to V3 will be recorded, as well as the outcome of the wean attempt.

<sup>d</sup> Weight will be collected at Screening (V1) and once during each 24 hour period of the initial study drug infusion period (V3-V8) and second infusion period (V3R-V8R, if applicable). Daily weight will be used to determine the appropriate infusion rate of each dose.

<sup>e</sup> Serum pregnancy test for females aged 10 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy. .

<sup>f</sup> Blood samples will be taken for hematology and serum chemistry and GFR calculation at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will document whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

<sup>g</sup> Blood samples will be taken at V11 or V11R for serum chemistry (renal panel only).

<sup>h</sup> Urine samples will be taken for urinalysis and NAG at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will add a comment about whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

<sup>i</sup> Vital signs will be recorded at the following time points relative to the start of each infusion of study drug: Screening (V1), at 0, 30, 60 minutes ( $\pm 15$  minutes), at 2, 4, and 8 hours ( $\pm 30$  minutes), and at 24, 48, 72, 96, 120, 144, 168, and 192 hours ( $\pm 2$  hours).

<sup>j</sup> ECG (12-lead) should be performed at Screening (V1) and at the following times relative to the start of study drug infusion. For the blinded (first) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 128, 136, 144, 152, 160, and 192 hours ( $\pm 2$  hours). For the open label SAGE-547 (second) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 126, 132, 138, 144, 152, 160, and 192 hours ( $\pm 2$  hours). Heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours.

<sup>k</sup> Plasma will be collected to assay for study drug concentrations at the following time points relative to the start of each infusion of study drug: For the blinded (first) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion. For the open label SAGE-547 (second) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open label SAGE-547 study drug infusion. Pre-dose samples may be taken within two hours before starting the infusion of study drug; timepoints up to and including 1h will have a time window of  $\pm 5$  minutes; all other timepoints will have a window of  $\pm 15$  minutes.

<sup>m</sup> FOUR Score assessments will be performed at Screening (V1), 24, 48, 72, 96, 120, 144, 168, and 192 hours (all  $\pm 2$  hours) relative to the start of each infusion of study drug, and at V11 or V11R, and at V12 or V12R.

<sup>n</sup> Modified Rankin Score (mRS) applicable for subjects  $\geq 17$  years old only.

<sup>o</sup> SRS at V1 will be a retrospective assessment of the supervision required by the subject immediately prior to admission that includes the index episode of the SE, and mRS at V1 will be a retrospective assessment of the disability and dependence of the subject immediately prior to admission that includes the index episode of the SE.

<sup>p</sup> Target for complete wean of all continuous IV third-line agents by 144 hours at V8/V8R if not completed by 120 hours at V7/V7R.

<sup>q</sup> Study drug infusion is intended for IV administration only with a dedicated peripheral IV line using Sage-approved IV administration bags and lines.

<sup>r</sup> At V10 only a decision to re-treat at a higher dose of SAGE-547 will be made by the Investigator if the continuous IV third-line agent wean has failed or the third-line agent requires re-introduction during V9. Subjects who become eligible for re-treatment at a higher dose of SAGE-547 will discontinue the planned visit schedule at V10, then repeat V3 (V3R) and all applicable subsequent visits.

<sup>s</sup> AEs will be collected from the time Informed Consent is obtained and prior to the start of study-specific screening procedures not considered standard of care. Collection of AEs will continue throughout the study from V1 through V12 or V12R.

<sup>t</sup> Subjects may enter the study on AEDs and be administered AEDs during the study. All Concomitant AEDs must be recorded on the CRF with details including date and time of starting/stopping each AED, the route of administration, changes in doses, and frequency of administration. Details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the CRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.

<sup>u</sup> All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Details will include the name of the drug, the start/stop dates and times, and, after consent, the doses with start/stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

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**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
AE	adverse event
AED	anti-epileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the time-concentration curve
AW	additional weans
BDZ	benzodiazepine
BIEEG	blinded infusion electroencephalogram
BUN	blood urea nitrogen
CBC	complete blood count
CEEG	consent electroencephalogram
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
C <sub>max</sub>	maximum plasma concentration
C <sub>min</sub>	minimum plasma concentration
CNS	central nervous system
CRF	case report form
CSR	clinical study report
CYP2C9	cytochrome P450 enzyme involved in drug metabolism
DNR	do not resuscitate
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EEG	electroencephalogram
EIND	Emergency Use Investigational New Drug Application
EP	European Pharmacopeia
ESETT	Established Status Epilepticus Treatment Trial
FDA	Food and Drug Administration
FOUR	Full Outline of UnResponsiveness
GABA	$\gamma$ -aminobutyric acid
GABA <sub>A</sub>	$\gamma$ -aminobutyric acid-gated chloride channel

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GOS	Glasgow Outcome Scale
H	hour
HPLC	high performance liquid chromatography
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent to Treat
IV	intravenous
IVRS	Interactive Voice Randomization System
LAR	legally authorized representative
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent to Treat
mRS-9Q	Modified Rankin Score - 9Q
MS/MS	tandem mass spectrometry
nM	nanomolar
NMDA	n-methyl-D-aspartic acid
OW	other weans
PAEEG	primary endpoint electroencephalogram
PD	pharmacodynamics
PK	pharmacokinetic
QOL	quality of life
QW	qualifying wean
QWEEG	qualifying wean electroencephalogram
RBC	red blood cell

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
RSE	refractory status epilepticus
SAE	serious adverse event
SAP	Statistical Analysis Plan
SE	status epilepticus
SOP	standard operating procedure
SRS	Severity Rating Scale
SRSE	Super-refractory status epilepticus
SSRI	Selective serotonin re-uptake inhibitors
STESS	Status Epilepticus Severity Score
SUSAR	Suspected Unexpected Serious Adverse Reactions
SWFI	Sterile Water for Injection
TAEEG	taper electroencephalogram
T <sub>max</sub>	time at maximum plasma concentration
TW	terminal wean
TWEEG	terminal wean electroencephalogram
US	United States
USP	United States Pharmacopeia

### 3. INTRODUCTION AND RATIONALE

#### 3.1. Status Epilepticus

Status epilepticus (SE) is a life-threatening seizure condition in which the brain is in a state of persistent seizure triggered by neuronal hyperexcitability. The Neurocritical Care Society defines SE as one continuous unremitting seizure lasting longer than five minutes or recurrent seizures without regaining consciousness between seizures for greater than five minutes (Brophy, Bell et al. 2012). Common causes of SE include preexisting epilepsy, cerebrovascular disease (in adults), electrolyte and metabolic disturbances, anoxia, encephalopathies, head trauma, high fever (in children, especially in the first year of life) and drug or substance intoxication. SE is associated with substantial morbidity and mortality.

##### 3.1.1. Epidemiology of SE

Geography, sex, age, and race influence the epidemiology of SE, whose incidence has a bimodal distribution, peaking in infants/young children and the elderly (Hauser 1990; DeLorenzo, Pellock et al. 1995; Wu, Shek et al. 2002). The incidence of SE in the elderly population is at least twice that in the general population. Concurrent medical conditions often exist in the elderly population, which can complicate therapy and worsen the prognosis of SE (Chapman, Smith et al. 2001).

The annual incidence of SE in the US is generally quoted to be within the range of 18/100,000 to 61/100,000, based on a 19-year retrospective study in Rochester, Minnesota (Hesdorffer, Logroscino et al. 1998) and a 2-year prospective study in Richmond, Virginia (DeLorenzo, Pellock et al. 1995), respectively. Two studies from Europe give annual incidences of a similar magnitude, ranging between 9.9/100,000 and 15.8/100,000 (Coeytaux, Jallon et al. 2000; Knake, Rosenow et al. 2001). It is thus estimated that in the United States each year there are as many as 150,000 cases of SE (DeLorenzo, Pellock et al. 1995).

#### 3.2. Refractory SE

When a patient begins to seize, the emergency medical technician will administer a first-line intravenous (IV) benzodiazepine (BDZ), such as diazepam, lorazepam or midazolam (Silbergleit, Durkalski et al. 2012), which is done either at the scene of the seizure or in the ambulance. If this is unsuccessful at abating the seizure, additional doses of the first-line therapy will be administered in the emergency room. Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line therapy, which is an IV anti-epileptic drug (AED) such as phenytoin or valproic acid (Novy, Logroscino et al. 2010; Shorvon 2011; Hocker, Britton et al. 2013).

Approximately 20-30% of patients refractory to first-line treatment will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to approximately 70-80% of patients who receive second-line therapy refractory to that therapy.

If a patient's SE continues after administration of BDZs and AEDs, the subject is diagnosed as having refractory status epilepticus (RSE), which must be treated quickly to terminate the seizure activity, maintain the patient's airway, and prevent cerebral damage. RSE patients are immediately admitted to the Intensive Care Unit (ICU) and placed in a medically-induced coma to stop all seizure-related activity. The drugs used to induce coma are continuously-infused IV agents,



commonly propofol, midazolam, or pentobarbital, referred to as third-line agents (Brophy, Bell et al. 2012).

The RSE patient is continually monitored using electroencephalography (EEG) to ensure burst suppression is achieved. Burst suppression is a pattern of brain waves seen on an EEG, characterized by periods of activity alternating with periods of little or no activity in the brain, informing medical personnel of the effectiveness of the medically-induced coma. The goal of burst suppression is to allow the brain and corresponding neuronal tissue to restore function and reset to normal pre-seizure levels.

### 3.2.1. Epidemiology of RSE

Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line AED therapy. In turn, approximately 20 – 30% of these patients treated with AEDs will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to 28% of the total estimated SE patient population refractory to second-line therapy. Based on the previously-cited estimated incidence in the US, this means that there are up to 42,000 incident cases of RSE in the USA, annually (DeLorenzo, Pellock et al. 1995).

### 3.3. Super-refractory SE

After 24 hours of burst suppression, the patient is weaned off of the third-line therapy. If the weaning is unsuccessful (neuronal activity has not returned to normal), the third-line agent is re-administered or a different third-line agent is started, and the patient is considered to be in super-refractory status epilepticus (SRSE) (Chapman, Smith et al. 2001; Shorvon 2011; Brophy, Bell et al. 2012). SAGE-547 is being developed as an adjunct to third-line therapy in patients in RSE who have failed standard treatment. In this protocol, the term “RSE that has failed standard treatment” is deemed to be equivalent to the term “SRSE” and the two may be used interchangeably.

#### 3.3.1. Epidemiology of SRSE

The incidence of SRSE is very poorly understood, mainly because the diagnostic codes used for SE do not generally differentiate its nature as responding or refractory to treatment. Based on the variable reporting of outcomes data, the incident cases of SRSE could represent between one and two-thirds of the RSE patients (Novy, Logroscino et al. 2010; Ferlisi and Shorvon 2012; Hocker, Britton et al. 2013; Sutter, Marsch et al. 2013). More detailed epidemiology studies are needed to better elucidate the proportion of RSE patients whose condition becomes super-refractory. A recent review of ICU discharge data in the USA suggests an annual incidence of approximately 35,000, based on patients who required at least three days in the ICU for SE [Sage data on file].

#### 3.3.2. Outcomes of SRSE

SE has varying degrees of mortality depending on the underlying etiologies. Table 4 outlines the acute mortality in patients with SE by etiology (Neligan and Shorvon 2010). The mortality rate of SRSE is estimated to be 30% to 50% using current standard of care.

The causes of death from SE (and therefore SRSE) are heterogeneous, resulting from neuronal cell death, complications of underlying medical conditions, or adverse effects of the current standard treatments. Prognosis worsens and mortality increases with longer duration of SE, i.e. with SE that develops into RSE or SRSE (Neligan and Shorvon 2010), and with longer duration of

medically-induced coma ([Ferlisi and Shorvon 2012](#)). There is an obvious unmet medical need to improve upon the current standard of care treatment regimens.

Morbidity is high and survivors have outcomes ranging from poor function to vegetative state ([Shorvon 2011](#)). Approximately one third of patients with RSE and SRSE will recover, but with chronic neurologic or other deficits ([Neligan and Shorvon 2010](#); [Hocker, Britton et al. 2013](#)). In all, it is estimated that less than 25-30% of all SRSE patients have a favorable functional outcome.

**Table 4: Approximate Mortality of Status Epilepticus in Different Etiologies**

Underlying Etiology	Associated Acute Mortality in Patients with SE (%)
Drug reduction/withdrawal, poor AED compliance, or low AED levels	0-10
Cerebrovascular Disease	20-60
Metabolic Disorders	10-35
Acute CNS Infection	0-30
Anoxia	60-100
Alcohol Abuse	0-10
Head Trauma	0-25
Drug Overdose/Toxicity	10-25
Brain Tumors	0-20
Cryptogenic/Idiopathic	5-20

### 3.3.3. Unmet Medical Need in Super-refractory Status Epilepticus

Treatment approaches for SRSE consist of diagnosis and treatment of underlying medical conditions, adding and changing anti-seizure drugs, and repeated attempts at weaning from IV anesthetic agents. Treatment of SRSE has three aims:

- to prevent excitotoxicity, which begins within 24 hours of SE onset;
- to prevent cerebral damage by initiating neuroprotective burst suppression;
- to prevent the complications of extended periods of anesthesia or unconsciousness ([Shorvon 2011](#)).

Currently, there are no therapies that have been specifically approved for RSE or SRSE. The primary drugs used to induce coma are continuously infused IV anesthetics such as propofol, midazolam, or pentobarbital, known as third-line agents. Use of these drugs to control SRSE has only been studied in small retrospective reviews or small prospective studies without controls ([Hocker, Britton et al. 2013](#)) therefore there is no agreement on which drug is optimal nor on an optimal dosing regimen for the treatments that are used.

The most common adverse effect of the third-line agents is hemodynamic instability; in addition, they are not universally effective, with breakthrough seizures and withdrawal seizures requiring dose adjustments and changes in third-line agent(s). The drug thought to be most effective in SRSE, pentobarbital, is also associated with the most toxic adverse effect profile, comprising

decreased blood pressure and cardiorespiratory collapse (Claassen, Hirsch et al. 2002). The ability to wean patients successfully off the third-line agents as quickly as possible is therefore paramount, and an adjunct to SRSE treatment that enhances the success of the third-line agents and supports their successful weaning in a short timeframe would be an important addition to the therapeutic armamentarium. Preliminary clinical data show that SAGE-547 has been a successful adjunct to third-line therapy in this regard.

### 3.4. SAGE-547 Injection

Allopregnanolone is an endogenous, naturally occurring neuroactive steroid formed in the corpus luteum of the ovary, adrenal cortex and central nervous system (CNS) (Holzbauer, Birmingham et al. 1985; Paul and Purdy 1992; Ottander, Poromaa et al. 2005). It is a metabolite of progesterone created by the actions of 5- $\alpha$  reductase and 3- $\alpha$  hydroxy-steroid dehydrogenase. Allopregnanolone is a potent positive allosteric modulator of both synaptic and extra-synaptic GABA<sub>A</sub> receptors.

SAGE-547 Injection (allopregnanolone aqueous formulation in Captisol<sup>®</sup>) is being developed for the treatment of patients in RSE who have not responded to standard treatment. SAGE-547 Injection is a solution of 5 mg/mL allopregnanolone in Sterile Water for Injection (SWFI), USP and 250 mg/mL betadex sulfobutyl-ether sodium, NF. It is further diluted with Sterile Water for Injection, USP (SWFI) in IV bags to achieve an allopregnanolone concentration of approximately 1.67 mg/mL in an approximately isotonic solution and will be administered intravenously.

#### 3.4.1. Scientific Rationale for SAGE-547 in SRSE

Ineffective recruitment of inhibitory neurotransmission, together with excessive neuronal excitation, likely plays a role in the initiation and propagation of the electrical disturbance occurring in SE. GABA ( $\gamma$ -aminobutyric acid), the major inhibitory neurotransmitter in the central nervous system (CNS), is released from GABAergic neurons and binds to several types of GABA receptors (GABA<sub>A</sub>, GABA<sub>B</sub>, and GABA<sub>C</sub>) on target neurons. GABA<sub>A</sub> receptors are macromolecular proteins that form a chloride ion channel complex and contain specific binding sites for GABA and a number of allosteric regulators, including barbiturates, benzodiazepines, and some anesthetic agents. GABA receptor-mediated inhibition contributes significantly to the normal termination of a seizure (Kapur and Macdonald 1997). SAGE-547 is a positive allosteric modulator of the GABA<sub>A</sub> receptor.

The importance of terminating seizure activity as soon as possible is underpinned by a growing body of evidence from research and clinical observation that SE becomes more difficult to control as its duration increases. It has been postulated that this occurs due to a mechanistic shift from inadequate GABAergic inhibitory receptor-mediated transmission to excessive N-methyl-D-aspartic acid (NMDA) excitatory receptor-mediated transmission (Kapur and Macdonald 1997). As prolonged epileptiform bursting results in a reduction of GABA<sub>A</sub>-mediated synaptic inhibition, antiepileptic treatments which rely on enhancing intrasynaptic GABA<sub>A</sub> neurotransmission become less effective the longer SE continues.

Furthermore, the constitutive process of synaptic GABA<sub>A</sub> receptor internalization is accelerated by the increased neuronal activity associated with seizures. These findings suggest that the rate of GABA<sub>A</sub> receptor internalization is regulated by neuronal activity, and its acceleration contributes to the reduction of inhibitory transmission observed during prolonged seizures (Kapur and Macdonald 1997). Of note is that SAGE-547 binds to extrasynaptic as well as intrasynaptic GABA<sub>A</sub> receptors;

extrasynaptic receptors remain active with ongoing seizure activity, resulting in a putative mode of action for SAGE-547 in SRSE.

Status epilepticus induces cerebral damage that includes neuronal cell necrosis, gliosis, and network reorganization. The major cause of cell death in cerebral damage is excitotoxicity, which is initiated by glutaminergic receptor over-activation, causing calcium to flood the cell, thereby leading to apoptosis and necrosis. This process is initiated within a few hours of the start of seizure activity, and provides the medical imperative to terminate SE as quickly as possible. To prevent the consequences of the excitotoxicity cascade, it is recommended that anesthesia be initiated within 1-2 hours of onset of seizures at doses designed to induce EEG burst suppression ([Shorvon and Ferlisi 2011](#)).

### **3.4.2. SAGE-547 Clinical Program in the Treatment of SRSE**

The current SAGE-547 development program includes:

- an ongoing Phase 2 open-label trial, Study 547-SSE-201;
- this proposed Phase 3 randomized, double-blind, placebo-controlled trial, Study 547-SSE-301;
- a planned open-label, expanded access protocol, Study 547-SSE-302;
- a number of EINDs for SAGE-547 in patients with SRSE.

The designs of these studies are all similar, with a five to six day infusion of SAGE-547 (or placebo), during which time attempts are made to wean the subject off all third-line agents. In the Phase 3 studies, those subjects who cannot be weaned off third-line agents while being administered SAGE-547 (or placebo) will be eligible for a second open-label infusion of SAGE-547 at a higher dose, which is also being employed for the latter patients being enrolled in the Phase 2 study. Follow up of subjects is for 21 – 30 days after the first infusion of study medication.

### **3.4.3. Data from the SAGE-547 Development Program**

The data from 30 subjects included in the on-going clinical evaluation of SAGE-547 for the treatment of adults and children with SRSE clearly offers preliminary evidence that SAGE-547 could provide substantial and clinically significant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate. These subjects comprise 20 from the ongoing Phase 2 trial (71% success rate in 12/17 evaluable subjects) and 10 subjects who received EIND treatments (78% success rate in 7/9 evaluable subjects).

Successful therapy of SRSE has been defined as “the SE is completely controlled by the therapy, without breakthrough of withdrawal seizures, or discontinuation due to side effects or death during therapy,” ([Ferlisi and Shorvon 2012](#)). By this definition, which is in accord with the efficacy assessments used in the overall clinical evaluation of SAGE-547, 19 of the 26 (73%) subjects with SRSE who completed the SAGE-547 infusion were treatment successes. As data collection is ongoing, this information is preliminary and subject to change upon further monitoring.

Published reports on RSE and SRSE have stated mortality rate ranges from 35% to 65%. The underlying etiologies of SE in the 547-SAGE-201 study and EINDs are heterogeneous, and each one conveys a different risk of mortality and longer term morbidity. However, the death rate in subjects who have received SAGE-547, 6 out of 30 (20%) subjects, appears to be lower than the published

rates. None of the deaths were considered related to SAGE-547: brain tumor, organophosphate toxicity, respiratory failure, respiratory arrest due to ventilator support withdrawal, and breast cancer.

In the Phase 2 study, 20 SAEs (15 non-fatal) have been reported in 13 (65%) subjects, and of these 3 events in 2 subjects (10%) were considered by the investigator to be related to SAGE-547: pulmonary emboli and tracheostomy dehiscence/infection. The Sponsor did not consider these events to be related to SAGE-547, rather to the underlying disease states. Four of the 20 subjects (20%) experienced AEs considered possibly related to SAGE-547 by the investigator, namely moderate myopathy and severe pulmonary emboli in 1 subject, moderate tracheostomy dehiscence and tracheostomy infection in 1 subject, moderate thrombocytosis in 1 subject and moderate BUN, ALT and AST elevation in 1 subject.

Review of the most current safety data from 547-SAGE-201 reveals that there were changes in serum chemistry, hematology, and urinalysis during the study, but that none of those changes were assessed as related to SAGE-547. There were also no SAGE-547-related changes to vital signs.

Despite the heterogeneity in the underlying causes of SE, the ages of the subject, comorbidities, which normally complicate the treatment of SE, and the fact that all subjects had failed current standard of care treatment, a large majority of subjects had a successful therapy outcome, with discontinuation of all third-line agents and resolution of SE.

Refer to the Investigational Brochure for further information on the pre-clinical and clinical data supporting the use of SAGE-547 in SRSE.

### **3.5. Study Rationale - SAGE-547 in SRSE**

#### **3.5.1. Justification for the Control Group**

Although SAGE-547 has demonstrated extremely promising activity in subjects with SRSE, both in the Phase 2 study and during the EINDs, these have been open-label investigations with no control data for comparison. Generally in the literature there are few data describing the success rates of wean attempts of third-line agents, and few comparative data on the effectiveness of the three main third-line agents, propofol, pentobarbital, and midazolam.

Several options for a control group in Study 547-SSE-301 were considered:

- No control group was thought to be unacceptable since there are no reliable published data on success rates in this population that could be used for broad comparisons;
- An active control was considered but found to be impractical since none of the third-line agents are approved for their use in SRSE, no standardized dosing regimens or treatment guidelines have been adopted for the management of SRSE, and clinicians were unlikely to agree which of the available third-line agents would be reserved for the active control arm;
- Historical controls were considered but abandoned because of the practical difficulties of obtaining high quality data, the lack of ability to prospectively match cases, and a suspicion that clinical practice in the standard of care of SRSE is evolving, mandating the use of prospective, concurrent control data;
- Comparison to standard of care alone was considered as a feasible design. However, in a field where no widely adopted treatment guidelines exist, there was a concern that knowledge of the treatment group (SAGE-547 plus standard of care versus standard of care

alone) would alter the behavior of the investigators such that they could be more aggressive with weaning in the SAGE-547 group;

- Placebo control is not without its challenges since the preliminary efficacy data for SAGE-547 show that the compound exerts central pharmacological effects and is associated with positive outcomes in around 70% of patients. There is therefore a potential ethical concern about administering placebo to desperately ill patients who have often exhausted all treatment options for SRSE. This concern has been addressed in two ways: firstly all patients receive current standard of care; secondly, all subjects who fail to be weaned from their third-line agents at the end of the blinded infusion of study drug will be administered open-label SAGE-547 without un-blinding their initial treatment allocation, so treatment with the investigational product is not denied, but delayed about a week in the setting of ongoing receipt of full current standard of care.

It was therefore decided that a blinded, placebo-controlled design was appropriate for Study 547-SSE-301.

### **3.5.2. Justification for the Dose Regimen**

The standard dose regimen has been studied in 19 subjects in the 547-SSE-201 Phase 2 trial; the average peak plasma concentration of SAGE-547 at the end of the loading dose was approximately 144 ng/ml. The average plasma concentration during the maintenance infusion was approximately 70 ng/ml. At these concentrations, there were no clear safety signals although two-thirds of subjects experienced an SAE and there were four deaths, all related to the underlying comorbid conditions. The standard dosing regimen was associated with an approximate 70% successful treatment outcome. For these reasons, the standard dosing regimen has been adopted for the initial SAGE-547 infusion to be compared in a blinded fashion to placebo.

In the 547-SSE-201 trial, three subjects have thus far received the higher dose regimen. This dose regimen has also been well tolerated. The average peak plasma concentrations at the end of the loading dose for both dosing regimens will be in the same range, as the loading dose is the same for both regimens. The average plasma concentrations observed during the higher maintenance dose are 102 ng/ml (n=2). The rationale for adopting the higher dose regimen as the open-label infusion of SAGE-547 for subjects who are retreated in this 547-SSE-301 trial is that those who fail on the standard SAGE-547 dose regimen are afforded the opportunity to have access to a higher dose. The justification to also administer the higher dose regimen to failures on placebo is that the regimen has thus far been well tolerated, and this methodology preserves the blind for the initial infusion.

A five-day dosing regimen with SAGE-547 was investigated in the Phase 2 study, 547-SSE-201. There were some cases when weaning off all third-line agents was not possible within 48 hours, but weaning was completed after the end of the infusion of SAGE-547. For this reason, the duration of dosing with SAGE-547 has been increased from 120 hours (five days) in Phase 2 to 144 hours (six days) in this Phase 3 study.

### **3.5.3. Rationale for Genetic Testing Sub-study**

Sage Therapeutics intends to perform genetic research in the SAGE-547 development program in order to explore how genetic variations may affect the metabolism and activity of SAGE-547. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials, and, possibly, to genetically-guided

treatment strategies for optimizing decision making with respect to individual benefit:risk. Participation of subjects in genetic research as part of the overall clinical study is optional.

### **3.6. Benefit-Risk Evaluation of the Present Study**

Previous reports of human administration of exogenous allopregnanolone indicate that for exposures in men and women up to 150 nM, the most commonly reported AEs were sedation (recorded as sleepiness or tiredness), feelings of intoxication (like alcohol), flushing, and mild headache (Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007). No SAEs were reported (Navarro, Kaddouz et al. 2003; Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007; Kask, Backstrom et al. 2008; Kask, Backstrom et al. 2009; Timby, Hedstrom et al. 2011a). In view of the reduced consciousness and sedation of study subjects at entry into this protocol, none of these previously-reported events are likely to impact subjects in this study.

To date, in the SAGE-547 Phase 2 study and the EIND subjects, a majority of subjects demonstrated a successful therapy outcome (>70%). The majority in the clinical trial (65%) have also experienced SAEs, but none has been considered related to SAGE-547 by the Sponsor (SAEs in 2 subjects (10%) were considered possibly related by Investigator). Five deaths have been reported in 30 subjects (20%), all related to the underlying cause of SRSE and not related to SAGE-547 – this is in the context of published mortality rates between 35% and 65%. These preliminary data suggest that SAGE-547 has the potential to provide clinically relevant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate.

The underlying etiologies of SE are heterogeneous, and each one conveys a different risk of mortality. Subjects who survive SRSE still have a high risk of severe morbidity (Neligan and Shorvon 2010). The subjects treated with SAGE-547 in Study 547-SSE-201, are heterogeneous in factors such as age and etiology of SE, factors that usually complicate treatment and can increase morbidity and mortality. Even with this heterogeneity, the preliminary efficacy and safety data for SAGE-547 are very encouraging, and the mortality rate suggests that the risk to benefit assessment of this treatment rests on the side of benefit.

## **4. ETHICS**

### **4.1. Institutional Review Board or Independent Ethics Committee**

This protocol will be reviewed and approved by the Institutional Review Board (IRB) where the study is conducted. The IRB will meet all FDA requirements governing IRBs (CFR, Title 21, Part 56).

### **4.2. Ethical Conduct of the Study**

The Sponsor, the Medical Monitor, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable ICH and GCP guidelines, and must also conduct the study in accordance with local regulations.

### **4.3. Subject Information and Informed Consent**

Subjects prospectively enrolled in this study will be unable to give consent. Therefore, consent will be given by proxy by a legally authorized representative (LAR). Written informed consent is required for each subject prior to any testing under this protocol not considered standard of care,



including screening tests and evaluations. Should a subject gain the ability to sufficiently comprehend the situation and consent during the course of the study, written informed consent or verbal assent will be documented as required or recommended by the institution's IRB.

The form of consent to be obtained will depend on the condition of the subject as determined by the Principal Investigator. The informed consent form (ICF), as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50.

It is the responsibility of the Investigator to obtain consent and to provide the subject's LAR with a copy of the signed and dated informed consent form. The informed consent form for subject participation must also be available as part of the subject file for review by the site's dedicated study monitor or any authorized auditor of the Sponsor or regulatory authorities.

All ICFs used in this study must be approved by the appropriate IRB and by the Sponsor. The ICF must not be altered without the prior agreement of the relevant IRB and the Sponsor.

#### **4.4. Ethical and Regulatory Considerations for Pharmacogenetic Sub-study**

##### **4.4.1. Informed Consent for Pharmacogenetics**

The genetic component of this study is optional and subjects may participate in other components of the main study without having to agree to participate in the genetic component. If subject chooses to participate in the genetic component of the study, the subject or LAR must sign and date a specific consent form for the genetic component of the study in addition to the main study consent form. The principal investigator(s) is responsible for ensuring that consent is freely given and that the subject understands that they may discontinue from the genetic aspect of the study independent of their decision to remain within or withdrawal from the main study.

##### **4.4.2. Subject Data Protection Relative to Pharmacogenomics**

Sage Therapeutics will not provide individual genotype results to subjects, their family members, their general physician, their employer or any insurance company unless required to do so by law. While extra precautions will be taken to preserve confidentiality and to prevent genetic data from being linked to an individual's identity outside of a restricted access site, in certain exceptional situations (e.g. in case of a medical emergency or as a consequence of a specific regulatory need), certain individuals may see both genetic data and the personal identifiers of a subject; however in all cases a subject's medical information and genetic files will remain physically separated.

## **5. STUDY OBJECTIVES**

### **5.1. Primary Objective**

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult and pediatric subjects with SRSE, and for the response to endure at least 24 hours after cessation of the SAGE-547 or placebo infusion (primary response).



## 5.2. Secondary Objectives

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in Clinical Global Impression Scale between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

## 5.3. Safety Objectives

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

## 5.4. Other Objectives

1. To evaluate the impact of retreatment with a higher dose of SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;

6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS) (age  $\geq 17$  years).

## **6. ENDPOINTS**

### **6.1. Primary Endpoint**

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### **6.2. Secondary Endpoints**

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) and to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### **6.3. Safety Endpoints**

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.

## 6.4. Other Endpoints

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who fail to respond to their randomized double blind treatment and are retreated with a higher dose of SAGE-547;
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS) (age  $\geq 17$  years).

## 7. INVESTIGATIONAL PLAN

### 7.1. Overview of Study Design

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

Figure 1 provides an overview of the study design and Figure 2 gives the details of treatment and follow-up on the active treatment arm. Patients will follow one of three paths to entry to the study. The first path is for patients who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst suppression with a third-line agent. These patients will be consented for the study after admission to the intensive care unit, but before any third-line agents are administered for burst suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their LAR. Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours. Once burst suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see Table 3). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of study drug.

The second path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst suppression pattern on the EEG. These patients may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at

least 24 hours of continuous burst suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of study drug.

The third path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These patients may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within six hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. Randomization will be stratified by concomitant pentobarbital use (yes or no) and number of previous third line agent wean attempts prior to randomization (one vs two or more).

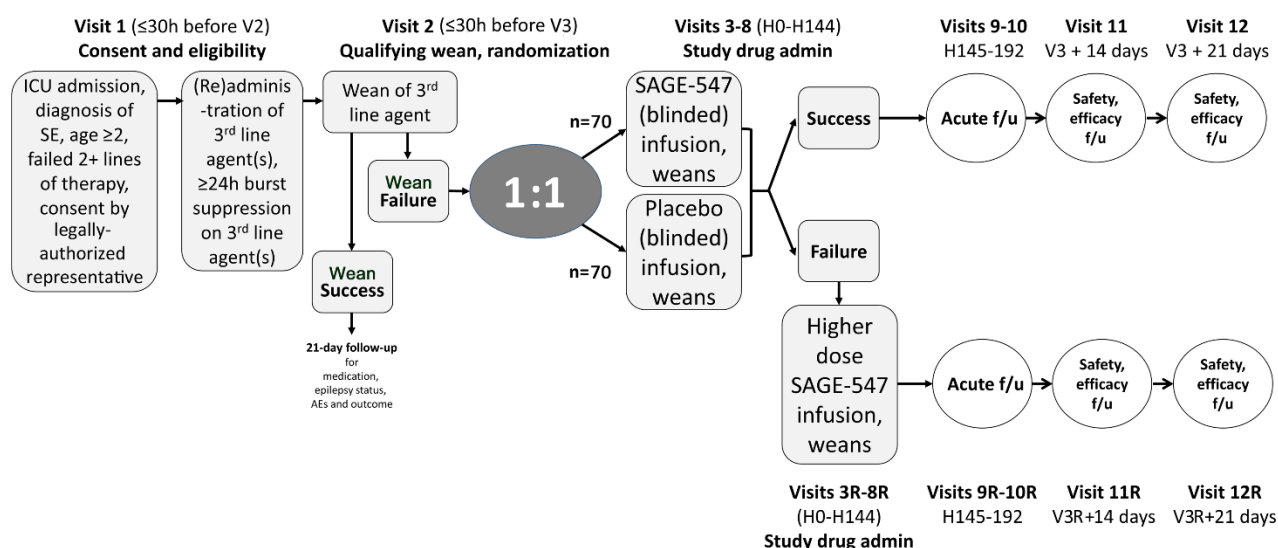
The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as the ability to wean the subject off all third-line agents before the end of the first infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication. Subjects must also have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) at the end of the primary endpoint assessment period as determined by EEG in order to be deemed a success. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#), [Table 2](#) and [Table 3](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. Eligibility for retreatment must be confirmed in writing by the medical monitor prior to the open-label infusion starting. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo will all subsequently be eligible to be administered SAGE-547 at the higher dose.

**Figure 1: Study Design**



## 7.2. Trial Conduct

This study will be conducted according to the principles of the World Medical Association Declaration of Helsinki and most recent amendment (2008), and in compliance with the protocol approved by the IRBs/Independent Ethics Committees (IECs), and in accordance with ICH Guidelines on GCP standards.

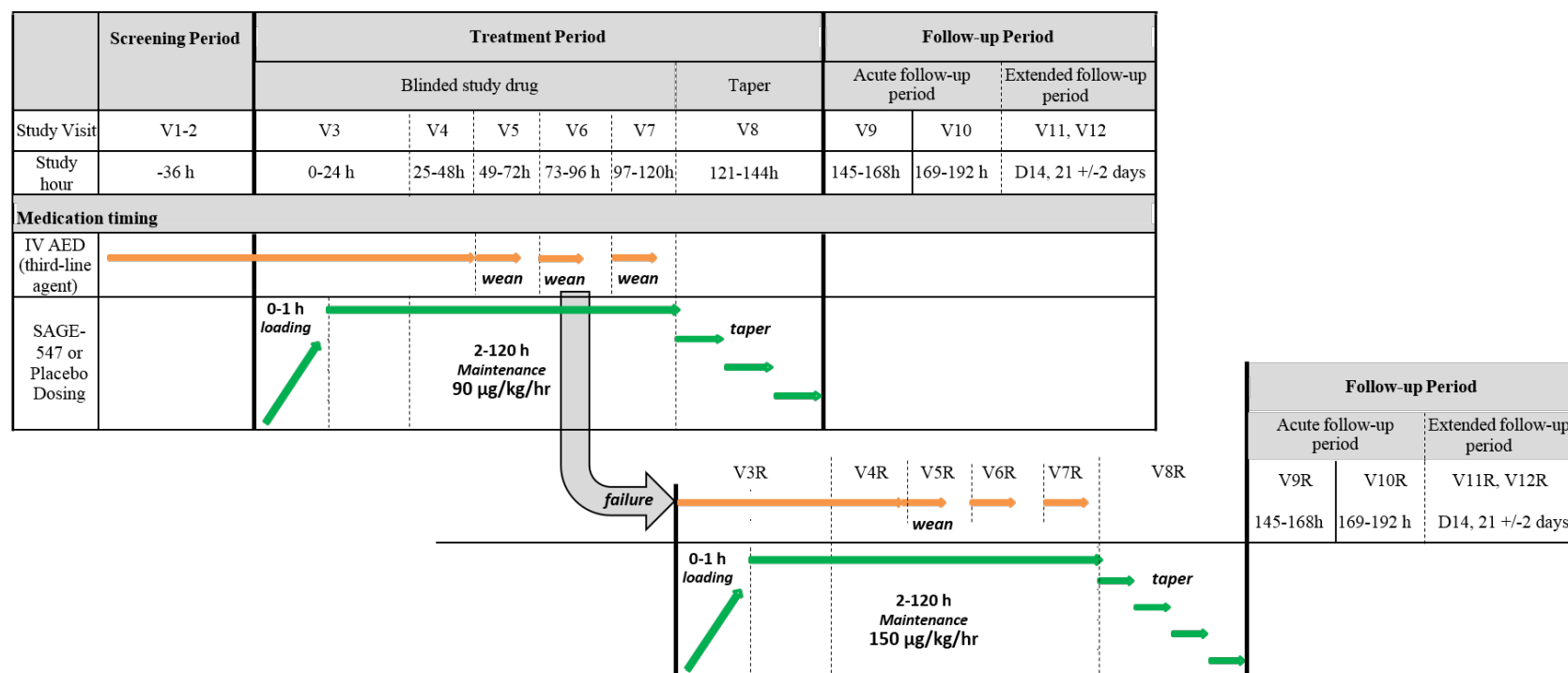
## 7.3. Blinding and Randomization

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo). Details of the dynamic randomization process will be included in the SAP.

The randomized portion of the study will be blinded, with the two treatment products (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

The second infusion of SAGE-547 will be administered on an open label basis to subjects who failed the primary endpoint wean.



**Figure 2: Details of Treatment Administration and Follow-up**

## 8. SELECTION AND WITHDRAWAL OF SUBJECTS

The study will randomize 140 patients at up to 150 sites. All subjects deemed eligible to enroll must have written Medical Monitor approval on a case-by-case basis prior to undertaking the qualifying wean.

### 8.1. Inclusion Criteria

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects two (2) years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; *or* who have previously failed one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst suppression pattern; *or* who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst suppression pattern.

### 8.2. Exclusion Criteria

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy.
4. Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing underlying neurological disorder.
5. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis but for whatever reason, dialysis is not planned or non-continuous dialysis planned (that would not adequately remove Captisol®);
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the experience of the investigator, is less than 30 days;
  - e. a do not resuscitate (DNR) order.



6. Subjects who are being administered more than three third-line agents concomitantly or for whom the qualifying wean cannot be completed within 24 hours or who are being administered a third-line agent for indications such as raised intra-cranial pressure that would preclude weaning according to this protocol.
7. Subjects with a living will that does not allow heroic measure.
8. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
9. Subjects who have been enrolled in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not withdraw or complete and then re-enroll).

### **8.3. Selection and Consent of Subjects for Pharmacogenetic Substudy**

All subjects will be asked to participate in pharmacogenetic research; however, participation in research is voluntary and a subject can decide to decline his/her participation without penalty or loss of benefit. Participation or lack thereof will not be a cause for exclusion from any aspect of the main study. In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **8.4. Subject Withdrawal / Study Termination**

#### **8.4.1. Withdrawal/Discontinuation of Individual Subjects**

The reasons for study drug discontinuation and/or subject withdrawal from the study must be recorded in the subject's electronic case report form (eCRF). The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject has been discontinued/withdrawn due to an AE.

##### **8.4.1.1. Withdrawal from the Study**

Subjects or their LAR may withdraw subjects from the study at any time for any reason without compromising the subject's medical care. The Investigator will also withdraw subjects upon the request of Sage Therapeutics or upon termination of the study.

Subjects who withdraw from the study prior to Visit 10 (or 10R) should complete the procedures scheduled for the day of study drug taper (hour 121-144; Visit8/8R) on the day of their withdrawal, including the SAGE-547 taper schedule, with the addition of the mortality assessment from Visit 12/12R. Subjects who withdraw from the study after Visit 10/10R should undergo study procedures as outlined for Visit 12/12R on the day of their withdrawal. In all cases, the reason for subject withdrawal will be recorded in the eCRF.

Withdrawal of subjects for any reason should be discussed with the Medical Monitor.

##### **8.4.1.2. Discontinuation of Study Drug**

If it is necessary to discontinue the study drug earlier than planned, subjects should continue to be followed per protocol to capture safety and efficacy assessments for the duration of the study period.

The investigator may withdraw the subject from the study drug for the following reasons:

- Upon subject's or LAR's request
- The subject or LAR is unwilling or unable to adhere to the protocol-specified visits
- The subject experiences an intolerable adverse event
- During the course of the study, the subject develops symptoms or conditions listed in the exclusion criteria.
- Other medical reason, at the discretion of the Investigator and/or the Medical Monitor

Subjects who discontinue the study due to an AE considered related to study drug should be followed until the event is resolved, considered stable, or the Investigator determines the event is no longer clinically significant. Study drug discontinuation due to AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

#### **8.4.2. Study Termination**

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of AEs or other findings suggesting unacceptable risk to subjects, administrative or operational reasons. In the event of study termination, Sage Therapeutics will provide written notification to the Investigator. Investigational sites must promptly notify their IRB and initiate withdrawal procedures for participating subjects.

## **9. INVESTIGATIONAL PRODUCT**

### **9.1. Identity of Investigational Product**

SAGE-547 Injection (allopregnanolone)

### **9.2. Clinical Supplies**

#### **9.2.1. SAGE-547**

Adequate supplies of SAGE-547 Injection and materials for intravenous administration will be provided to each site.

SAGE-547 Injection is a clear, colorless sterile solution of allopregnanolone intended for intravenous injection. SAGE-547 Injection is an aqueous solution of 5 mg/mL allopregnanolone in 250 mg/mL Captisol® (betadex sulfobutyl-ether sodium, NF). It is presented either un-buffered or buffered with 10 mM citrate at a pH of 6.0 in either 20 mL or 50 mL vials. SAGE-547 is further diluted according to the Pharmacy Manual to achieve an approximately isotonic solution and will be administered intravenously.

No preservatives are included in the drug product, which is intended to be used as a single-use vial. All inactive components (excipients) used in the formulation are compendial grade and conform to current USP/EP, and include sodium citrate, citric acid and betadex sulfobutyl-ether sodium (Captisol®).

**9.2.2. Placebo**

Placebo will be identical to SAGE-547 and presented in identical vials. Placebo will be manufactured in a similar way to SAGE-547 and comprises all excipients but no SAGE-547.

**9.2.3. Blinding**

The vials of SAGE-547 and placebo will be identical in every way so that they are indistinguishable by the pharmacist, investigator, anyone treating or managing the patient, the monitors, and the sponsor. In this way the first infusion of study drug administered to each patient will be double-blind.

For the blinded study drug infusions, subject-specific dosing kits will be provided. These dosing kits will be pre-labelled with kit number for the first blinded infusion. For the second-infusion, open-label kits will be provided, which will require subject assignment by the pharmacy for reconciliation purposes. The study kits must be stored under refrigerated conditions (2-8 °C). IV administration bags and lines may be provided for the blinded and open-label infusions. Refer to the Pharmacy Manual for additional details.

The label for the SAGE-547 Injection vials will include standard product identification information according to the Code of Federal Regulations, 21CFR 312.6. All study labels will also contain the following statement:

Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use.

**9.3. Preparation of SAGE-547 or Placebo Injection for Dosing**

The Pharmacy will be responsible for preparing the blinded and open-label study drug for subject dosing. The prepared admixture will be assigned a room temperature (20-25 °C) storage shelf life of 24 hours from time of compounding.

SAGE-547, which is hypertonic, will require dilution with SWFI to achieve an approximately isotonic solution according to the instructions provided in the Pharmacy Manual. Exactly the same procedures will be used to prepare the placebo admixture, so that all site staff remain blinded as to treatment allocation for the first infusion of study drug. SAGE-547 Injection is not intended to be administered to patients undiluted.

Refer to the Pharmacy Manual for specific instructions regarding infusion preparation.

**9.4. Administration and Accountability**

The Pharmacy will maintain accurate records of all investigational product supplies. Accurate records will be kept regarding the volume of SAGE-547 Injection or placebo used for each IV preparation, as well as the required infusion rate or rates, and the date and time of preparation. Reasons for departure from the expected dosing regimen must also be recorded. To satisfy regulatory requirements regarding drug accountability, all study medication will be reconciled in full. Refer to the Pharmacy Manual for additional details.

## 10. TREATMENT OF SUBJECTS

### 10.1. Dosing Schedule (Blinded Infusions)

SAGE-547 Injection or placebo will be administered according to the dosing schedules in Table 5. The infusion rates to accomplish these  $\mu\text{g/kg/h}$  doses will be calculated according to the weight of the subject. The infusion rates will be applied to blinded study drug for the first infusion of study medication.

**Table 5: SAGE-547 or Placebo Dosing Schedule**

Hour	Type and Duration of Study Drug Infusion	Description
H1	One hour loading Infusion	300 $\mu\text{g/kg/h}$
H2 – H120	119 hour maintenance infusion	90 $\mu\text{g/kg/h}$
H121 – H128	8 hour taper	65 $\mu\text{g/kg/h}$
H129 – H136	8 hour taper	45 $\mu\text{g/kg/h}$
H137 – H144	8 hour taper	25 $\mu\text{g/kg/h}$

### 10.2. Dosing Schedule (Open-Label Infusions)

If a subject fails wean from third-line agent(s) or requires re-instatement of third-line therapy within 24 hours of discontinuing the initial infusion of study drug, SAGE-547 Injection will be re-administered according to the dosing schedule in Table 6. The infusion rates to accomplish these  $\mu\text{g/kg/h}$  doses will be calculated according to the weight of the subject. These infusion rates will be applied to SAGE-547 re-treatment for the open-label second infusions of study medication.

**Table 6: SAGE-547 Open Label Dosing Schedule**

Hour	Type and Duration of SAGE-547 Infusion	Description
H1	One hour loading Infusion	300 $\mu\text{g/kg/h}$
H2 – H120	119 hour maintenance infusion	150 $\mu\text{g/kg/h}$
H121 – H126	6 hour taper	125 $\mu\text{g/kg/h}$
H127 – H132	6 hour taper	95 $\mu\text{g/kg/h}$
H133 – H138	6 hour taper	65 $\mu\text{g/kg/h}$
H139 – H144	6 hour taper	35 $\mu\text{g/kg/h}$

### 10.3. Route of Administration

SAGE-547 Injection is intended for IV administration only. The compatibility of SAGE-547 with other drugs is unknown, and the product should be administered via a dedicated peripheral IV line using any Sage-supplied study-specific IV administration bags and lines. In order to preserve blinding, these instructions also apply to the blinded placebo infusions.

### 10.4. Treatment Period

The treatment period with double-blind SAGE-547 or placebo is six 24-hour periods (144 hours), which may encompass 6-7 calendar days. The retreatment period is of identical duration.

## **10.5. Concomitant Medications, Procedures and Treatments**

Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. All concomitant medications, procedures, and treatments should be documented throughout the study from Screening through Visit 12/12R and recorded on the eCRF.

SAGE-547 has demonstrated inhibitory effects on cytochrome P450 isoenzyme 2C9 (CYP2C9). Therefore, AEDs such as phenytoin and phenobarbital that are primarily metabolized by CYP2C9 should be closely monitored during SAGE-547 administration to ensure target exposures are maintained.

### **10.5.1. Concomitant AEDs**

Subjects may enter the study on AEDs, and be administered AEDs during the study. All of these must be recorded on the eCRF with details including date and time of starting and stopping each AED, the route of administration, changes in doses, and frequency of administration. In addition, details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the eCRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.

### **10.5.2. Concomitant Third-Line Agents**

All third-line agents (as defined in [Section 8](#)) administered since the diagnosis of SE will be recorded on the eCRF, whatever path the patient took for entry into the study. Details will include the name of the drug, the start and stop dates and times, and, after consent, the doses with start and stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

In addition, those changes in dose that constitute a wean attempt will be marked as such on the eCRF. In this way the start and stop dates and times of all wean attempts (see [Section 11](#) for definitions) will be recorded, as will the type of wean (QW, OW, or TW) and the outcome of the wean attempt (successful, failed and dose of this third-line agent increased or failed and this third-line agent stopped and another third-line agent started). Those wean attempts that occur after the TW up to and including Visit 12/12R will be marked “AW”.

Some third-line agents (such as propofol) are also used to induce sedation to facilitate a subject’s ability to tolerate the ventilator. For subjects requiring such sedation, propofol is the preferred agent unless there are contraindications. The eCRF will make clear from the indication for the third-line agent when it is being used for burst or seizure suppression and when it is being used as ventilator support or for another purpose. The investigator will add a note to the eCRF to justify that the doses used are appropriate for sedation and not for seizure or burst suppression. The doses used for ventilator support and other similar uses are usually much lower than those used for seizure or burst suppression, and use of these third-line agents for these other purposes does not constitute a wean failure under this protocol.

### **10.5.3. Concomitant Pressors**

The start and stop dates and times of all pressors will be recorded as well as the start and stop dates and times of all dose changes.

#### **10.5.4. Other Concomitant Medications**

All other concomitant medications must be recorded on the eCRF with details including date and time of starting and stopping, the route of administration, dose, and frequency of administration.

### **11. STUDY ASSESSMENTS**

#### **11.1. Efficacy Assessments**

##### **11.1.1. Primary Efficacy**

Success or failure will be determined, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo infusion and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the blinded (first) infusion of SAGE-547 or placebo. In addition, subjects must have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) to be deemed to be successes. All subjects who fail to complete their infusion of randomized treatment or do not have at least one attempt during study treatment to wean off all third-line agents will be considered as “failures” for the primary endpoint.

##### **11.1.1.1. Weaning**

Third-line agents are anesthetic agents that are administered in order to reach a seizure or burst suppression EEG pattern. For the purposes of this study, third-line agents are defined as continuous intravenous infusions of pentobarbital, midazolam, propofol, and ketamine at maintenance doses alone or in combination sufficient to produce a burst suppression pattern on the EEG. The following are considered to be minimum maintenance doses of these agents that may be expected alone or in combination to achieve EEG burst suppression. If subjects are on lower doses than these and are not in EEG burst suppression for the 24 hours prior to the QW or the first 12 hours of the blinded study drug infusion, they will be considered to be screen failures/protocol violators and will exit the study.

- Pentobarbital: 1 mg/kg/hour
- Midazolam: 0.1 mg/kg/hour
- Propofol: 3 mg/kg/hour
- Ketamine 1.2 mg/kg/hour

The timing and nature of the third-line agent weans will be guided by the Clinical Standardization Guidelines for the study, and the clinical judgment of the investigator, and will always be primarily done in the best medical interests of the subject. Advice about weaning may be sought from the Clinical Standardization Team, a group of fellow investigators with experience of performing clinical trials in subjects with SRSE. The Clinical Standardization Team will be able to review EEGs in real time related to key study timepoints (qualifying wean, terminal wean, and the period after the end of the blinded study drug infusion) in order to provide advice about compliance with the Clinical Standardization Guidelines.

The following guidance for weaning applies to all weans of third-line agents undertaken during the study. These weans include the qualifying wean (QW); the terminal wean (TW), which is the wean

of the third-line agent if the subject is on only one third-line agent or the wean of the last third-line agent if the subject is on more than one third-line agent; the other weans (OW), which are the weans of the third-line agents other than the TW if the subject is on more than one third-line agent. The guidance also applies to additional weans (AW), which are the weans from third line agents that take place after the TW for the first blinded study drug infusion or the second open-label study drug infusion.

### **QW Guidance**

- Wean to be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace that third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Investigators should allow 24 hours to lapse after the end of a “successful” qualifying wean before finally declaring the QW a success. If a third-line agent needs to be re-instituted within that 24 hours, the QW is a failure, and the subject may then be randomized in the study.

### **OW Guidance**

- First OW should not begin before H49 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- If the subject is on two third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the TW. However the OW may be completed over a shorter or longer time period and may overlap if clinically indicated with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- If the subject is on three third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the wean of the second agent. The second agent should be weaned over 24 hours and that wean completed before starting the TW. However the OWs may be completed over a shorter or longer time period and may overlap if clinically indicated with each other and with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- All OWs should be completed before H96 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **TW Guidance**

- The TW is defined as the wean of the last third-line agent.

- If the subject is on one third-line agent, the TW should not begin before H49 and should begin no later than H97 after starting administration of study drug or starting the open-label infusion of SAGE-547. If the subject has had one or more OWs, the TW should ideally begin as soon as the last OW is complete but in any case not later than H97 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- The TW must be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace this third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Every effort must be made to complete the TW before H120 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547, but the TW must be complete before H144 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

#### **AW Guidance**

- AWs will take place when medically indicated in the opinion of the investigator.
- Ideally the AW should take place over 24 hours, but completion may be over a shorter or longer time period than this. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.

#### **11.1.1.2. EEG**

Electroencephalographs (EEGs) that are representative of the intermittent or continuous EEG being used to support key investigator decisions will be collected at the following time points:

- A six-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst suppression for the second path to eligibility, and a variable pattern for the third path to eligibility.
- EEG will be performed to cover the qualifying wean (QWEEG). EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for the one hour after the end of the QW. The duration of the QWEEG will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s) or the decision to re-institute a third-line agent(s) at doses intended to induce burst suppression.
- EEG will be performed from three hours prior to the start of the blinded infusion to five hours after the start of the blinded infusion. This will be called the BIEEG. The intent of this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG.



- EEG will be performed to cover the final or terminal wean of third-line agent (TWEEG). The TW is the wean of the final third-line agent during the blinded administration of study drug or the open-label infusion of SAGE-547; if the subject was on one third-line agent, the TW is the wean of that agent. If the subject was on three third-line agents, the TW is the wean of the third and final agent. EEG recording will start 30 minutes prior to the start of the TW, continue for up to 24 hours during the TW, and then continue for the one hour after the end of the TW. The duration of the TWEEG will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the final third-line agent or the decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity could not be managed using intermittent bolus doses of AEDs.
- EEG will be performed during the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 (TAEED). The TAEED is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the start of the taper (at Hour 119.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours during the taper, and then continue for the one hour after the end of the taper (to Hour 145 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547). The duration of the TAEED will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity seen during the taper could not be managed using intermittent bolus doses of AEDs.
- EEG will be obtained to cover the end of the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 and the ensuing 24-hour period, during which the primary endpoint is assessed (PAEED). The PAEED is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the end of taper (at Hour 143.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours after the end of the blinded administration of study treatment or the open-label infusion of SAGE-547, and then continue for the one hour after the end of the 24-hour assessment period (to Hour 169 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547). The duration of the PAEED will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity seen in the 24 hours following the end of the blinded administration of study treatment or the open-label infusion of SAGE-547 that could not be managed using intermittent bolus doses of AEDs.

In practice, most subjects are on continuous EEG monitoring or long periods of intermittent EEG monitoring. However, this protocol does not mandate continuous EEG monitoring and breaks from EEG monitoring to provide relief to the scalp from the irritating effects of the electrodes are advised, particularly in children, according to local practice. If a break in EEG monitoring is mandated by local practice guidelines at a time when one of the protocolled EEG segments is to be collected, the break in EEG monitoring will take precedence, with the reason for missing the EEG reading noted on the eCRF. The EEGs obtained for the study are therefore part of the existing EEG record rather than being obtained de-novo at each timepoint. For timepoints where there might be some

ambiguity, such as the TWEEG, the final EEG record is that of the final attempt to wean the last third-line agent, even if earlier attempts to wean that agent took place. In some cases (the TAEEG and PAEEG, for instance), the EEG records will overlap, but different cuts are taken to service the different EEG record requirements.

The electronic EEG file will be de-identified, the date and time of the start and stop of the EEG and the subject number will be attached to the file, and the study time point will be indicated (CEEG, QWEEG, BIEEG, TWEEG, TAEEG, and PAEEG). The PI will indicate on the eCRF what the EEG shows, as follows:

- For the CEEG, the PI will describe the EEG pattern that determined which path to eligibility the subject was on.
- For the QWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure on the qualifying wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the qualifying wean).
- For the BIEEG, the PI will note the date and time of the start of the EEG and the pattern seen on the EEG.
- For the TWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure on the terminal wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the terminal wean).
- For the TAEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst suppression before the end of the SAGE-547 infusion).
- For the PAEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst suppression in the 24 hours following the end of the SAGE-547 infusion).

A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm the PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period (average EEG power at the end of Visit 9 of more than two microvolts).

- All subjects will have the CEEG and QWEEG collected and stored, and the QWEEG read;
- Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;
- Those subjects randomized who are not retreated will have the BIEEG, TWEEG, TAEEG and PAEEG related to the blinded study drug infusion collected and stored, and the QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read;

- Those subjects randomized who are retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion and the TWEEG, TAEED, and PAEEG related to the open-label study drug infusion collected and stored, and the QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read.

All EEG records may be subject to quantitative EEG analysis.

### **11.1.2. Secondary Efficacy**

#### **11.1.2.1. Clinical Global Impression Scale (CGI)**

The clinical global impression scales are often utilized in clinical trials to allow clinicians to integrate several sources of information into a single rating of the subject's condition. Both the CGI-Severity (Question 1, CGI-S) and the CGI-Improvement (Question 2, CGI-I) employ a 7-point Likert scale measuring severity of the disease state in the subject and improvement, respectively. All severity assessments after initiation of SAGE-547 treatment should consider the general state of the subject over the preceding week. The third question on the scale will not be employed in this trial, and where the scale states "mental illness", this means "physical illness" in this trial.

The CGI-S will be evaluated at Visit 1 and at the last visit, Visit 12 or 12R. The CGI-I will be evaluated at Visit 12 or 12R.

#### **11.1.2.2. Epilepsy Status**

At Visit 1, the diagnosis of epilepsy will be documented as a no/yes question. If there was a previous diagnosis of epilepsy, further details will be documented, including:

- Date of diagnosis;
- Details of anti-epileptic drugs currently being taken;
- Type of epilepsy;
- Seizure frequency in the past month.

Information about the current (index) episode of status epilepticus will be obtained at Visit 1:

- Date of onset
- Date of failure to respond to first line agent(s) and the name(s) of the agent(s)
- Date of failure to respond to second line agent(s) and the name(s) of the agent(s)
- Any previous treatment with third line agents and the response to those agents (details of the third line agent drugs and previous wean attempts will be recorded on the Third Line Agent Medication CRF)
- The cause of the index episode of status epilepticus
- If the subject was transferred from another hospital or from within the hospital, the reason for the transfer will be recorded (such as for study enrollment, due to lack of medical options at original hospital or unit, due to lack of beds at the original hospital or unit, family request, other)

Previous (non-index) diagnosis of status epilepticus will be documented as a no/yes question. If SE did occur in the past, further information will be gathered, including:

- SE, RSE, or SRSE diagnosis, whichever was the most severe diagnosis for each episode;
- Cause;
- Treatment, including experimental treatments and need for intubation/ventilation;
- Dates of onset and duration if the episode of status epilepticus occurred in the past 12 months.

At Visit 12 or Visit 12R, the following information will be gathered:

- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of SE up to and including Visit 12 or Visit 12R;
- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of seizures (convulsive and non-convulsive) up to and including Visit 12 or Visit 12R;
- Number of separate episodes of SE after H144 at the end of Visit 8 or Visit 8R (no/yes); if yes,
  - SE, RSE, or SRSE diagnosis;
  - Cause;
  - Treatment, including experimental treatments and need for intubation/ventilation;
  - Dates of onset and duration.

Note that a separate episode of SE is defined as an episode of SE separated from other periods of status epilepticus by at least 24 hours.

- Diagnosis of epilepsy since Visit 11 or Visit 11R will be documented as a no/yes question. If a diagnosis of epilepsy has been made, further details will be documented, including:
  - Status as ongoing or new epilepsy since Visit 11 or Visit 11R after initiation of SAGE-547 treatment;
  - Details of anti-epileptic drugs currently being taken;
  - Type of epilepsy and seizure frequency in the past week.

## **11.2. Safety Assessments**

The safety and tolerability of SAGE-547 will be assessed using adverse events, clinical laboratory measures, vital signs, ECG intervals and morphology, and mortality. All safety assessments should be performed per hospital standard of care and will be collected periodically throughout the study according to [Table 1](#), [Table 2](#), and [Table 3](#) (Schedules of Assessments).

### **11.2.1. Adverse Events**

AEs will be collected after informed consent has been signed and prior to study-specific screening procedures not considered standard of care, during subject preparation for SAGE-547 administration and through Visit 12 or Visit 12R. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™) coding system (current version). See [Section 14](#) for additional details.

### **11.2.2. Clinical Laboratory Tests**

Blood samples will be taken for hematology, and serum chemistry and GFR will be calculated at:

- Visit 1 and then at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.
- Blood samples will be taken at Visit 11 or Visit 11R for serum chemistry (renal panel only).

Urine samples (20 ml) will be taken for urinalysis and urine NAG analysis at:

- Visit 1 and at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.

These samples will be analyzed at a central laboratory; hour-to-hour medical decisions will be based on sampling for laboratory testing done outside the protocol as part of normal standard of care. GFR will be calculated using values from local laboratory tests.

Any out-of-range values will be flagged by the laboratory; the investigator will add a comment about whether the abnormality is clinically significant. Clinical significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

#### **11.2.2.1. Hematology and Serum Chemistry**

Hematology will include complete blood count (CBC) white blood cell count with differential, platelet count and red blood cell (RBC) count, hemoglobin and hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose.

#### **11.2.2.2. Pregnancy Test**

Females of child-bearing potential will be tested for pregnancy by serum pregnancy test at Visit 1. In this study, since an accurate history of menstruation in girls and menopause in older women may not be available at Visit 1, "child-bearing potential" is taken to mean any female aged 10 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy. Female subjects with a positive pregnancy test will be ineligible for study participation.

#### **11.2.2.3. Urinalysis**

Urinalysis will include assessment of protein, blood, leukocytes, glucose, ketones, urobilinogen, pH, and specific gravity.

### **11.2.3. Vital Signs**

Blood pressure, heart rate, and temperature will be recorded at the following time points relative to the first infusion of study drug, and to the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547:

- Visit 1;
- At 0, +30, +60 minutes (+/-15 minutes) and +2, +4 and +8 hours (+/- 30 minutes) after the start of the infusion;
- At +24, +48, +72, +96, +120, +144, +168, and +192 hours (+/- 2 hours) after the start of the infusion.

#### **11.2.4. Weight and Height**

Weight and height will be measured at Visit 1 and weight will also be measured once during each 24 hour period of the first infusion of study drug, and of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547. These daily weights will be used to modify the dose of SAGE-547 if required.

#### **11.2.5. ECG**

12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours; at other times the allowed time window for ECGs is +/- 2 hours:

- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +128, +136, +144, +152, +160, and +192 hours after the start of the blinded (first) study drug infusion
- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +126, +132, +138, +144, +152, +160, and +192 hours after the start of the open-label (second) study drug

The heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm.

#### **11.2.6. Mortality**

Mortality will be recorded on the Visit 12 or Visit 12R case report form. If the subject has died, the following information will be collected:

- Date of death;
- Cause of death.

As accurate as possible cause of death will be collected, which will be further categorized as due to one of the following causes:

- SE;
- complications of long term intubation and third-line agent infusions;
- underlying cause of qualifying SE;
- co-morbidity existing at the time of the qualifying SE;
- new co-morbidity or trauma;
- study drug;
- other (specify).

### 11.2.7. Pharmacogenetic Samples

If a subject's LAR consents to pharmacogenetic sampling, a blood sample for genetic research will be collected at Visit 1 in order to avoid the possible introduction of bias through the exclusion of patients who may withdraw from study due to an AE (a subject population that may be of specific interest for subsequent genetic analysis). If for any reason a sample cannot be taken prior to treatment, a sample can be drawn at any point prior to completion with the restriction that no more than one genetic sample be taken per subject.

The objective of this research is to collect and store blood samples for possible DNA extraction and exploratory research into how genes or specific genetic variation may influence response (i.e. distribution, safety, tolerability, and efficacy) to SAGE-547. Specific genetic variations of interest include but are not limited to: classes of metabolizing enzymes (e.g. Cytochrome P450 supra-family genes), genes encoding enzymes involved in the production and metabolism of allopregnanolone (e.g. AKR1C4 (3 $\alpha$ -hydroxysteroid dehydrogenase)), genes associated with the GABA receptor (e.g. GABRA1-A6, GABRB1-B3, GABRD, GABRE, GABRG1-3) and genes associated with the production and degradation of GABA.

Future research may suggest other genes or gene categories as candidates for influencing not only response to SAGE-547 but also susceptibility to disorders for which SAGE-547 is being evaluated. Thus, the genetic research may involve study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.

#### 11.2.7.1. Biological Sampling and Coding Procedures (Pharmacogenetics)

To ensure patient confidentiality, utmost care will be taken in the coding and storage of pharmacogenetic samples.

*Extraction and coding:* DNA will be extracted from the blood sample and the DNA sample will be assigned a unique number replacing information from sampling tube. The assigned DNA number will be used to identify the sample and its corresponding information within Sage Therapeutics or at any designated contract laboratory for the purpose of sequencing of other DNA specific analysis. No personal details sufficient for individual identification will be available to any person (internal or external to Sage Therapeutics) working with the DNA.

*Genotype/Phenotype Analysis:* Samples and data from genetic analysis will be coded. The link between subject enrollment / randomization code and DNA number will be maintained and stored in a secure environment with restricted access. The established link will be used to identify relevant DNA samples for analysis, facilitated correlation of genotype results with clinical data, allow regulatory audit, and to trace samples for destruction in case of withdrawal of consent.

#### 11.2.7.2. Retention of Biological Samples for Pharmacogenetic Analysis

Extracted DNA is a finite research that is destroyed in the process of being analyzed. Primary blood samples from which DNA can be extracted will be stored and used until no further analyses are possible, a maximum storage period of 25 years from time of last subject last visit has been reached, or an individual or LAR withdraws his/her or their consent.

## 11.2.8. Other Outcomes

### 11.2.8.1. Pharmacokinetic Data

Formal plasma and urine analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS)). In addition, all samples will be analyzed for important SAGE-547 metabolites (if and when these are identified) and Captisol® concentrations.

#### Plasma Analysis

Plasma will be collected to assay for SAGE-547 concentrations at the following time points relative to the start of each infusion of study drug:

- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion.
- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open label SAGE-547 study drug infusion.
- All samples will also be analyzed for plasma concentrations of important metabolites of SAGE-547 if and when these are identified.
- All samples will also be analyzed for plasma concentrations of Captisol®.

The plasma samples will be drawn from the arm contralateral to that used for drug administration. Drawing samples from peripheral arterial or venous lines or from a central line is permissible. PK collection times should be adhered to as strictly as possible. The allowed time window for all samples is: pre-dose in the two hours prior to starting the infusion of study drug; samples up to and including 1h, +/- 5 minutes; subsequent samples, +/- 15 minutes. Subject-specific PK kits for sampling including instructions on collection and processing methods, and storage and shipping conditions, will be provided separately. To maintain the blind, all subjects will have samples taken as outlined above: subjects receiving SAGE-547 will have all samples analyzed for all analytes. Subjects on placebo may have samples analyzed to investigate endogenous allopregnanolone and metabolite concentrations, as well as Captisol® concentrations; experience with the plasma concentration data will determine if and which placebo samples are analyzed.

Each blood sample will be 3 ml in volume for adults and children weighing 30 kg or more, and 2 ml in volume for children weighing less than 30 kg. Separate aliquots will be obtained from each sample to service the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum blood draw for PK analysis for a subject having two infusions of study drug will be 99 ml (66 ml for children weighing less than 30 kg).

Plasma PK parameters for SAGE-547 will be calculated where appropriate (e.g.,  $C_{max}$ ,  $C_{min}$ ,  $t_{max}$ ,  $AUC_{last}$ ,  $AUC_{\infty}$ ,  $CL_s$ ). In addition, similar PK parameters will be calculated for Captisol®. PK parameters for important metabolites of SAGE-547 may be calculated. An evaluation will be made



of the feasibility of adopting a population-PK approach to assess drug-drug-interactions with SAGE-547 as victim of AEDs.

In addition, the Visit 9 sample may be analyzed for plasma concentrations of third-line agents.

#### Other Analysis

If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations.

Full details of all pharmacokinetic analyses will be described in the Pharmacokinetic Analysis Plan.

#### **11.2.8.2. Correlation of QT/QTc Changes and Plasma Concentrations of SAGE-547**

An analysis will be performed to determine whether there is any correlation between changes in QT/QTc interval and plasma concentrations of SAGE-547, in order to investigate any effect that SAGE-547 may have on QT/QTc interval.

#### **11.2.8.3. Pharmacoeconomic Data**

At Visit 12 or Visit 12R, the following information will be collected: number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital. If the subject dies before Visit 12 or Visit 12R, data will be collected up to the date of death. The definition of “hospital” is the institution that the subject was initially treated in. If the subject is transferred to another hospital, that hospital would be the “discharge destination from the hospital” and the “number of days in hospital” would be the number of days in the initial treating hospital.

For those subjects discharged from hospital before Visit 12/12R, the following questions will be asked:

- On what study day was the subject discharged from hospital?
- What type of facility was the subject discharged to (another hospital, a rehabilitation center, a supported care facility, home, other)?
- How many days did the subject stay in this facility?

The following questions will be answered regarding the stay in the ICU and hospital:

- Was the subject still in the ICU at the end of Visit 10/10R?
- If the FOUR Score was  $\geq 12$  at Visit 10/10R and the subject was in the ICU at Visit 10/10R, what was the reason for the subject not being discharged from the ICU (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, other)?
- Was the subject still an in-patient in the hospital at the end of Visit 12/12R?
- If the FOUR Score was  $\geq 15$  at Visit 12/12R and the subject was in the hospital at Visit 12/12R, what was the reason for the subject not being discharged from the hospital (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, unsuitable home circumstances, other)?

#### **11.2.8.4. STESS**

The STESS will be assessed during Visit 1 in order to assess the severity of the status epilepticus.

#### **11.2.8.5. FOUR Score**

The Full Outline of UnResponsiveness or FOUR Score is designed to assess conscious level and unlike other scores, is suitable for subjects who are intubated. It assesses four domains of neurological function (eye responses, motor responses, brainstem reflexes, and breathing pattern).

The FOUR Score will be collected at the following time points relative to each infusion of study drug (the initial blinded infusion and the second open-label infusion if this is administered):

- baseline, +24, +48, +72, +96, +120, +144, +168, and +192 hours (all +/- 2 hours) after the start of the infusion, and at Visit 11/11R and Visit 12/12R.

#### **11.2.8.6. Glasgow Outcome Scale (GOS)**

The GOS is a relatively common assessment scale used to standardize descriptions of the objective degree of recovery from brain injury such as cerebral trauma, or in this case SRSE. It was first used in 1975 ([Jennett and Bond 1975](#)) and allows a prediction of the long-term course of rehabilitation to return to work and everyday life. The scale classifies subjects into 5 groups:

- Death
- Persistent vegetative state
- Severe disability
- Moderate disability
- Good recovery

The GOS will be assessed at Visit 12 or Visit 12R.

#### **11.2.8.7. Supervision Rating Scale (SRS)**

The Supervision Rating (SRS) measures the level of supervision that a patient/subject receives from caregivers. The SRS rates level of supervision on a 13-point ordinal scale that can optionally be grouped into five ranked categories (Independent, Overnight Supervision, Part-Time Supervision, Full-Time Indirect Supervision, and Full-Time Direct Supervision). The SRS was designed to be rated by a clinician based on interviews with the subject and an informant who has observed at first hand the level of supervision received by the subject ([Boake 2000](#)). Scoring is a one-step procedure in which the clinician assigns the rating that is closest to the subject's level. Ratings are based on the level of supervision received, not on how much supervision a subject is judged or predicted to need.

The SRS will be assessed at Visit 1 and Visit 12 or Visit 12R. The Visit 1 assessment will be a retrospective assessment of the supervision required by the subject immediately prior to the admission that included the index episode of status epilepticus.

#### **11.2.8.8. Modified Rankin Scale – 9Q (mRS-9Q)**

The Modified Rankin Scale (mRS) is a commonly used scale to determine disability and functional dependence due to neurological insult such as stroke in adults. The 7-point scale (0 – 6) denotes functional capacity from no symptoms (0) to severe disability (5) and death (6). The Modified

Rankin Scale – 9Q is a shortened version consisting of 9 questions that reliably determines the mRS score and was developed to both simplify the assessment and expand the rater base to non- medically trained personnel (Patel, Rao et al. 2012). The assessment is a web-based tool in the public domain with automatic score calculation and error checking found at [www.modifiedrankin.com](http://www.modifiedrankin.com).

The mRS will be assessed at Visit 1 and at Visit 12 or Visit 12R in subjects  $\geq 17$  years of age. The baseline assessment will be a retrospective assessment of the disability and dependence of the subject immediately prior to the admission that included the index episode of status epilepticus.

## 12. STUDY PROCEDURES

The study procedures listed below by study day reflect the required data collection times for this protocol. When a time window is necessary, this is specified below. If no time window is specified, the test may be performed at any time within the specified 24-hour period.

### 12.1. Visit 1 (V2-≤30h)

The baseline period will be up to approximately 84 hours prior to starting blinded study treatment and should include the assessments/procedures listed below and summarized in Table 1 and Table 2 (for retreatment), the Schedules of Events.

- Informed consent
- Eligibility checklist
- Verification of inclusion/exclusion criteria.
- Demographic information and medical history obtained by proxy and confirmed by the subject when possible.
- SE and wean history
- Blood will be collected from female subjects 10 years to 55 years for a serum pregnancy test unless they are known to be pre-menstrual or post-menopausal or to have had a hysterectomy.
- Blood and urine samples collected for clinical laboratory testing.
- Pharmacogenetic sample will be collected from consenting/eligible subjects.
- Vital signs
- Height
- Weight
- An ECG reading taken.
- Administration of the STESS.
- Administration of the FOUR Score.
- Administration of SRS.
- Administration of the mRS-9Q assessment.
- Assessment of the CGI scale.
- Evaluation of epilepsy status.
- Administration of continuous IV third-line agents.
- Perform EEG.
- Recording of adverse events.
- Recording of previous and concomitant anti-epileptic drugs.
- Recording of previous and concomitant third-line agents.
- Recording of concomitant pressors.

- Recording of other concomitant medications, procedures, and treatments.

## **12.2. Visit 2 (V3-≤54h)**

- Recording of adverse events.
- Recording of concomitant anti-epileptic drugs.
- Recording of concomitant third-line agents.
- Recording of concomitant pressors.
- Recording of other concomitant medications, procedures, and treatments.
- Wean of continuous third-line agent:
  - If wean is successful, subject is followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (these subjects are Qualifying Wean Success subjects or QWS subjects);
  - If wean is not successful, there is ongoing intravenous administration of at least one continuous IV third-line agent and EEG is performed and the subject is randomized.

## **12.3. SAGE-547 Treatment Period**

### **12.3.1. Visit 3/3R (0-24 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs will be recorded at:
  - 0, +30, +60 minutes (+/-15 minutes) and +2, +4, +8 (+/- 30 minutes) and +24 hours (+/- 2 hours) after the start of the infusion
- ECG readings will be recorded immediately after PK sampling at:
  - 0 (pre-dose) and at +0.5, +1, +3, +6, +12, and +24 hours after the start of the blinded study drug infusion.
- A blood sample for PK analysis should be collected at the following time points (all +/- 15 minutes except where otherwise stated):
  - 0 (pre-dose, within two hours of the start of the infusion) and at +0.5, +1 (+/- 5 minutes), +3, +6, +12, and +24 hours after the start of the blinded study drug infusion.
- Completion of the FOUR Score
  - +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the end of the QW)
- Ongoing intravenous administration of a continuous IV third-line agent.
- Study drug administration in loading (Hour 0-1) and maintenance infusions (at completion of Hour 1).

- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.3.2. Visit 4/4R (25-48 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +48 hours (+/- 2 hours) after the start of the infusion
- An ECG reading taken immediately after PK sampling:
  - +48 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +48 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +48 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent.
- Ongoing study drug maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.3.3. Visit 5/5R (49-72 hours)**

- Weight
- Vital signs should be recorded at:
  - +72 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +72 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +72 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +72 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:

- initiate weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.4. Visit 6/6R (73-96 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +96 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +96 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +96 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +96 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Perform EEG.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.5. Visit 7/7R (97-120 hours)**

- Weight
- Vital signs should be recorded at:
  - +120 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +120 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:

- +120 hours (+/- 15 minutes) after the start of study drug infusion, immediately prior to the end of the maintenance infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +120 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled. Complete wean by 120 hours if at all possible.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## 12.4. SAGE-547 Taper Period

### 12.4.1. Visit 8/8R (121-144 hours)

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +144 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after each PK sampling:
  - +128, +136 hours and +144 hours after the start of the study drug infusion
  - During the open-label retreatment phase of the study ECG readings at: +126, +132, +138 hours and +144 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected (+/- 15 minutes unless otherwise stated):
  - +128 (immediately prior to the end of the first taper step), +136 hours (+/- 5 minutes, immediately prior to the end of the second taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of study drug infusion.
  - During the open-label retreatment phase of the study PK blood draws at: +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 hours (+/- 5 minutes, immediately prior to the end of the third taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of the study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +144 hours (+/- 2 hours) after the start of the infusion
- Complete wean of third line agents by H144 if not completed by H120.



- Perform EEG.
- Taper of SAGE-547 infusion begins at hour 121.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## **12.5. Follow-up Period**

### **12.5.1. Visit 9/9R (145-168 hours)**

- Vital signs should be recorded at:
  - +168 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +152, +160 hours (+/- 2 hours) after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +152 and +160 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +168 hours (+/- 2 hours) after the start of the infusion
- Perform EEG.
- Assessment of the presence of physiologic brain activity using EEG.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.5.2. Visit 10/10R (169-192 hours)**

- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +192 hours (+/- 2 hours) after the start of the infusion
- At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine retreatment with higher dose of study drug. All patients for retreatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.

- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.3. Visit 11/11R (Visit 3/3R + 14d (±2))**

- Blood samples collected for clinical laboratory testing (renal panel only).
- Completion of the FOUR Score (QWS subjects also).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.4. Visit 12/12R (Visit 3/3R + 21d (±2))**

All assessments also performed for QWS subjects.

- Completion of the FOUR Score.
- Administration of the GOS.
- Administration of the SRS.
- Administration of the mRS-9Q assessment.
- Evaluation of epilepsy status (see [Section 11.1.2.2](#) for details).
- Assessment of the CGI Scale.
- Recording of adverse events.
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications.
- Collection of pharmacoeconomic data.
- Mortality will be assessed throughout the study period.

## **13. STATISTICS**

### **13.1. Statistical Plan**

Complete details for the analysis and reporting of data from this study will be contained in the Statistical Analysis Plan (SAP).

#### **13.1.1. Interim Analysis**

When approximately 50% of subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### 13.1.2. Study Populations

The **Safety Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to actual treatment. This analysis population will be used for all safety analyses.

The **Intent to Treat Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to randomized treatment. This analysis population will be used for all efficacy analyses.

The **Modified Intent to Treat Population** is defined as all subjects who:

1. complete their initial course of blinded SAGE-547 or placebo treatment unless the non-completion was due a drug-related adverse event; and
2. have at least one attempt to wean from third-line agents prior to the end of blinded study treatment infusion unless the failure to wean was because seizures were not controlled.

Subjects will be classified according to randomized treatment. This analysis population will be used for sensitivity analyses of the primary endpoint and select secondary efficacy endpoints.

Narratives will be prepared for all subjects who do not complete the infusion of blinded study medication or were not subjected to any wean attempts. Narratives will include details of the cause of SE, the comorbid conditions, the adverse event(s), and reasons for non-completion of the infusion or failure to attempt weaning. This blinded narrative will be reviewed by the medical monitors and the patient adjudicated as MITT eligible or ineligible. Acceptable reasons for defining a subject as MITT ineligible include death or withdrawal of consent due to progression of the underlying cause of SE or comorbid conditions, unless the cause of death or progression of disease were thought by the investigator, sponsor, or DSMB to be related to study drug.

The **Per-Protocol (PP) Population** is defined as a subset of the MITT population but will exclude data from all subjects with significant protocol violations or deviations. Subjects will be classified according to actual treatment received. This data set will be used for sensitivity analyses to examine the robustness of results for the primary and key secondary efficacy endpoints.

The **Pharmacokinetics Population** is defined as all subjects who at least had an infusion of blinded SAGE-547 initiated and have at least one pharmacokinetic sample collected.

The **Pharmacogenetic Population** is defined all subjects who consent to being included in the pharmacogenetic assessment and provide a pharmacogenetic sample.

Summary statistics of all data collected will be presented for subjects who were QW successes.

### 13.1.3. General Aspects

Tabular displays of descriptive statistics will be provided for all variables. Summary tables will include n, mean, mean, standard deviation, minimum and maximum for continuous variable and frequency and percentage for categorical variables.

### 13.1.4. Analysis of Primary Endpoint

The analysis of response to treatment (see Section 11.1.1 for definition of primary endpoint) between SAGE-547 treated subjects and placebo treated subjects will be performed on the ITT population using a Cochran-Mantel-Haenszel (CMH) test with variables for treatment, concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to

randomization (one vs two or more). The CMH general association statistic and its associated p-value will be presented. The comparison of treatment response rates will be conducted at the 5% level of significance. To confirm the CMH results, a permutation test will also be conducted.

An additional analysis of the primary endpoint will also be performed on the MITT population. In addition sensitivity analyses of the primary endpoint will be performed using the ITT population based on:

- the number of third-line agents (one, two, or three) subjects were administered post-randomization; and
- which third line agent was the subject of the first TW.

### **13.1.5. Analysis of Secondary Efficacy Endpoints**

Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section ([Section 6](#)). Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. The analysis of the secondary endpoints will also be performed on the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

### **13.1.6. Analysis of Other Endpoints**

Safety and “Other” endpoints will only be summarized by treatment group.

Summaries of safety endpoints will be based on the overall Safety Population.

### **13.1.7. Epilepsy and SRSE Status**

Diagnosis of epilepsy and recurrence of RSE or SRSE will be documented as the percentage of subjects by time point and overall. Kaplan-Meier curves may be plotted if sufficient data are available.

Utilization of AEDs during follow-up and during recurrence will be summarized.

### **13.1.8. Questionnaires**

The data collected from each questionnaire will be interpreted according to the standard methodology for that questionnaire. There will be no adjustment for missing values.

### **13.1.9. Pharmacokinetic Data Analysis**

Details of the pharmacokinetic data analysis will be described in detail in a separate Pharmacokinetic Analysis Plan.

### **13.1.10. Pharmacogenetic Data Analysis**

Any genotype data generated in this study will be stored within a secured database within Sage Therapeutics and / or a third party contracted to work with Sage Therapeutics to analyze the samples. Because the number of subjects agreeing to participate in the genetic research component of the study is unknown, it is not possible to establish, a priori, whether sufficient samples will be obtained to support formal statistical evaluation of data. As a consequence a Pharmacogenetic Analysis Plan will only be prepared where appropriate and the results obtained from any genetic research will be reported in a report separate from the main study CSR.

### **13.1.11. Retreated Subjects**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are retreated with SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo.

### **13.1.12. EEG-Responders**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who are classified as EEG-responders/non-responders based on the independent assessment of the PAEEG. Summaries will be derived for the two randomized treatment groups.

### **13.1.13. QT/QTc Assessment**

An analysis of the correlation between changes in QT/QTc intervals and SAGE-547 plasma levels will be performed to investigate if there is a potential effect that SAGE-547 may have on QT/QTc interval. A detailed description of the QT/QTc assessment will be included in the SAP.

### **13.1.14. Quantitative EEG**

The six EEG records for each subject may be subjected to exploratory quantitative EEG analysis, the details of which will be included in the EEG Analysis Plan. In summary the following comparisons may be made, SAGE-547 versus placebo: the QWEEG versus the TWEEG (main analysis); the CEEG versus PAEEG (subsidiary analysis); and TAEEG versus PAEEG (exploratory analysis).

## **13.2. Determination of Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between treatment groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

### **13.3. Statistical Analysis Plan**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

## **14. ADVERSE EVENTS**

The safety procedures in this study will be detailed in a Safety Management Plan, which will be agreed and signed before the first subject is randomized in the study. Section 14.1 summarizes Investigator responsibilities regarding the identification and documentation of AEs, the classification of AEs for relationship to study drug and severity, and the reporting of AE information to the Sponsor and the IRB.

[Section 14.2](#) summarizes Sponsor/Medical Monitor Responsibilities regarding monitoring of AE data and reporting relevant safety information to FDA.

[Section 14.3](#) lists important AE definitions.

### **14.1. Investigator Responsibilities**

#### **14.1.1. Identification and Documentation of Adverse Events by Investigator**

Subjects will be evaluated and questioned generally (if possible) to identify AEs during the course of the study. AEs will be collected from the signature of the consent form through Visit 12/12R. Adverse events that occur prior to completion of screening will be captured on the Medical History eCRF. Adverse events that occur after completion of screening will be recorded on the Adverse Event eCRF.

All AEs revealed by observation, other diagnostic procedures, or spontaneously reported by the subject and/or in response to an open question from study personnel will be recorded on the Adverse Event Form. Any clinically significant deterioration in laboratory assessments or other clinical findings are considered an AE and must be recorded on the Adverse Event Form, unless otherwise stated. AE information recorded will be entered into the database on an ongoing basis.

AEs with a relationship considered related to study drug (probable, possible) should be followed until the event is resolved or the Investigator determines the event is stable or no longer clinically significant. AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

For SAEs, an electronic Serious Adverse Event eCRF must be completed with as much information as possible and submitted in the time frame described below in [Section 14.1.3](#). When new significant information is obtained as well as when the outcome of an event is known, the electronic SAE eCRF should be updated within 24 hours. If the subject was an outpatient at the time of the SAE and was re-hospitalized due to the SAE, a copy of relevant hospital records (e.g., admission report, laboratory test results, discharge summary, etc.) may be requested to be included as part of the subject medical file.

All SAEs will be followed until resolved or until a stable status has been achieved.

**14.1.2. Adverse Event Classification****14.1.2.1. Relationship to Investigational Drug**

None:	No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state.
Possible:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject, but this is not known for sure.
Probable:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

**14.1.2.2. Severity**

Mild	Discomfort noticed, but no disruption to daily activity.  For subjects that are unconscious, this may be a slight or minor change in a lab result or clinical sign or symptom that does not require immediate corrective action.
Moderate	Discomfort sufficient to reduce or affect normal daily activity, but is not hazardous to health; prescription drug therapy may be employed to treat the AE.  For subjects that are unconscious, this may be a clinically meaningful change that may require immediate corrective action.
Severe	Inability to work or perform normal daily activity and represented a definite hazard to health; prescription drug therapy and/or hospitalization may be employed to treat the AE.  For unconscious subjects, this may be a significant clinical change that requires immediate corrective action.

**14.1.2.3. Action Taken with Investigational Drug**

None	Study medication was continued without change.
Discontinued	Study medication was terminated.
Dose adjusted	Study medication dose/infusion rate was changed and then continued per protocol.
Interrupted	Study medication was interrupted and then continued per protocol.
Unknown	The action taken with regard to study medication is unknown.
Not applicable	Administration of study medication was not ongoing.



**14.1.2.4. Assessment of Outcome**

Ongoing	At the end of the study, the event has not resolved or stabilized.
Ongoing and stable	The event is ongoing but has stabilized and is unlikely to change
Resolved	The event has resolved or the subject recovered without sequelae.
Resolved with sequelae	The event has at least one secondary outcome that may result in permanent disability and/or functional limitation.
Unknown	The status of the event is unknown.
Death	The subject has expired.

**14.1.3. Investigator Reporting to Sponsor and Sponsor Emergency Contact**

All new SAEs that come to the Investigator and/or Sponsor's notice during the course of the study (up to and including the last study visit) must be reported by the Investigator on the designated electronic report form within 24 hours of the point in time when the Investigator becomes aware of the SAE. As additional information becomes available, the designated electronic report form must be updated within 24 hours.

Investigators must report any SAE, whether or not considered drug related. The report must include an assessment of whether there is a reasonable possibility that the drug caused the event.

In a medical emergency (ie, an event that requires immediate attention regarding the treatment of a subject, operation of the clinical study, and/or the use of investigational drug), study site staff will apply appropriate medical intervention according to current standards of care, and contact the Medical Monitor.

**14.1.4. Medical Monitor and Emergency Contact Information**

[REDACTED], MD  
[REDACTED]

**14.1.5. SAE Reporting Contact Information**

Contact information and reporting instructions are provided in the Safety Management Plan.

**14.1.6. Reporting to Institutional Review Boards (IRBs)**

It is the responsibility of the Investigator to promptly notify the institution's IRB of all serious and unexpected suspected adverse reactions (see [Section 14.3](#) for definitions).

## **14.2. Sponsor/Medical Monitor Responsibilities**

### **14.2.1. Monitoring of Adverse Event Data**

The Medical Monitor will review any newly reported adverse events in an ongoing basis. If the aggregate assessment indicates that an event is occurring more frequently than would normally be expected in this population, or as previously observed, and the sponsor believes that the events are causally related to the administration of SAGE-547, the Sponsor will then report that information in an IND safety report.

### **14.2.2. Data Safety Monitoring Board**

An independent DSMB will monitor the clinical, PK and PD data for safety signals throughout the study and will be asked to assess the placebo response rate at the time of the interim analysis to determine final sample size. In order to perform their monitoring function the DSMB will have access to un-blinded safety data as necessary.

The composition and procedures for the board will be described in a separate DSMB Charter.

### **14.2.3. Reporting to FDA**

The Sponsor must report in an IND safety report any suspected adverse reaction to study treatment that is both serious and unexpected (21 CFR 312.32(c)(1)(i)). Before submitting an IND safety report, the Sponsor will ensure the event meets all three of the definitions: (1) suspected adverse reaction, (2) serious, (3) unexpected. If the AE does not meet all three of the definitions, it should not be submitted as an IND safety report. The Sponsor should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the adverse event and, therefore, that the event meets the definition of a suspected adverse reaction.

If there is a serious and unexpected suspected adverse reaction, the Sponsor will notify the appropriate regulatory agency(ies) and all appropriate parties on an expedited basis. In addition, Sponsors must submit expedited reports of an increased rate of occurrence or severity of serious suspected adverse reactions over that listed in the protocol or Investigational Brochure.

SUSARs will be unblinded prior to reporting to FDA. Unless it is necessary to unblind for the safety of the patient, the investigator will not be informed of the unblinding of the subject.

Under 21 CFR 312.32, Sponsors should identify in the protocol SAEs that it does not plan to report individually in an expedited manner, because they are known consequences of the disease or otherwise common in the study population. Given the grave condition and prognosis of SRSE being studied, individual occurrences of seizures or seizure activity will not be reported expeditiously in this study. Regardless of which events are reported in an expedited manner, all adverse events will be closely monitored throughout the study.

## **14.3. Adverse Event Definitions**

### **14.3.1. Adverse Event**

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

### **14.3.2. Suspected Adverse Reaction**

Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

### **14.3.3. Life-Threatening**

An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

### **14.3.4. Serious**

An AE or suspected adverse reaction is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE – see definition above
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disability
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

### **14.3.5. Unexpected**

An AE or suspected adverse reaction is considered “unexpected”:

- If it is not listed in the Investigational Brochure or is not listed at the specificity or severity that has been observed, or
- If an Investigational Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigational Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigational Brochure listed only cerebral vascular accidents.

“Unexpected,” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigational Brochure as occurring with a class of drugs or as anticipated from

the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

#### **14.4. Emergency Identification of Study Medication**

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject's treatment in the study via the IVRS; this normally requires prior approval by the medical monitor. However, if the subject is at immediate risk and the Investigator believes that immediate knowledge of the study treatment will alter medical management, discussion with the medical monitor may take place after unblinding. The Investigator will not unblind the medical monitor during that discussion. The process of unblinding will ensure that only the investigator is unblinded; the medical monitor, study management team, and data management team will not be made aware of the treatment allocation of an individual subject. All cases of emergency unblinding will be fully documented in a way that does not unblind the medical monitor, study management team, and data management team.

### **15. STUDY ADMINISTRATIVE CONSIDERATIONS**

#### **15.1. Quality Control and Quality Assurance**

The Investigators and institutions will permit trial related monitoring, audits, IRB review, and regulatory inspections as requested by FDA, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed informed consent forms, etc.) in addition to case report forms.

Quality assurance and quality control systems with written standard operating procedures (SOPs) will be followed to ensure this trial will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The site's dedicated study monitor will arrange to visit the Investigator at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be identified and resolved. The study monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality assurance officers named by Sage Therapeutics or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements, made by the Sponsor with the Investigator/institution and any other parties involved with the clinical trial, will be in writing in a separate agreement.

## **15.2. Data Handling and Recordkeeping**

### **15.2.1. Data Handling**

Procedures for data handling (including electronic data) used in this protocol will be documented in a Data Management Plan.

### **15.2.2. Case Report Form Completion**

eCRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of demographics, study drug administration, study procedures, AEs, questionnaire completion, efficacy assessments and subject status, including survival.

The Investigator will maintain copies of the eCRFs at the study site. For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate eCRF.

### **15.2.3. Retention of Study Records**

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval and until there are no pending or contemplated marketing applications or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to an appropriate person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

## **15.3. Confidentiality**

To maintain subject privacy, all eCRFs, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available trial registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by Sage Therapeutics to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

#### **15.4. Publication Policy**

All information concerning SAGE-547 is considered confidential and shall remain the sole property of Sage Therapeutics. The Investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval from Sage Therapeutics. No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between Sage Therapeutics and the Investigator.

#### **15.5. Protocol Amendments**

Changes to the conduct of the study should be prepared as a protocol amendment by the Sponsor. Protocol amendments should receive written IRB/IEC approval prior to implementation at the investigative site, except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the trial (eg, change of monitor, telephone numbers). In this case, Sage Therapeutics will amend and implement the protocol change and subsequently notify the regulatory authorities and the Investigative sites who will notify the respective IRB, as appropriate.

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**APPENDIX 1. APPENDIX 1: FOUR SCORE****FOUR score****Full Outline of UnResponsiveness****Eye response**

- E4: eyelids open or opened, tracking, or blinking to command
- E3: eyelids open but not tracking
- E2: eyelids closed but open to loud voice
- E1: eyelids closed but open to pain
- E0: eyelids remain closed with pain

**Motor response**

- M4: thumbs-up, fist or peace sign
- M3: localizing to pain
- M2: flexion response to pain
- M1: extension response to pain
- M0: no response to pain or generalized myoclonus status

**Brainstem reflexes**

- B4: pupil and corneal reflexes present
- B3: one pupil wide and fixed
- B2: pupil or corneal reflexes absent
- B1: pupil and corneal reflexes absent
- B0: absent pupil, corneal and cough reflex

**Respiration pattern**

- R4: not intubated, regular breathing pattern
- R3: not intubated, Cheyne-Stokes breathing pattern
- R2: not intubated, irregular breathing
- R1: breathes above ventilatory rate
- R0: breathes at ventilator rate or apnea

Reference ([Iyer, Hoel et al. 2009](#)).

**APPENDIX 2. GLASGOW OUTCOME SCALE (GOS)****GLASGOW  
OUTCOME  
SCALE**

Patient Name: \_\_\_\_\_  
 Rater Name: \_\_\_\_\_  
 Date: \_\_\_\_\_

*Note:* The scale presented here is based on the original article by Jennett and Bond. It has become common practice in clinical trial administration, however, to use a modified version that places the scores in reverse order (i.e., "good recovery" = 1, "moderate disability" =2, etc.).

Score	Description
1	DEATH
2	PERSISTENT VEGETATIVE STATE Patient exhibits no <i>obvious cortical</i> function.
3	SEVERE DISABILITY (Conscious but disabled). Patient depends upon others for daily support due to mental or physical disability or both.
4	MODERATE DISABILITY (Disabled but independent). Patient is independent as far as daily life is concerned. The disabilities found include varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes.
5	GOOD RECOVERY Resumption of normal activities even though there may be minor neurological or psychological deficits.

**TOTAL (1-5):** \_\_\_\_\_

Reference ([Jennett and Bond 1975](#)).

## APPENDIX 3. SUPERVISION RATING SCALE (SRS)

### SUPERVISION RATING SCALE (SRS)

**Instructions:** Circle the rating that is closest to the amount of supervision that the patient *actually receives*. "Supervision" means that someone is responsible for being with the patient.

<u>Rating</u>	<u>Description</u>
<b>Level 1: INDEPENDENT</b>	
1	The patient lives alone or independently. Other persons can live with the patient, but they cannot take responsibility for supervision (for example, a child or elderly person).
2	The patient is unsupervised overnight. The patient lives with one or more persons who <i>could</i> be responsible for supervision (for example, a spouse or roommate), but they are <i>all</i> sometimes absent overnight.
<b>Level 2: OVERNIGHT SUPERVISION</b>	
3	The patient is only supervised overnight. One or more supervising persons are always present overnight but they are <i>all</i> sometimes absent for the rest of the day.
<b>Level 3: PART-TIME SUPERVISION</b>	
4	The patient is supervised overnight and part-time during waking hours, but is allowed on independent outings. One or more supervising persons are always present overnight and are also present during part of waking hours every day. However, the patient is sometimes allowed to leave the residence without being accompanied by someone who is responsible for supervision.
5	The patient is supervised overnight and part-time during waking hours, but is unsupervised during working hours. Supervising persons are <i>all</i> sometimes absent for enough time for them to work full-time outside the home.
6	The patient is supervised overnight and during most waking hours. Supervising persons are <i>all</i> sometimes absent for periods longer than one hour, but less than the time needed to hold a full-time job away from home.
7	The patient is supervised overnight and during almost all waking hours. Supervising persons are <i>all</i> sometimes absent for periods shorter than one hour.
<b>Level 4: FULL-TIME INDIRECT SUPERVISION</b>	
8	The patient is under full-time indirect supervision. At least one supervising person is <i>always</i> present, but the supervising person does not check on the patient more than once every 30 minutes.
9	Same as #8 plus requires overnight safety precautions (for example, a deadbolt on outside door).
<b>Level 5: FULL-TIME DIRECT SUPERVISION</b>	
10	The patient is under full-time direct supervision. At least one supervising person is always present and the supervising person checks on the patient more than once every thirty minutes.
11	The patient lives in a setting in which the exits are physically controlled by others (for example, a locked ward).
12	Same as #11 plus a supervising person is designated to provide full-time line-of-sight supervision (for example, an escape watch or suicide watch).
13	The patient is in physical restraints.

3/12/93

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## APPENDIX 4. MODIFIED RANKIN SCALE – LEVEL OF FUNCTION SURVEY (mRS-9Q)

1. Do you have any symptoms that are bothering you? (For example, trouble with reading or writing, trouble speaking, problems with vision, numbness, weakness, balance trouble, or problems with swallowing?)	YES <input type="radio"/>	NO <input type="radio"/>
2. Are you able to do the same work as before?	YES <input type="radio"/>	NO <input type="radio"/>
3. Are you able to keep up with your hobbies?	YES <input type="radio"/>	NO <input type="radio"/>
4. Have you maintained your ties to friends and family?	YES <input type="radio"/>	NO <input type="radio"/>
5. Do you need help making a simple meal, doing household chores, or balancing a checkbook?	YES <input type="radio"/>	NO <input type="radio"/>
6. Do you need help with shopping or traveling close to home?	YES <input type="radio"/>	NO <input type="radio"/>
7. Do you need another person to help you walk?	YES <input type="radio"/>	NO <input type="radio"/>
8. Do you need help with eating, going to the toilet, or bathing?	YES <input type="radio"/>	NO <input type="radio"/>
9. Do you stay in bed most of the day and need constant nursing care?	YES <input type="radio"/>	NO <input type="radio"/>

## APPENDIX 5. CLINICAL GLOBAL IMPRESSION (CGI)

### Clinical Global Impression (CGI)

#### 1. Severity of illness

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- |                             |   |
|-----------------------------|---|
| 0 = Not assessed            | 4 = Moderately ill                        |
| 1 = Normal, not at all ill  | 5 = Markedly ill                          |
| 2 = Borderline mentally ill | 6 = Severely ill                          |
| 3 = Mildly ill              | 7 = Among the most extremely ill patients |

#### 2. Global improvement: Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.

Compared to his condition at admission to the project, how much has he changed?

- |                        |                     |
|------------------------|---------------------|
| 0 = Not assessed       | 4 = No change       |
| 1 = Very much improved | 5 = Minimally worse |
| 2 = Much improved      | 6 = Much worse      |
| 3 = Minimally improved | 7 = Very much worse |

#### 3. Efficacy index: Rate this item on the basis of drug effect only.

Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.

EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect		Side effects			
		None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
<b>Marked</b>	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
<b>Moderate</b>	Decided improvement. Partial remission of symptoms	05	06	07	08
<b>Minimal</b>	Slight improvement which doesn't alter status of care of patient	09	10	11	12
<b>Unchanged or worse</b>		13	14	15	16
Not assessed = 00					

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

**APPENDIX 6. STATUS EPILEPTICUS SEVERITY SCORE (STESS)**

Outcome Predictor	Feature	Score
Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type (prior to first treatment)	Simple-partial, complex-parial, absence, myoclonic (complicating idiopathic generalized epilepsy)	0
	Generalized-convulsive	1
	Nonconvulsive status epilepticus in coma	2
Age	< 65 years	0
	≥ 65 years	2
History of previous seizures	Yes	0
	No or unknown	1
Summed Total		

**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY  
TO EVALUATE THE EFFICACY AND SAFETY OF SAGE-547 INJECTION  
IN THE TREATMENT OF SUBJECTS WITH SUPER-REFRACTORY  
STATUS EPILEPTICUS**

**PROTOCOL NUMBER: 547-SSE-301  
ADULT ONLY VERSION**

**IND NUMBER: 117901**

**EudraCT Number: 2015-002142-31**

Product: SAGE-547 Injection (allopregnanolone)

Sponsor Contact: [REDACTED], MD

[REDACTED]  
Sage Therapeutics  
215 First Street  
Cambridge, MA 02142  
[REDACTED]

Medical Monitor: [REDACTED], MD

Date of Protocol: 09 March 2015  
Date of Amendment One 27 May 2015  
Date of Amendment For 28 October 2015  
Adults Only

**Confidentiality Statement**

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

**PROTOCOL NUMBER: 547-SSE-301**

Sponsor [REDACTED]:

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]:

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

CRO [REDACTED]:

[REDACTED]



## 1. SIGNATURE PAGE

Title of Protocol:

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus

Protocol No: 547-SSE-301

### Sponsor Approval

[Redacted Signature]  
[Redacted Title] MD  
[Redacted Name]

03 Nov 2015

Date (dd/mmm/yyyy)

Sage Therapeutics

### Investigator Agreement

By signing this page I attest that I have read and understand the contents of Clinical Protocol 547-SSE-301 and any current amendments. I agree to adhere to the design, conduct, and reporting requirements of the study as stated in the clinical protocol and to my obligations to the Sponsor as described in the protocol and executed contracts between myself, my Institution, and the Sponsor. I also agree to adhere to any subsequent amendments to the clinical protocol.

Investigator's Signature: \_\_\_\_\_

Investigator's Name: \_\_\_\_\_

Institution: \_\_\_\_\_

Date: \_\_\_\_\_

## 2. SYNOPSIS

<b>Name of Sponsor:</b> Sage Therapeutics 215 First Street Cambridge, MA 02142		
<b>Protocol No.</b> 547-SSE-301	<b>Phase:</b> 3	
<b>Name of Investigational Product:</b> SAGE-547 Injection		
<b>Name of Active Ingredient:</b> Allopregnanolone		
<b>Title of the Protocol:</b> A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus		
<b>Dosing Regimen: SAGE-547 or Placebo Dosing Schedule</b>		
<b>Hour</b>	<b>Type and Duration of SAGE-547 Infusions</b>	<b>Dose</b>
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	90 µg/kg/h
H121 – H128	8 hour taper	65 µg/kg/h
H129 – H136	8 hour taper	45 µg/kg/h
H137 – H144	8 hour taper	25 µg/kg/h
<b>Dosing Regimen: SAGE-547 Open Label Dosing Schedule</b>		
<b>Hour</b>	<b>Type and Duration of SAGE-547 Infusion</b>	<b>Dose</b>
H1	One hour loading infusion	300 µg/kg/h
H2 –H120	119 hour maintenance infusion	150 µg/kg/h
H121 – H126	6 hour taper	125 µg/kg/h
H127 – H132	6 hour taper	95 µg/kg/h
H133 – H138	6 hour taper	65 µg/kg/h
H139 – H144	6 hour taper	35 µg/kg/h
<b>Study Sites</b> Up to 150 sites in the USA, Europe, and Canada.		
<b>Number of Subjects</b>		

The study will randomize 140 subjects at up to 150 sites.
<b>Study Population</b> <p>Subjects will be aged 17 years or more, in SRSE<sup>1</sup> (as defined in the Inclusion Criteria <a href="#">Section 8.1</a>), and being managed in an intensive care setting.</p>
<b>Duration of Subject Involvement</b> <p>Individual subject participation will be up to 30 days.</p>
<b>Study Design</b> <p>This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.</p> <p>Patients will follow one of three paths to entry to the study. The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst suppression with a third-line agent. These subjects will be consented for the study after admission to the intensive care unit, but before any third-line agents are administered for burst suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their legally authorized representative (LAR). Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours. Once burst suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of study drug.</p> <p>The second path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst suppression pattern on the EEG. These subjects may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of study drug.</p> <p>The third path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst</p>

<sup>1</sup> In this study, the term Super-Refractory Status Epilepticus or SRSE is equivalent to “Refractory Status Epilepticus (RSE) that has failed standard treatment” and the two terms are used interchangeably.

suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These subjects may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 treatment or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within six hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo).

The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that subjects, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as both the ability to wean the subject off all third-line agents before the end of the infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication infusion, and concurrent signs of physiologic brain activity as determined by EEG. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#) and [Table 2](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo will all subsequently be eligible to be administered SAGE-547 at the higher dose.

### Visit Schedule

The visit schedule and an overview of events at each visit is provided in [Table 1](#), [Table 2](#) and [Table 3](#) Schedule of Assessments.

### Study Objectives

**Primary objective:**

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult subjects with SRSE, and for the response to endure at least 24 hours after the end of the SAGE-547 or placebo infusion (primary response).

**Secondary objectives:**

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in the Clinical Global Impression scale (CGI) between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

**Safety objectives:**

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

**Other objectives:**

1. To evaluate the impact of retreatment with a higher dose SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;

4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;
6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS).

## Endpoints

### *Primary endpoint:*

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### *Secondary endpoints:*

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### *Safety endpoints:*

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.

### *Other endpoints:*

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who fail to respond to their randomized double blind treatment and are retreated with a higher dose of SAGE-547.
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS).

### **Inclusion Criteria**

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects 17 years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst suppression pattern; or who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst suppression pattern.

### **Exclusion Criteria**

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone or any excipients in SAGE-547.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy.
4. Subjects who have any of the following:

- a. a GFR low enough to warrant dialysis for whatever reason, but dialysis is not planned or non-continuous dialysis is planned (that would not adequately remove Captisol<sup>®</sup>);
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the opinion of the investigator, of less than 30 days;
  - e. a do not resuscitate (DNR) order.
5. Subjects who are being administered more than three third-line agents concomitantly or in whom the qualifying wean cannot be completed within 24 hours, or who are being administered a third-line agent for other indications such as management of raised intra-cranial pressure that would preclude weaning according to this protocol.
  6. Subjects with a living will that does not allow heroic measures.
  7. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
  8. Subjects who have been enrolled in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not withdraw or complete and then re-enroll).

### Pharmacogenetic Research

In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### Statistical Analysis

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

### Interim Analysis

When approximately 50% of the subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### Analysis of Primary Endpoint

The analysis of response to treatment between SAGE-547 treated subjects and placebo treated subjects will be performed using a Cochran-Mantel-Haenszel test with variables for treatment, concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). In this analysis, a treatment responder is a subject who is successfully weaned off



all third-line agents and blinded study medication prior to the end of study treatment infusion and remains off third-line agents for at least 24 hours following cessation of the blinded study medication, and who has concurrent signs of physiologic brain activity as determined by EEG. The analysis will be based on the ITT Population. The comparison of treatment response rates will be conducted at the 5% level of significance.

### **Analysis of Secondary Efficacy Endpoints**

The primary analysis will be repeated for the MITT population. Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section. Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. Secondary analyses will be repeated for the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from Baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third-line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

Summaries of safety endpoints will be based on the overall Safety Population which is defined as all subjects who at least initiated the infusion with blinded study treatment.

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are retreated with SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo. Summary statistics will be presented for subjects who were QW successes.

### **Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

**Table 1: Schedule of Assessments for Protocol 547-SSE-301: One Infusion of Study Drug (blinded)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical/SE/Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X		X	X	X	X	X	X				
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X		X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X		X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X		X	X		X		X		X		
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X			
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>n</sup>											X
Modified Rankin Score (mRS)	X <sup>n</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV 3rd-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>o</sup>				
EEG	X	X				X		X	X			
Randomization		X										
Study Drug Administration <sup>p</sup>			X	X	X	X	X	X				
TW Outcome & Retreat Decision										X <sup>q</sup>		
Physiologic Brain Activity									X			
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

**Table 2: Schedule of Assessments for Protocol 547-SSE-301: Two Infusions of Study Drug (one blinded, one open-label)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V3R
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	0-24h
Eligibility Checklist	X										S
Informed Consent <sup>a</sup>	X										E
Inclusion/Exclusion Criteria	X										E
Demography <sup>b</sup>	X										
Medical and SE and Wean History <sup>c</sup>	X										T
Height	X										A
Weight <sup>d</sup>	X		X	X	X	X	X	X			B
Serum Pregnancy Test <sup>e</sup>	X										L
Hematology <sup>f</sup>	X		X	X		X		X		X	E
Serum Chemistry and GFR <sup>f</sup>	X		X	X		X		X		X	
Urinalysis <sup>h</sup>	X		X	X		X		X		X	E
Pharmacogenetic sample	X										X
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X	T
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X	E
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X		N
STESS	X										I
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	O
Glasgow Outcome Score (GOS)											N
Supervision Rating Scale (SRS)	X <sup>n</sup>										
Modified Rankin Score (mRS)	X <sup>n</sup>										
Epilepsy Status	X										N
Clinical Global Impression (CGI)	X										E
Continuous IV Third-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>o</sup>			X
EEG	X	X				X		X	X		T
Randomization		X									
Study Drug Administration <sup>p</sup>			X	X	X	X	X	X			
TW Outcome and Retreat Decision										X <sup>q</sup>	P
Physiologic Brain Activity									X		
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X	A
Concomitant Anti-Epileptic Drugs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	G
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	E
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X	
Pharmacoeconomic Data											
Mortality											

Table 2 continued

	V3R	V4R	V5R	V6R	V7R	V8R	V9R	V10R	V11R	V12R
	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3R+14d (±2d)	V3R+21d (±2d)
Weight <sup>d</sup>	X	X	X	X	X	X				
Serum Pregnancy Test <sup>e</sup>										
Hematology <sup>f</sup>	X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X	X		X		X		X		
Vital Signs <sup>i</sup>	X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>	X	X	X	X	X	X	X			
STESS										
FOUR Score <sup>m</sup>	X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)										X
Supervision Rating Scale (SRS)										X
Modified Rankin Score (mRS)										X
Epilepsy Status										X
Clinical Global Impression Scale (CGI)										X
Continuous IV Third-Line Agent(s)	X	X	Wean	Wean	Wean	Wean <sup>o</sup>				
EEG			X			X	X			
Randomization										
Study Drug Administration <sup>p</sup>	X	X	X	X	X	X				
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data										X
Mortality										X

**Table 3: Schedule of Assessments for Protocol 547-SSE-301: Qualifying Wean Successes**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical and SE and Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X											
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X											
Serum Chemistry and GFR <sup>f</sup>	X											
Urinalysis <sup>h</sup>	X											
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X											
ECG <sup>j</sup>	X											
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>n</sup>											X
Modified Rankin Score (mRS)	X <sup>n</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV Third-Line Agent(s)	X	Wean										
EEG	X	X										
Adverse Events <sup>r</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

<sup>a</sup> Written informed consent by proxy (LAR) will be obtained prior to starting any study-related procedures not considered standard of care.

<sup>b</sup> Demographic information will be obtained by proxy and confirmed by the subject when possible.

<sup>c</sup> Medical history will be obtained by proxy and confirmed by the subject when possible. All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Dosing changes with the third-line agent(s) that constitute a wean attempt will be marked as such on the CRF, and the start/stop dates and times of all wean attempts prior to V3 will be recorded, as well as the outcome of the wean attempt.

- <sup>d</sup> Weight will be collected at Screening (V1) and once during each 24 hour period of the initial study drug infusion period (V3-V8) and second infusion period (V3R-V8R, if applicable). Daily weight will be used to determine the appropriate infusion rate of each dose.
- <sup>e</sup> Serum pregnancy test for females aged 17 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy.
- <sup>f</sup> Blood samples will be taken for hematology and serum chemistry and GFR calculation at V1, at 24, 48, 96, 144 and 192 hours ( $\pm$  2 hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will document whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.
- <sup>g</sup> Blood samples will be taken at V11 or V11R for serum chemistry (renal panel only).
- <sup>h</sup> Urine samples will be taken for urinalysis and NAG at V1, at 24, 48, 96, 144 and 192 hours ( $\pm$  2 hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will add a comment about whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.
- <sup>i</sup> Vital signs will be recorded at the following time points relative to the start of each infusion of study drug: Screening (V1), at 0, 30, 60 minutes ( $\pm$  15 minutes), at 2, 4, and 8 hours ( $\pm$  30 minutes), and at 24, 48, 72, 96, 120, 144, 168, and 192 hours ( $\pm$  2 hours).
- <sup>j</sup> ECG (12-lead) should be performed at Screening (V1) and at the following times relative to the start of study drug infusion. For the blinded (first) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 128, 136, 144, 152, 160, and 192 hours ( $\pm$  2 hours). For the open label SAGE-547 (second) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 126, 132, 138, 144, 152, 160, and 192 hours ( $\pm$  2 hours). Heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours.
- <sup>k</sup> Plasma will be collected to assay for study drug concentrations at the following time points relative to the start of each infusion of study drug: For the blinded (first) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion. For the open label SAGE-547 (second) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open label SAGE-547 study drug infusion. Pre-dose samples may be taken within two hours before starting the infusion of study drug; timepoints up to and including 1h will have a time window of  $\pm$  5 minutes; all other timepoints will have a window of  $\pm$  15 minutes.
- <sup>m</sup> FOUR Score assessments will be performed at Screening (V1), 24, 48, 72, 96, 120, 144, 168, and 192 hours (all  $\pm$  2 hours) relative to the start of each infusion of study drug, and at V11 or V11R, and at V12 or V12R.
- <sup>n</sup> SRS at V1 will be a retrospective assessment of the supervision required by the subject immediately prior to admission that includes the index episode of the SE, and mRS at V1 will be a retrospective assessment of the disability and dependence of the subject immediately prior to admission that includes the index episode of the SE.
- <sup>o</sup> Target for complete wean of all continuous IV third-line agents by 144 hours at V8/V8R if not completed by 120 hours at V7/V7R.
- <sup>p</sup> Study drug infusion is intended for IV administration only with a dedicated peripheral IV line using Sage-approved IV administration bags and lines.
- <sup>q</sup> At V10 only a decision to re-treat at a higher dose of SAGE-547 will be made by the Investigator if the continuous IV third-line agent wean has failed or the third-line agent requires re-introduction during V9. Subjects who become eligible for re-treatment at a higher dose of SAGE-547 will discontinue the planned visit schedule at V10, then repeat V3 (V3R) and all applicable subsequent visits.
- <sup>r</sup> AEs will be collected from the time Informed Consent is obtained and prior to the start of study-specific screening procedures not considered standard of care. Collection of AEs will continue throughout the study from V1 through V12 or V12R.
- <sup>s</sup> Subjects may enter the study on AEDs and be administered AEDs during the study. All Concomitant AEDs must be recorded on the CRF with details including date and time of starting/stopping each AED, the route of administration, changes in doses, and frequency of administration. Details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the CRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.
- <sup>t</sup> All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Details will include the name of the drug, the start/stop dates and times, and, after consent, the doses with start/stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

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**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
AE	adverse event
AED	anti-epileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the time-concentration curve
AW	additional weans
BDZ	benzodiazepine
BIEEG	blinded infusion electroencephalogram
BUN	blood urea nitrogen
CBC	complete blood count
CEEG	consent electroencephalogram
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
C <sub>max</sub>	maximum plasma concentration
C <sub>min</sub>	minimum plasma concentration
CNS	central nervous system
CRF	case report form
CSR	clinical study report
CYP2C9	cytochrome P450 enzyme involved in drug metabolism
DNR	do not resuscitate
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EEG	electroencephalogram
EIND	Emergency Use Investigational New Drug Application
EP	European Pharmacopeia
ESETT	Established Status Epilepticus Treatment Trial
FDA	Food and Drug Administration
FOUR	Full Outline of UnResponsiveness
GABA	$\gamma$ -aminobutyric acid
GABA <sub>A</sub>	$\gamma$ -aminobutyric acid-gated chloride channel

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GOS	Glasgow Outcome Scale
H	hour
HPLC	high performance liquid chromatography
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent to Treat
IV	intravenous
IVRS	Interactive Voice Randomization System
LAR	legally authorized representative
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent to Treat
mRS-9Q	Modified Rankin Score - 9Q
MS/MS	tandem mass spectrometry
nM	nanomolar
NMDA	n-methyl-D-aspartic acid
OW	other weans
PAEEG	primary endpoint electroencephalogram
PD	pharmacodynamics
PK	pharmacokinetic
QOL	quality of life
QW	qualifying wean
QWEEG	qualifying wean electroencephalogram
RBC	red blood cell

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
RSE	refractory status epilepticus
SAE	serious adverse event
SAP	Statistical Analysis Plan
SE	status epilepticus
SOP	standard operating procedure
SRS	Severity Rating Scale
SRSE	Super-refractory status epilepticus
SSRI	Selective serotonin re-uptake inhibitors
STESS	Status Epilepticus Severity Score
SUSAR	Suspected Unexpected Serious Adverse Reactions
SWFI	Sterile Water for Injection
TAEEG	taper electroencephalogram
T <sub>max</sub>	time at maximum plasma concentration
TW	terminal wean
TWEEG	terminal wean electroencephalogram
US	United States
USP	United States Pharmacopeia



### 3. INTRODUCTION AND RATIONALE

#### 3.1. Status Epilepticus

Status epilepticus (SE) is a life-threatening seizure condition in which the brain is in a state of persistent seizure triggered by neuronal hyperexcitability. The Neurocritical Care Society defines SE as one continuous unremitting seizure lasting longer than five minutes or recurrent seizures without regaining consciousness between seizures for greater than five minutes (Brophy, Bell et al. 2012). Common causes of SE include preexisting epilepsy, cerebrovascular disease (in adults), electrolyte and metabolic disturbances, anoxia, encephalopathies, head trauma, high fever (in children, especially in the first year of life) and drug or substance intoxication. SE is associated with substantial morbidity and mortality.

##### 3.1.1. Epidemiology of SE

Geography, sex, age, and race influence the epidemiology of SE, whose incidence has a bimodal distribution, peaking in infants/young children and the elderly (Hauser 1990; DeLorenzo, Pellock et al. 1995; Wu, Shek et al. 2002). The incidence of SE in the elderly population is at least twice that in the general population. Concurrent medical conditions often exist in the elderly population, which can complicate therapy and worsen the prognosis of SE (Chapman, Smith et al. 2001).

The annual incidence of SE in the US is generally quoted to be within the range of 18/100,000 to 61/100,000, based on a 19-year retrospective study in Rochester, Minnesota (Hesdorffer, Logroscino et al. 1998) and a 2-year prospective study in Richmond, Virginia (DeLorenzo, Pellock et al. 1995), respectively. Two studies from Europe give annual incidences of a similar magnitude, ranging between 9.9/100,000 and 15.8/100,000 (Coeytaux, Jallon et al. 2000; Knake, Rosenow et al. 2001). It is thus estimated that in the United States each year there are as many as 150,000 cases of SE (DeLorenzo, Pellock et al. 1995).

#### 3.2. Refractory SE

When a patient begins to seize, the emergency medical technician will administer a first-line intravenous (IV) benzodiazepine (BDZ), such as diazepam, lorazepam or midazolam (Silbergleit, Durkalski et al. 2012), which is done either at the scene of the seizure or in the ambulance. If this is unsuccessful at abating the seizure, additional doses of the first-line therapy will be administered in the emergency room. Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line therapy, which is an IV anti-epileptic drug (AED) such as phenytoin or valproic acid (Novy, Logroscino et al. 2010; Shorvon 2011; Hocker, Britton et al. 2013).

Approximately 20-30% of patients refractory to first-line treatment will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to approximately 70-80% of patients who receive second-line therapy refractory to that therapy.

If a patient's SE continues after administration of BDZs and AEDs, the subject is diagnosed as having refractory status epilepticus (RSE), which must be treated quickly to terminate the seizure activity, maintain the patient's airway, and prevent cerebral damage. RSE patients are immediately admitted to the Intensive Care Unit (ICU) and placed in a medically-induced coma to stop all seizure-related activity. The drugs used to induce coma are continuously-infused IV agents,

commonly propofol, midazolam, or pentobarbital, referred to as third-line agents (Brophy, Bell et al. 2012).

The RSE patient is continually monitored using electroencephalography (EEG) to ensure burst suppression is achieved. Burst suppression is a pattern of brain waves seen on an EEG, characterized by periods of activity alternating with periods of little or no activity in the brain, informing medical personnel of the effectiveness of the medically-induced coma. The goal of burst suppression is to allow the brain and corresponding neuronal tissue to restore function and reset to normal pre-seizure levels.

### 3.2.1. Epidemiology of RSE

Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line AED therapy. In turn, approximately 20 – 30% of these patients treated with AEDs will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to 28% of the total estimated SE patient population refractory to second-line therapy. Based on the previously-cited estimated incidence in the US, this means that there are up to 42,000 incident cases of RSE in the USA, annually (DeLorenzo, Pellock et al. 1995).

### 3.3. Super-refractory SE

After 24 hours of burst suppression, the patient is weaned off of the third-line therapy. If the weaning is unsuccessful (neuronal activity has not returned to normal), the third-line agent is re-administered or a different third-line agent is started, and the patient is considered to be in super-refractory status epilepticus (SRSE) (Chapman, Smith et al. 2001; Shorvon 2011; Brophy, Bell et al. 2012). SAGE-547 is being developed as an adjunct to third-line therapy in patients in RSE who have failed standard treatment. In this protocol, the term “RSE that has failed standard treatment” is deemed to be equivalent to the term “SRSE” and the two may be used interchangeably.

#### 3.3.1. Epidemiology of SRSE

The incidence of SRSE is very poorly understood, mainly because the diagnostic codes used for SE do not generally differentiate its nature as responding or refractory to treatment. Based on the variable reporting of outcomes data, the incident cases of SRSE could represent between one and two-thirds of the RSE patients (Novy, Logroscino et al. 2010; Ferlisi and Shorvon 2012; Hocker, Britton et al. 2013; Sutter, Marsch et al. 2013). More detailed epidemiology studies are needed to better elucidate the proportion of RSE patients whose condition becomes super-refractory. A recent review of ICU discharge data in the USA suggests an annual incidence of approximately 35,000, based on patients who required at least three days in the ICU for SE [Sage data on file].

#### 3.3.2. Outcomes of SRSE

SE has varying degrees of mortality depending on the underlying etiologies. Table 4 outlines the acute mortality in patients with SE by etiology (Neligan and Shorvon 2010). The mortality rate of SRSE is estimated to be 30% to 50% using current standard of care.

The causes of death from SE (and therefore SRSE) are heterogeneous, resulting from neuronal cell death, complications of underlying medical conditions, or adverse effects of the current standard treatments. Prognosis worsens and mortality increases with longer duration of SE, i.e. with SE that develops into RSE or SRSE (Neligan and Shorvon 2010), and with longer duration of

medically-induced coma ([Ferlisi and Shorvon 2012](#)). There is an obvious unmet medical need to improve upon the current standard of care treatment regimens.

Morbidity is high and survivors have outcomes ranging from poor function to vegetative state ([Shorvon 2011](#)). Approximately one third of patients with RSE and SRSE will recover, but with chronic neurologic or other deficits ([Neligan and Shorvon 2010](#); [Hocker, Britton et al. 2013](#)). In all, it is estimated that less than 25-30% of all SRSE patients have a favorable functional outcome.

**Table 4: Approximate Mortality of Status Epilepticus in Different Etiologies**

Underlying Etiology	Associated Acute Mortality in Patients with SE (%)
Drug reduction/withdrawal, poor AED compliance, or low AED levels	0-10
Cerebrovascular Disease	20-60
Metabolic Disorders	10-35
Acute CNS Infection	0-30
Anoxia	60-100
Alcohol Abuse	0-10
Head Trauma	0-25
Drug Overdose/Toxicity	10-25
Brain Tumors	0-20
Cryptogenic/Idiopathic	5-20

### 3.3.3. Unmet Medical Need in Super-refractory Status Epilepticus

Treatment approaches for SRSE consist of diagnosis and treatment of underlying medical conditions, adding and changing anti-seizure drugs, and repeated attempts at weaning from IV anesthetic agents. Treatment of SRSE has three aims:

- to prevent excitotoxicity, which begins within 24 hours of SE onset;
- to prevent cerebral damage by initiating neuroprotective burst suppression;
- to prevent the complications of extended periods of anesthesia or unconsciousness ([Shorvon 2011](#)).

Currently, there are no therapies that have been specifically approved for RSE or SRSE. The primary drugs used to induce coma are continuously infused IV anesthetics such as propofol, midazolam, or pentobarbital, known as third-line agents. Use of these drugs to control SRSE has only been studied in small retrospective reviews or small prospective studies without controls ([Hocker, Britton et al. 2013](#)) therefore there is no agreement on which drug is optimal nor on an optimal dosing regimen for the treatments that are used.

The most common adverse effect of the third-line agents is hemodynamic instability; in addition, they are not universally effective, with breakthrough seizures and withdrawal seizures requiring dose adjustments and changes in third-line agent(s). The drug thought to be most effective in SRSE, pentobarbital, is also associated with the most toxic adverse effect profile, comprising

decreased blood pressure and cardiorespiratory collapse (Claassen, Hirsch et al. 2002). The ability to wean patients successfully off the third-line agents as quickly as possible is therefore paramount, and an adjunct to SRSE treatment that enhances the success of the third-line agents and supports their successful weaning in a short timeframe would be an important addition to the therapeutic armamentarium. Preliminary clinical data show that SAGE-547 has been a successful adjunct to third-line therapy in this regard.

### 3.4. SAGE-547 Injection

Allopregnanolone is an endogenous, naturally occurring neuroactive steroid formed in the corpus luteum of the ovary, adrenal cortex and central nervous system (CNS) (Holzbauer, Birmingham et al. 1985; Paul and Purdy 1992; Ottander, Poromaa et al. 2005). It is a metabolite of progesterone created by the actions of 5- $\alpha$  reductase and 3- $\alpha$  hydroxy-steroid dehydrogenase. Allopregnanolone is a potent positive allosteric modulator of both synaptic and extra-synaptic GABA<sub>A</sub> receptors.

SAGE-547 Injection (allopregnanolone aqueous formulation in Captisol<sup>®</sup>) is being developed for the treatment of patients in RSE who have not responded to standard treatment. SAGE-547 Injection is a solution of 5 mg/mL allopregnanolone in Sterile Water for Injection (SWFI), USP and 250 mg/mL betadex sulfobutyl-ether sodium, NF. It is further diluted with Sterile Water for Injection, USP (SWFI) in IV bags to achieve an allopregnanolone concentration of approximately 1.67 mg/mL in an approximately isotonic solution and will be administered intravenously.

#### 3.4.1. Scientific Rationale for SAGE-547 in SRSE

Ineffective recruitment of inhibitory neurotransmission, together with excessive neuronal excitation, likely plays a role in the initiation and propagation of the electrical disturbance occurring in SE. GABA ( $\gamma$ -aminobutyric acid), the major inhibitory neurotransmitter in the central nervous system (CNS), is released from GABAergic neurons and binds to several types of GABA receptors (GABA<sub>A</sub>, GABA<sub>B</sub>, and GABA<sub>C</sub>) on target neurons. GABA<sub>A</sub> receptors are macromolecular proteins that form a chloride ion channel complex and contain specific binding sites for GABA and a number of allosteric regulators, including barbiturates, benzodiazepines, and some anesthetic agents. GABA receptor-mediated inhibition contributes significantly to the normal termination of a seizure (Kapur and Macdonald 1997). SAGE-547 is a positive allosteric modulator of the GABA<sub>A</sub> receptor.

The importance of terminating seizure activity as soon as possible is underpinned by a growing body of evidence from research and clinical observation that SE becomes more difficult to control as its duration increases. It has been postulated that this occurs due to a mechanistic shift from inadequate GABAergic inhibitory receptor-mediated transmission to excessive N-methyl-D-aspartic acid (NMDA) excitatory receptor-mediated transmission (Kapur and Macdonald 1997). As prolonged epileptiform bursting results in a reduction of GABA<sub>A</sub>-mediated synaptic inhibition, antiepileptic treatments which rely on enhancing intrasynaptic GABA<sub>A</sub> neurotransmission become less effective the longer SE continues.

Furthermore, the constitutive process of synaptic GABA<sub>A</sub> receptor internalization is accelerated by the increased neuronal activity associated with seizures. These findings suggest that the rate of GABA<sub>A</sub> receptor internalization is regulated by neuronal activity, and its acceleration contributes to the reduction of inhibitory transmission observed during prolonged seizures (Kapur and Macdonald 1997). Of note is that SAGE-547 binds to extrasynaptic as well as intrasynaptic GABA<sub>A</sub> receptors;

extrasynaptic receptors remain active with ongoing seizure activity, resulting in a putative mode of action for SAGE-547 in SRSE.

Status epilepticus induces cerebral damage that includes neuronal cell necrosis, gliosis, and network reorganization. The major cause of cell death in cerebral damage is excitotoxicity, which is initiated by glutaminergic receptor over-activation, causing calcium to flood the cell, thereby leading to apoptosis and necrosis. This process is initiated within a few hours of the start of seizure activity, and provides the medical imperative to terminate SE as quickly as possible. To prevent the consequences of the excitotoxicity cascade, it is recommended that anesthesia be initiated within 1-2 hours of onset of seizures at doses designed to induce EEG burst suppression ([Shorvon and Ferlisi 2011](#)).

### **3.4.2. SAGE-547 Clinical Program in the Treatment of SRSE**

The current SAGE-547 development program includes:

- an ongoing Phase 2 open-label trial, Study 547-SSE-201;
- this proposed Phase 3 randomized, double-blind, placebo-controlled trial, Study 547-SSE-301;
- a planned open-label, expanded access protocol, Study 547-SSE-302;
- a number of EINDs for SAGE-547 in patients with SRSE.

The designs of these studies are all similar, with a five to six day infusion of SAGE-547 (or placebo), during which time attempts are made to wean the subject off all third-line agents. In the Phase 3 studies, those subjects who cannot be weaned off third-line agents while being administered SAGE-547 (or placebo) will be eligible for a second open-label infusion of SAGE-547 at a higher dose, which is also being employed for the latter patients being enrolled in the Phase 2 study. Follow up of subjects is for 21 – 30 days after the first infusion of study medication.

### **3.4.3. Data from the SAGE-547 Development Program**

The data from 30 subjects included in the on-going clinical evaluation of SAGE-547 for the treatment of adults and children with SRSE clearly offers preliminary evidence that SAGE-547 could provide substantial and clinically significant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate. These subjects comprise 20 from the ongoing Phase 2 trial (71% success rate in 12/17 evaluable subjects) and 10 subjects who received EIND treatments (78% success rate in 7/9 evaluable subjects).

Successful therapy of SRSE has been defined as “the SE is completely controlled by the therapy, without breakthrough of withdrawal seizures, or discontinuation due to side effects or death during therapy,” ([Ferlisi and Shorvon 2012](#)). By this definition, which is in accord with the efficacy assessments used in the overall clinical evaluation of SAGE-547, 19 of the 26 (73%) subjects with SRSE who completed the SAGE-547 infusion were treatment successes. As data collection is ongoing, this information is preliminary and subject to change upon further monitoring.

Published reports on RSE and SRSE have stated mortality rate ranges from 35% to 65%. The underlying etiologies of SE in the 547-SAGE-201 study and EINDs are heterogeneous, and each one conveys a different risk of mortality and longer term morbidity. However, the death rate in subjects who have received SAGE-547, 6 out of 30 (20%) subjects, appears to be lower than the published

rates. None of the deaths were considered related to SAGE-547: brain tumor, organophosphate toxicity, respiratory failure, respiratory arrest due to ventilator support withdrawal, and breast cancer.

In the Phase 2 study, 20 SAEs (15 non-fatal) have been reported in 13 (65%) subjects, and of these 3 events in 2 subjects (10%) were considered by the investigator to be related to SAGE-547: pulmonary emboli and tracheostomy dehiscence/infection. The Sponsor did not consider these events to be related to SAGE-547, rather to the underlying disease states. Four of the 20 subjects (20%) experienced AEs considered possibly related to SAGE-547 by the investigator, namely moderate myopathy and severe pulmonary emboli in 1 subject, moderate tracheostomy dehiscence and tracheostomy infection in 1 subject, moderate thrombocytosis in 1 subject and moderate BUN, ALT and AST elevation in 1 subject.

Review of the most current safety data from 547-SAGE-201 reveals that there were changes in serum chemistry, hematology, and urinalysis during the study, but that none of those changes were assessed as related to SAGE-547. There were also no SAGE-547-related changes to vital signs.

Despite the heterogeneity in the underlying causes of SE, the ages of the subject, comorbidities, which normally complicate the treatment of SE, and the fact that all subjects had failed current standard of care treatment, a large majority of subjects had a successful therapy outcome, with discontinuation of all third-line agents and resolution of SE.

Refer to the Investigational Brochure for further information on the pre-clinical and clinical data supporting the use of SAGE-547 in SRSE.

### **3.5. Study Rationale - SAGE-547 in SRSE**

#### **3.5.1. Justification for the Control Group**

Although SAGE-547 has demonstrated extremely promising activity in subjects with SRSE, both in the Phase 2 study and during the EINDs, these have been open-label investigations with no control data for comparison. Generally in the literature there are few data describing the success rates of wean attempts of third-line agents, and few comparative data on the effectiveness of the three main third-line agents, propofol, pentobarbital, and midazolam.

Several options for a control group in Study 547-SSE-301 were considered:

- No control group was thought to be unacceptable since there are no reliable published data on success rates in this population that could be used for broad comparisons;
- An active control was considered but found to be impractical since none of the third-line agents are approved for their use in SRSE, no standardized dosing regimens or treatment guidelines have been adopted for the management of SRSE, and clinicians were unlikely to agree which of the available third-line agents would be reserved for the active control arm;
- Historical controls were considered but abandoned because of the practical difficulties of obtaining high quality data, the lack of ability to prospectively match cases, and a suspicion that clinical practice in the standard of care of SRSE is evolving, mandating the use of prospective, concurrent control data;
- Comparison to standard of care alone was considered as a feasible design. However, in a field where no widely adopted treatment guidelines exist, there was a concern that knowledge of the treatment group (SAGE-547 plus standard of care versus standard of care



alone) would alter the behavior of the investigators such that they could be more aggressive with weaning in the SAGE-547 group;

- Placebo control is not without its challenges since the preliminary efficacy data for SAGE-547 show that the compound exerts central pharmacological effects and is associated with positive outcomes in around 70% of patients. There is therefore a potential ethical concern about administering placebo to desperately ill patients who have often exhausted all treatment options for SRSE. This concern has been addressed in two ways: firstly all patients receive current standard of care; secondly, all subjects who fail to be weaned from their third-line agents at the end of the blinded infusion of study drug will be administered open-label SAGE-547 without un-blinding their initial treatment allocation, so treatment with the investigational product is not denied, but delayed about a week in the setting of ongoing receipt of full current standard of care.

It was therefore decided that a blinded, placebo-controlled design was appropriate for Study 547-SSE-301.

### **3.5.2. Justification for the Dose Regimen**

The standard dose regimen has been studied in 19 subjects in the 547-SSE-201 Phase 2 trial; the average peak plasma concentration of SAGE-547 at the end of the loading dose was approximately 144 ng/ml. The average plasma concentration during the maintenance infusion was approximately 70 ng/ml. At these concentrations, there were no clear safety signals although two-thirds of subjects experienced an SAE and there were four deaths, all related to the underlying comorbid conditions. The standard dosing regimen was associated with an approximate 70% successful treatment outcome. For these reasons, the standard dosing regimen has been adopted for the initial SAGE-547 infusion to be compared in a blinded fashion to placebo.

In the 547-SSE-201 trial, three subjects have thus far received the higher dose regimen. This dose regimen has also been well tolerated. The average peak plasma concentrations at the end of the loading dose for both dosing regimens will be in the same range, as the loading dose is the same for both regimens. The average plasma concentrations observed during the higher maintenance dose are 102 ng/ml (n=2). The rationale for adopting the higher dose regimen as the open-label infusion of SAGE-547 for subjects who are retreated in this 547-SSE-301 trial is that those who fail on the standard SAGE-547 dose regimen are afforded the opportunity to have access to a higher dose. The justification to also administer the higher dose regimen to failures on placebo is that the regimen has thus far been well tolerated, and this methodology preserves the blind for the initial infusion.

A five-day dosing regimen with SAGE-547 was investigated in the Phase 2 study, 547-SSE-201. There were some cases when weaning off all third-line agents was not possible within 48 hours, but weaning was completed after the end of the infusion of SAGE-547. For this reason, the duration of dosing with SAGE-547 has been increased from 120 hours (five days) in Phase 2 to 144 hours (six days) in this Phase 3 study.

### **3.5.3. Rationale for Genetic Testing Sub-study**

Sage Therapeutics intends to perform genetic research in the SAGE-547 development program in order to explore how genetic variations may affect the metabolism and activity of SAGE-547. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials, and, possibly, to genetically-guided

treatment strategies for optimizing decision making with respect to individual benefit:risk. Participation of subjects in genetic research as part of the overall clinical study is optional.

### **3.6. Benefit-Risk Evaluation of the Present Study**

Previous reports of human administration of exogenous allopregnanolone indicate that for exposures in men and women up to 150 nM, the most commonly reported AEs were sedation (recorded as sleepiness or tiredness), feelings of intoxication (like alcohol), flushing, and mild headache (Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007). No SAEs were reported (Navarro, Kaddouz et al. 2003; Timby, Balgard et al. 2006; van Broekhoven F, T et al. 2007; Kask, Backstrom et al. 2008; Kask, Backstrom et al. 2009; Timby, Hedstrom et al. 2011a). In view of the reduced consciousness and sedation of study subjects at entry into this protocol, none of these previously-reported events are likely to impact subjects in this study.

To date, in the SAGE-547 Phase 2 study and the EIND subjects, a majority of subjects demonstrated a successful therapy outcome (>70%). The majority in the clinical trial (65%) have also experienced SAEs, but none has been considered related to SAGE-547 by the Sponsor (SAEs in 2 subjects (10%) were considered possibly related by Investigator). Five deaths have been reported in 30 subjects (20%), all related to the underlying cause of SRSE and not related to SAGE-547 – this is in the context of published mortality rates between 35% and 65%. These preliminary data suggest that SAGE-547 has the potential to provide clinically relevant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate.

The underlying etiologies of SE are heterogeneous, and each one conveys a different risk of mortality. Subjects who survive SRSE still have a high risk of severe morbidity (Neligan and Shorvon 2010). The subjects treated with SAGE-547 in Study 547-SSE-201, are heterogeneous in factors such as age and etiology of SE, factors that usually complicate treatment and can increase morbidity and mortality. Even with this heterogeneity, the preliminary efficacy and safety data for SAGE-547 are very encouraging, and the mortality rate suggests that the risk to benefit assessment of this treatment rests on the side of benefit.

## **4. ETHICS**

### **4.1. Institutional Review Board or Independent Ethics Committee**

This protocol will be reviewed and approved by the Institutional Review Board (IRB) where the study is conducted. The IRB will meet all FDA requirements governing IRBs (CFR, Title 21, Part 56).

### **4.2. Ethical Conduct of the Study**

The Sponsor, the Medical Monitor, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable ICH and GCP guidelines, and must also conduct the study in accordance with local regulations.

### **4.3. Subject Information and Informed Consent**

Subjects prospectively enrolled in this study will be unable to give consent. Therefore, consent will be given by proxy by a legally authorized representative (LAR). Written informed consent is required for each subject prior to any testing under this protocol not considered standard of care,



including screening tests and evaluations. Should a subject gain the ability to sufficiently comprehend the situation and consent during the course of the study, written informed consent or verbal assent will be documented as required or recommended by the institution's IRB.

The form of consent to be obtained will depend on the condition of the subject as determined by the Principal Investigator. The informed consent form (ICF), as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50.

It is the responsibility of the Investigator to obtain consent and to provide the subject's LAR with a copy of the signed and dated informed consent form. The informed consent form for subject participation must also be available as part of the subject file for review by the site's dedicated study monitor or any authorized auditor of the Sponsor or regulatory authorities.

All ICFs used in this study must be approved by the appropriate IRB and by the Sponsor. The ICF must not be altered without the prior agreement of the relevant IRB and the Sponsor.

#### **4.4. Ethical and Regulatory Considerations for Pharmacogenetic Sub-study**

##### **4.4.1. Informed Consent for Pharmacogenetics**

The genetic component of this study is optional and subjects may participate in other components of the main study without having to agree to participate in the genetic component. If subject chooses to participate in the genetic component of the study, the subject or LAR must sign and date a specific consent form for the genetic component of the study in addition to the main study consent form. The principal investigator(s) is responsible for ensuring that consent is freely given and that the subject understands that they may discontinue from the genetic aspect of the study independent of their decision to remain within or withdrawal from the main study.

##### **4.4.2. Subject Data Protection Relative to Pharmacogenomics**

Sage Therapeutics will not provide individual genotype results to subjects, their family members, their general physician, their employer or any insurance company unless required to do so by law. While extra precautions will be taken to preserve confidentiality and to prevent genetic data from being linked to an individual's identity outside of a restricted access site, in certain exceptional situations (e.g. in case of a medical emergency or as a consequence of a specific regulatory need), certain individuals may see both genetic data and the personal identifiers of a subject; however in all cases a subject's medical information and genetic files will remain physically separated.

## **5. STUDY OBJECTIVES**

### **5.1. Primary Objective**

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult subjects with SRSE, and for the response to endure at least 24 hours after cessation of the SAGE-547 or placebo infusion (primary response).

## 5.2. Secondary Objectives

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in Clinical Global Impression Scale between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

## 5.3. Safety Objectives

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

## 5.4. Other Objectives

1. To evaluate the impact of retreatment with a higher dose of SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;

6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS).

## **6. ENDPOINTS**

### **6.1. Primary Endpoint**

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### **6.2. Secondary Endpoints**

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) and to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### **6.3. Safety Endpoints**

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.

## 6.4. Other Endpoints

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who fail to respond to their randomized double blind treatment and are retreated with a higher dose of SAGE-547;
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol® and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS).

## 7. INVESTIGATIONAL PLAN

### 7.1. Overview of Study Design

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

Figure 1 provides an overview of the study design and Figure 2 gives the details of treatment and follow-up on the active treatment arm. Patients will follow one of three paths to entry to the study. The first path is for patients who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst suppression with a third-line agent. These patients will be consented for the study after admission to the intensive care unit, but before any third-line agents are administered for burst suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their LAR. Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours. Once burst suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see Table 3). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of study drug.

The second path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst suppression pattern on the EEG. These patients may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at

least 24 hours of continuous burst suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of study drug.

The third path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These patients may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within six hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. Randomization will be stratified by concomitant pentobarbital use (yes or no) and number of previous third line agent wean attempts prior to randomization (one vs two or more).

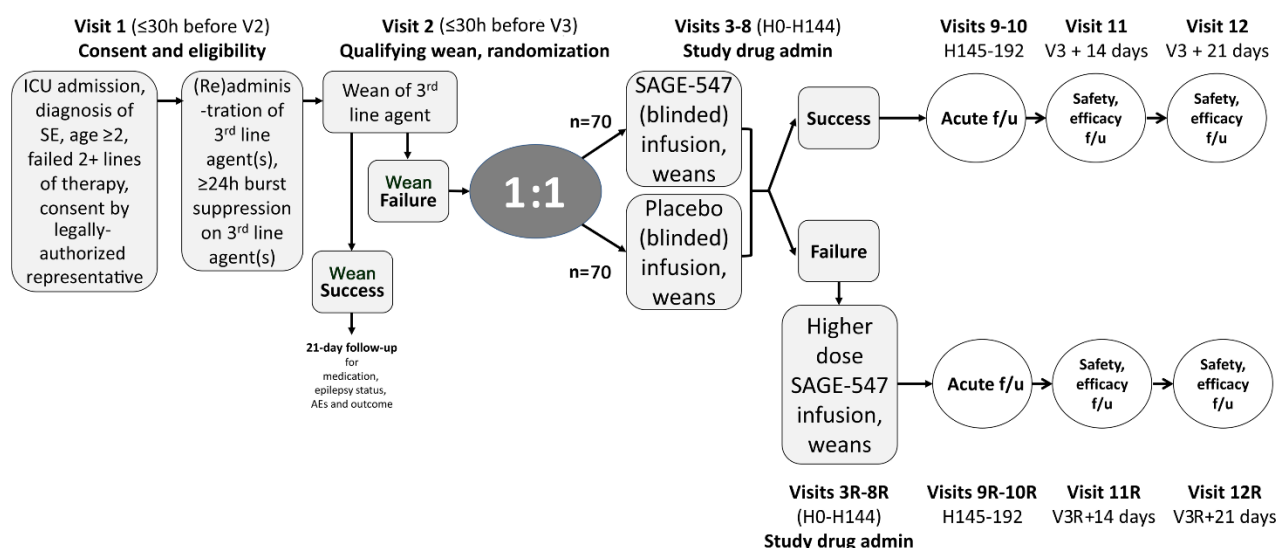
The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as the ability to wean the subject off all third-line agents before the end of the first infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication. Subjects must also have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) at the end of the primary endpoint assessment period as determined by EEG in order to be deemed a success. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#), [Table 2](#) and [Table 3](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. Eligibility for retreatment must be confirmed in writing by the medical monitor prior to the open-label infusion starting. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo will all subsequently be eligible to be administered SAGE-547 at the higher dose.

**Figure 1: Study Design**



## 7.2. Trial Conduct

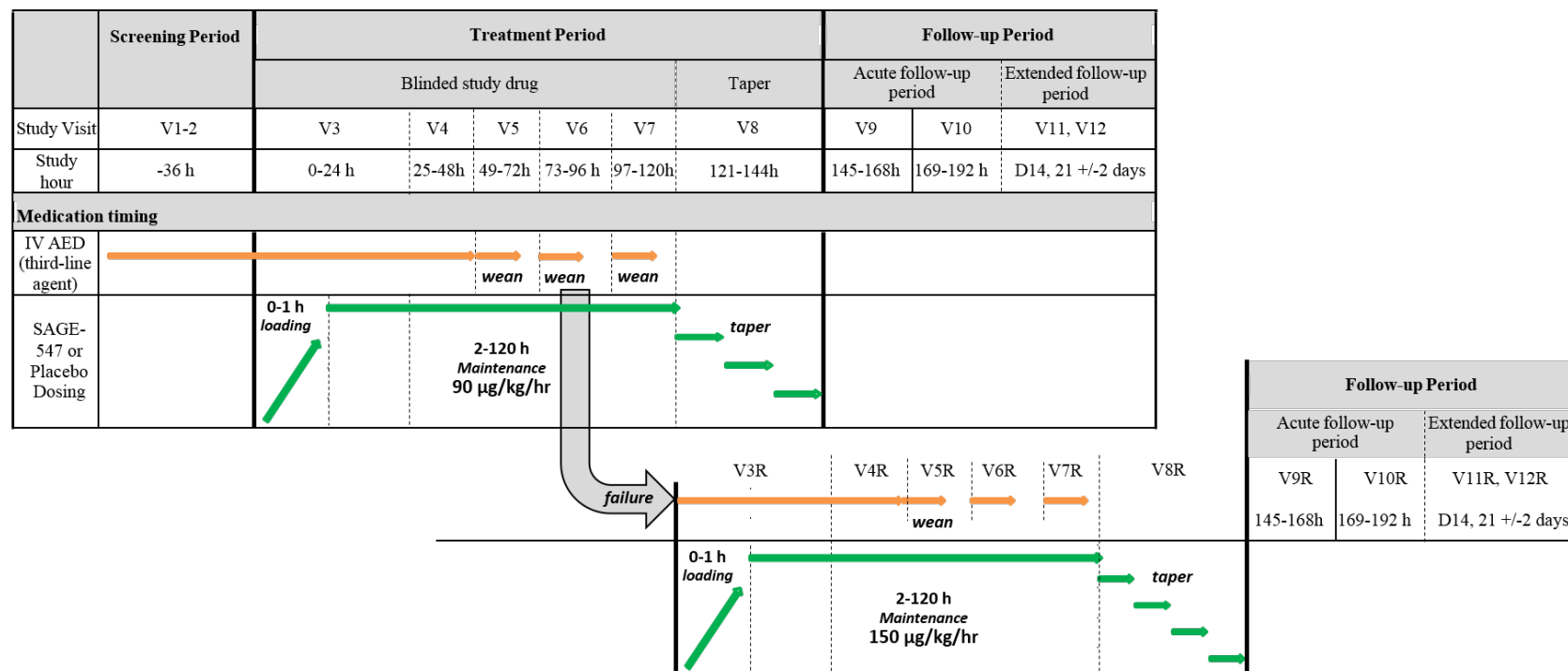
This study will be conducted according to the principles of the World Medical Association Declaration of Helsinki and most recent amendment (2008), and in compliance with the protocol approved by the IRBs/Independent Ethics Committees (IECs), and in accordance with ICH Guidelines on GCP standards.

## 7.3. Blinding and Randomization

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo). Details of the dynamic randomization process will be included in the SAP.

The randomized portion of the study will be blinded, with the two treatment products (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

The second infusion of SAGE-547 will be administered on an open label basis to subjects who failed the primary endpoint wean.

**Figure 2: Details of Treatment Administration and Follow-up**

## 8. SELECTION AND WITHDRAWAL OF SUBJECTS

The study will randomize 140 patients at up to 150 sites. All subjects deemed eligible to enroll must have written Medical Monitor approval on a case-by-case basis prior to undertaking the qualifying wean.

### 8.1. Inclusion Criteria

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects 17 years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; *or* who have previously failed one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst suppression pattern; *or* who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst suppression pattern.

### 8.2. Exclusion Criteria

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy.
4. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis but for whatever reason, dialysis is not planned or non-continuous dialysis planned (that would not adequately remove Captisol®);
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the experience of the investigator, is less than 30 days;
  - e. a do not resuscitate (DNR) order.
5. Subjects who are being administered more than three third-line agents concomitantly or for whom the qualifying wean cannot be completed within 24 hours or who are being



administered a third-line agent for indications such as raised intra-cranial pressure that would preclude weaning according to this protocol.

6. Subjects with a living will that does not allow heroic measure.
7. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
8. Subjects who have been enrolled in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not withdraw or complete and then re-enroll).

### **8.3. Selection and Consent of Subjects for Pharmacogenetic Substudy**

All subjects will be asked to participate in pharmacogenetic research; however, participation in research is voluntary and a subject can decide to decline his/her participation without penalty or loss of benefit. Participation or lack thereof will not be a cause for exclusion from any aspect of the main study. In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **8.4. Subject Withdrawal / Study Termination**

#### **8.4.1. Withdrawal/Discontinuation of Individual Subjects**

The reasons for study drug discontinuation and/or subject withdrawal from the study must be recorded in the subject's electronic case report form (eCRF). The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject has been discontinued/withdrawn due to an AE.

##### **8.4.1.1. Withdrawal from the Study**

Subjects or their LAR may withdraw subjects from the study at any time for any reason without compromising the subject's medical care. The Investigator will also withdraw subjects upon the request of Sage Therapeutics or upon termination of the study.

Subjects who withdraw from the study prior to Visit 10 (or 10R) should complete the procedures scheduled for the day of study drug taper (hour 121-144; Visit8/8R) on the day of their withdrawal, including the SAGE-547 taper schedule, with the addition of the mortality assessment from Visit 12/12R. Subjects who withdraw from the study after Visit 10/10R should undergo study procedures as outlined for Visit 12/12R on the day of their withdrawal. In all cases, the reason for subject withdrawal will be recorded in the eCRF.

Withdrawal of subjects for any reason should be discussed with the Medical Monitor.

##### **8.4.1.2. Discontinuation of Study Drug**

If it is necessary to discontinue the study drug earlier than planned, subjects should continue to be followed per protocol to capture safety and efficacy assessments for the duration of the study period.

The investigator may withdraw the subject from the study drug for the following reasons:

- Upon subject's or LAR's request

- The subject or LAR is unwilling or unable to adhere to the protocol-specified visits
- The subject experiences an intolerable adverse event
- During the course of the study, the subject develops symptoms or conditions listed in the exclusion criteria.
- Other medical reason, at the discretion of the Investigator and/or the Medical Monitor

Subjects who discontinue the study due to an AE considered related to study drug should be followed until the event is resolved, considered stable, or the Investigator determines the event is no longer clinically significant. Study drug discontinuation due to AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

#### **8.4.2. Study Termination**

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of AEs or other findings suggesting unacceptable risk to subjects, administrative or operational reasons. In the event of study termination, Sage Therapeutics will provide written notification to the Investigator. Investigational sites must promptly notify their IRB and initiate withdrawal procedures for participating subjects.

## **9. INVESTIGATIONAL PRODUCT**

### **9.1. Identity of Investigational Product**

SAGE-547 Injection (allopregnanolone)

### **9.2. Clinical Supplies**

#### **9.2.1. SAGE-547**

Adequate supplies of SAGE-547 Injection and materials for intravenous administration will be provided to each site.

SAGE-547 Injection is a clear, colorless sterile solution of allopregnanolone intended for intravenous injection. SAGE-547 Injection is an aqueous solution of 5 mg/mL allopregnanolone in 250 mg/mL Captisol® (betadex sulfobutyl-ether sodium, NF). It is presented either un-buffered or buffered with 10 mM citrate at a pH of 6.0 in either 20 mL or 50 mL vials. SAGE-547 is further diluted according to the Pharmacy Manual to achieve an approximately isotonic solution and will be administered intravenously.

No preservatives are included in the drug product, which is intended to be used as a single-use vial. All inactive components (excipients) used in the formulation are compendial grade and conform to current USP/EP, and include sodium citrate, citric acid and betadex sulfobutyl-ether sodium (Captisol®).

#### **9.2.2. Placebo**

Placebo will be identical to SAGE-547 and presented in identical vials. Placebo will be manufactured in a similar way to SAGE-547 and comprises all excipients but no SAGE-547.

### 9.2.3. Blinding

The vials of SAGE-547 and placebo will be identical in every way so that they are indistinguishable by the pharmacist, investigator, anyone treating or managing the patient, the monitors, and the sponsor. In this way the first infusion of study drug administered to each patient will be double-blind.

For the blinded study drug infusions, subject-specific dosing kits will be provided. These dosing kits will be pre-labelled with kit number for the first blinded infusion. For the second-infusion, open-label kits will be provided, which will require subject assignment by the pharmacy for reconciliation purposes. The study kits must be stored under refrigerated conditions (2-8 °C). IV administration bags and lines may be provided for the blinded and open-label infusions. Refer to the Pharmacy Manual for additional details.

The label for the SAGE-547 Injection vials will include standard product identification information according to the Code of Federal Regulations, 21CFR 312.6. All study labels will also contain the following statement:

Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use.

### 9.3. Preparation of SAGE-547 or Placebo Injection for Dosing

The Pharmacy will be responsible for preparing the blinded and open-label study drug for subject dosing. The prepared admixture will be assigned a room temperature (20-25 °C) storage shelf life of 30 hours from time of compounding.

SAGE-547, which is hypertonic, will require dilution with SWFI to achieve an approximately isotonic solution according to the instructions provided in the Pharmacy Manual. Exactly the same procedures will be used to prepare the placebo admixture, so that all site staff remain blinded as to treatment allocation for the first infusion of study drug. SAGE-547 Injection is not intended to be administered to patients undiluted.

Refer to the Pharmacy Manual for specific instructions regarding infusion preparation.

### 9.4. Administration and Accountability

The Pharmacy will maintain accurate records of all investigational product supplies. Accurate records will be kept regarding the volume of SAGE-547 Injection or placebo used for each IV preparation, as well as the required infusion rate or rates, and the date and time of preparation. Reasons for departure from the expected dosing regimen must also be recorded. To satisfy regulatory requirements regarding drug accountability, all study medication will be reconciled in full. Refer to the Pharmacy Manual for additional details.

## 10. TREATMENT OF SUBJECTS

### 10.1. Dosing Schedule (Blinded Infusions)

SAGE-547 Injection or placebo will be administered according to the dosing schedules in [Table 5](#). The infusion rates to accomplish these µg/kg/h doses will be calculated according to the weight of the subject. The infusion rates will be applied to blinded study drug for the first infusion of study medication.

**Table 5: SAGE-547 or Placebo Dosing Schedule**

Hour	Type and Duration of Study Drug Infusion	Description
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	90 µg/kg/h
H121 – H128	8 hour taper	65 µg/kg/h
H129 – H136	8 hour taper	45 µg/kg/h
H137 – H144	8 hour taper	25 µg/kg/h

## 10.2. Dosing Schedule (Open-Label Infusions)

If a subject fails wean from third-line agent(s) or requires re-instatement of third-line therapy within 24 hours of discontinuing the initial infusion of study drug, SAGE-547 Injection will be re-administered according to the dosing schedule in Table 6. The infusion rates to accomplish these µg/kg/h doses will be calculated according to the weight of the subject. These infusion rates will be applied to SAGE-547 re-treatment for the open-label second infusions of study medication.

**Table 6: SAGE-547 Open Label Dosing Schedule**

Hour	Type and Duration of SAGE-547 Infusion	Description
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	150 µg/kg/h
H121 – H126	6 hour taper	125 µg/kg/h
H127 – H132	6 hour taper	95 µg/kg/h
H133 – H138	6 hour taper	65 µg/kg/h
H139 – H144	6 hour taper	35 µg/kg/h

## 10.3. Route of Administration

SAGE-547 Injection is intended for IV administration only. The compatibility of SAGE-547 with other drugs is unknown, and the product should be administered via a dedicated peripheral IV line using any Sage-supplied study-specific IV administration bags and lines. In order to preserve blinding, these instructions also apply to the blinded placebo infusions.

## 10.4. Treatment Period

The treatment period with double-blind SAGE-547 or placebo is six 24-hour periods (144 hours), which may encompass 6-7 calendar days. The retreatment period is of identical duration.

## 10.5. Concomitant Medications, Procedures and Treatments

Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. All concomitant medications, procedures, and treatments should be documented throughout the study from Screening through Visit 12/12R and recorded on the eCRF.

SAGE-547 has demonstrated inhibitory effects on cytochrome P450 isoenzyme 2C9 (CYP2C9).

Therefore, AEDs such as phenytoin and phenobarbital that are primarily metabolized by CYP2C9 should be closely monitored during SAGE-547 administration to ensure target exposures are maintained.

#### **10.5.1. Concomitant AEDs**

Subjects may enter the study on AEDs, and be administered AEDs during the study. All of these must be recorded on the eCRF with details including date and time of starting and stopping each AED, the route of administration, changes in doses, and frequency of administration. In addition, details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the eCRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.

#### **10.5.2. Concomitant Third-Line Agents**

All third-line agents (as defined in [Section 8](#)) administered since the diagnosis of SE will be recorded on the eCRF, whatever path the patient took for entry into the study. Details will include the name of the drug, the start and stop dates and times, and, after consent, the doses with start and stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

In addition, those changes in dose that constitute a wean attempt will be marked as such on the eCRF. In this way the start and stop dates and times of all wean attempts (see [Section 11](#) for definitions) will be recorded, as will the type of wean (QW, OW, or TW) and the outcome of the wean attempt (successful, failed and dose of this third-line agent increased or failed and this third-line agent stopped and another third-line agent started). Those wean attempts that occur after the TW up to and including Visit 12/12R will be marked “AW”.

Some third-line agents (such as propofol) are also used to induce sedation to facilitate a subject’s ability to tolerate the ventilator. For subjects requiring such sedation, propofol is the preferred agent unless there are contraindications. The eCRF will make clear from the indication for the third-line agent when it is being used for burst or seizure suppression and when it is being used as ventilator support or for another purpose. The investigator will add a note to the eCRF to justify that the doses used are appropriate for sedation and not for seizure or burst suppression. The doses used for ventilator support and other similar uses are usually much lower than those used for seizure or burst suppression, and use of these third-line agents for these other purposes does not constitute a wean failure under this protocol.

#### **10.5.3. Concomitant Pressors**

The start and stop dates and times of all pressors will be recorded as well as the start and stop dates and times of all dose changes.

#### **10.5.4. Other Concomitant Medications**

All other concomitant medications must be recorded on the eCRF with details including date and time of starting and stopping, the route of administration, dose, and frequency of administration.

## **11. STUDY ASSESSMENTS**

### **11.1. Efficacy Assessments**

#### **11.1.1. Primary Efficacy**

Success or failure will be determined, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo infusion and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the blinded (first) infusion of SAGE-547 or placebo. In addition, subjects must have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) to be deemed to be successes. All subjects who fail to complete their infusion of randomized treatment or do not have at least one attempt during study treatment to wean off all third-line agents will be considered as “failures” for the primary endpoint.

##### **11.1.1.1. Weaning**

Third-line agents are anesthetic agents that are administered in order to reach a seizure or burst suppression EEG pattern. For the purposes of this study, third-line agents are defined as continuous intravenous infusions of pentobarbital, midazolam, propofol, and ketamine at maintenance doses alone or in combination sufficient to produce a burst suppression pattern on the EEG. The following are considered to be minimum maintenance doses of these agents that may be expected alone or in combination to achieve EEG burst suppression. If subjects are on lower doses than these and are not in EEG burst suppression for the 24 hours prior to the QW or the first 12 hours of the blinded study drug infusion, they will be considered to be screen failures/protocol violators and will exit the study.

- Pentobarbital: 1 mg/kg/hour
- Midazolam: 0.1 mg/kg/hour
- Propofol: 3 mg/kg/hour
- Ketamine 1.2 mg/kg/hour

The timing and nature of the third-line agent weans will be guided by the Clinical Standardization Guidelines for the study, and the clinical judgment of the investigator, and will always be primarily done in the best medical interests of the subject. Advice about weaning may be sought from the Clinical Standardization Team, a group of fellow investigators with experience of performing clinical trials in subjects with SRSE. The Clinical Standardization Team will be able to review EEGs in real time related to key study timepoints (qualifying wean, terminal wean, and the period after the end of the blinded study drug infusion) in order to provide advice about compliance with the Clinical Standardization Guidelines.

The following guidance for weaning applies to all weans of third-line agents undertaken during the study. These weans include the qualifying wean (QW); the terminal wean (TW), which is the wean of the third-line agent if the subject is on only one third-line agent or the wean of the last third-line agent if the subject is on more than one third-line agent; the other weans (OW), which are the weans of the third-line agents other than the TW if the subject is on more than one third-line agent. The guidance also applies to additional weans (AW), which are the weans from third line agents that take place after the TW for the first blinded study drug infusion or the second open-label study drug infusion.

**QW Guidance**

- Wean to be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace that third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Investigators should allow 24 hours to lapse after the end of a “successful” qualifying wean before finally declaring the QW a success. If a third-line agent needs to be re-instituted within that 24 hours, the QW is a failure, and the subject may then be randomized in the study.

**OW Guidance**

- First OW should not begin before H49 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- If the subject is on two third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the TW. However the OW may be completed over a shorter or longer time period and may overlap if clinically indicated with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- If the subject is on three third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the wean of the second agent. The second agent should be weaned over 24 hours and that wean completed before starting the TW. However the OWs may be completed over a shorter or longer time period and may overlap if clinically indicated with each other and with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- All OWs should be completed before H96 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

**TW Guidance**

- The TW is defined as the wean of the last third-line agent.
- If the subject is on one third-line agent, the TW should not begin before H49 and should begin no later than H97 after starting administration of study drug or starting the open-label infusion of SAGE-547. If the subject has had one or more OWs, the TW should ideally begin as soon as the last OW is complete but in any case not later than H97 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

- The TW must be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace this third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Every effort must be made to complete the TW before H120 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547, but the TW must be complete before H144 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **AW Guidance**

- AWs will take place when medically indicated in the opinion of the investigator.
- Ideally the AW should take place over 24 hours, but completion may be over a shorter or longer time period than this. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.

### **11.1.1.2. EEG**

Electroencephalographs (EEGs) that are representative of the intermittent or continuous EEG being used to support key investigator decisions will be collected at the following time points:

- A six-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst suppression for the second path to eligibility, and a variable pattern for the third path to eligibility.
- EEG will be performed to cover the qualifying wean (QWEEG). EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for the one hour after the end of the QW. The duration of the QWEEG will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s) or the decision to re-institute a third-line agent(s) at doses intended to induce burst suppression.
- EEG will be performed from three hours prior to the start of the blinded infusion to five hours after the start of the blinded infusion. This will be called the BIEEG. The intent of this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG.
- EEG will be performed to cover the final or terminal wean of third-line agent (TWEEG). The TW is the wean of the final third-line agent during the blinded administration of study drug or the open-label infusion of SAGE-547; if the subject was on one third-line agent, the TW is the wean of that agent. If the subject was on three third-line agents, the TW is the wean of the third and final agent. EEG recording will start 30 minutes prior to the start of the TW, continue for up to 24 hours during the TW, and then continue for the one hour after



the end of the TW. The duration of the TWEEG will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the final third-line agent or the decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity could not be managed using intermittent bolus doses of AEDs.

- EEG will be performed during the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 (TAEED). The TAEED is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the start of the taper (at Hour 119.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours during the taper, and then continue for the one hour after the end of the taper (to Hour 145 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547). The duration of the TAEED will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity seen during the taper could not be managed using intermittent bolus doses of AEDs.
- EEG will be obtained to cover the end of the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 and the ensuing 24-hour period, during which the primary endpoint is assessed (PAEED). The PAEED is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the end of taper (at Hour 143.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours after the end of the blinded administration of study treatment or the open-label infusion of SAGE-547, and then continue for the one hour after the end of the 24-hour assessment period (to Hour 169 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547). The duration of the PAEED will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity seen in the 24 hours following the end of the blinded administration of study treatment or the open-label infusion of SAGE-547 that could not be managed using intermittent bolus doses of AEDs.

In practice, most subjects are on continuous EEG monitoring or long periods of intermittent EEG monitoring. However, this protocol does not mandate continuous EEG monitoring and breaks from EEG monitoring to provide relief to the scalp from the irritating effects of the electrodes are advised, according to local practice. If a break in EEG monitoring is mandated by local practice guidelines at a time when one of the protocolled EEG segments is to be collected, the break in EEG monitoring will take precedence, with the reason for missing the EEG reading noted on the eCRF. The EEGs obtained for the study are therefore part of the existing EEG record rather than being obtained de-novo at each timepoint. For timepoints where there might be some ambiguity, such as the TWEEG, the final EEG record is that of the final attempt to wean the last third-line agent, even if earlier attempts to wean that agent took place. In some cases (the TAEED and PAEED, for instance), the EEG records will overlap, but different cuts are taken to service the different EEG record requirements.

The electronic EEG file will be de-identified, the date and time of the start and stop of the EEG and the subject number will be attached to the file, and the study time point will be indicated (CEEG, QWEEG, BIEEG, TWEEG, TAEED, and PAEEG). The PI will indicate on the eCRF what the EEG shows, as follows:

- For the CEEG, the PI will describe the EEG pattern that determined which path to eligibility the subject was on.
- For the QWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure on the qualifying wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the qualifying wean).
- For the BIEEG, the PI will note the date and time of the start of the EEG and the pattern seen on the EEG.
- For the TWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure on the terminal wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the terminal wean).
- For the TAEED, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst suppression before the end of the SAGE-547 infusion).
- For the PAEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst suppression in the 24 hours following the end of the SAGE-547 infusion).

A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm the PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period (average EEG power at the end of Visit 9 of more than two microvolts).

- All subjects will have the CEEG and QWEEG collected and stored, and the QWEEG read;
- Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;
- Those subjects randomized who are not retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read;
- Those subjects randomized who are retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion and the TWEEG, TAEED, and PAEEG related to the open-label study drug infusion collected and stored, and the QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read.

All EEG records may be subject to quantitative EEG analysis.

### **11.1.2. Secondary Efficacy**

#### **11.1.2.1. Clinical Global Impression Scale (CGI)**

The clinical global impression scales are often utilized in clinical trials to allow clinicians to integrate several sources of information into a single rating of the subject's condition. Both the CGI-Severity (Question 1, CGI-S) and the CGI-Improvement (Question 2, CGI-I) employ a 7-point Likert scale measuring severity of the disease state in the subject and improvement, respectively. All severity assessments after initiation of SAGE-547 treatment should consider the general state of the subject over the preceding week. The third question on the scale will not be employed in this trial, and where the scale states "mental illness", this means "physical illness" in this trial.

The CGI-S will be evaluated at Visit 1 and at the last visit, Visit 12 or 12R. The CGI-I will be evaluated at Visit 12 or 12R.

#### **11.1.2.2. Epilepsy Status**

At Visit 1, the diagnosis of epilepsy will be documented as a no/yes question. If there was a previous diagnosis of epilepsy, further details will be documented, including:

- Date of diagnosis;
- Details of anti-epileptic drugs currently being taken;
- Type of epilepsy;
- Seizure frequency in the past month.

Information about the current (index) episode of status epilepticus will be obtained at Visit 1:

- Date of onset
- Date of failure to respond to first line agent(s) and the name(s) of the agent(s)
- Date of failure to respond to second line agent(s) and the name(s) of the agent(s)
- Any previous treatment with third line agents and the response to those agents (details of the third line agent drugs and previous wean attempts will be recorded on the Third Line Agent Medication CRF)
- The cause of the index episode of status epilepticus
- If the subject was transferred from another hospital or from within the hospital, the reason for the transfer will be recorded (such as for study enrollment, due to lack of medical options at original hospital or unit, due to lack of beds at the original hospital or unit, family request, other)

Previous (non-index) diagnosis of status epilepticus will be documented as a no/yes question. If SE did occur in the past, further information will be gathered, including:

- SE, RSE, or SRSE diagnosis, whichever was the most severe diagnosis for each episode;
- Cause;
- Treatment, including experimental treatments and need for intubation/ventilation;

- Dates of onset and duration if the episode of status epilepticus occurred in the past 12 months.

At Visit 12 or Visit 12R, the following information will be gathered:

- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of SE up to and including Visit 12 or Visit 12R;
- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of seizures (convulsive and non-convulsive) up to and including Visit 12 or Visit 12R;
- Number of separate episodes of SE after H144 at the end of Visit 8 or Visit 8R (no/yes); if yes,
  - SE, RSE, or SRSE diagnosis;
  - Cause;
  - Treatment, including experimental treatments and need for intubation/ventilation;
  - Dates of onset and duration.

Note that a separate episode of SE is defined as an episode of SE separated from other periods of status epilepticus by at least 24 hours.

- Diagnosis of epilepsy since Visit 11 or Visit 11R will be documented as a no/yes question. If a diagnosis of epilepsy has been made, further details will be documented, including:
  - Status as ongoing or new epilepsy since Visit 11 or Visit 11R after initiation of SAGE-547 treatment;
  - Details of anti-epileptic drugs currently being taken;
  - Type of epilepsy and seizure frequency in the past week.

## **11.2. Safety Assessments**

The safety and tolerability of SAGE-547 will be assessed using adverse events, clinical laboratory measures, vital signs, ECG intervals and morphology, and mortality. All safety assessments should be performed per hospital standard of care and will be collected periodically throughout the study according to [Table 1](#), [Table 2](#), and [Table 3](#) (Schedules of Assessments).

### **11.2.1. Adverse Events**

AEs will be collected after informed consent has been signed and prior to study-specific screening procedures not considered standard of care, during subject preparation for SAGE-547 administration and through Visit 12 or Visit 12R. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™) coding system (current version). See [Section 14](#) for additional details.

### **11.2.2. Clinical Laboratory Tests**

Blood samples will be taken for hematology, and serum chemistry and GFR will be calculated at:

- Visit 1 and then at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.
- Blood samples will be taken at Visit 11 or Visit 11R for serum chemistry (renal panel only).

Urine samples (20 ml) will be taken for urinalysis and urine NAG analysis at:

- Visit 1 and at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.

These samples will be analyzed at a central laboratory; hour-to-hour medical decisions will be based on sampling for laboratory testing done outside the protocol as part of normal standard of care. GFR will be calculated using values from local laboratory tests.

Any out-of-range values will be flagged by the laboratory; the investigator will add a comment about whether the abnormality is clinically significant. Clinical significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

#### **11.2.2.1. Hematology and Serum Chemistry**

Hematology will include complete blood count (CBC) white blood cell count with differential, platelet count and red blood cell (RBC) count, hemoglobin and hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose.

#### **11.2.2.2. Pregnancy Test**

Females of child-bearing potential will be tested for pregnancy by serum pregnancy test at Visit 1. In this study, since an accurate history of menstruation in girls and menopause in older women may not be available at Visit 1, "child-bearing potential" is taken to mean any female aged 17 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy. Female subjects with a positive pregnancy test will be ineligible for study participation.

#### **11.2.2.3. Urinalysis**

Urinalysis will include assessment of protein, blood, leukocytes, glucose, ketones, urobilinogen, pH, and specific gravity.

#### **11.2.3. Vital Signs**

Blood pressure, heart rate, and temperature will be recorded at the following time points relative to the first infusion of study drug, and to the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547:

- Visit 1;

- At 0, +30, +60 minutes (+/-15 minutes) and +2, +4 and +8 hours (+/- 30 minutes) after the start of the infusion;
- At +24, +48, +72, +96, +120, +144, +168, and +192 hours (+/- 2 hours) after the start of the infusion.

#### **11.2.4. Weight and Height**

Weight and height will be measured at Visit 1 and weight will also be measured once during each 24 hour period of the first infusion of study drug, and of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547. These daily weights will be used to modify the dose of SAGE-547 if required.

#### **11.2.5. ECG**

12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours; at other times the allowed time window for ECGs is +/- 2 hours:

- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +128, +136, +144, +152, +160, and +192 hours after the start of the blinded (first) study drug infusion
- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +126, +132, +138, +144, +152, +160, and +192 hours after the start of the open-label (second) study drug

The heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm.

#### **11.2.6. Mortality**

Mortality will be recorded on the Visit 12 or Visit 12R case report form. If the subject has died, the following information will be collected:

- Date of death;
- Cause of death.

As accurate as possible cause of death will be collected, which will be further categorized as due to one of the following causes:

- SE;
- complications of long term intubation and third-line agent infusions;
- underlying cause of qualifying SE;
- co-morbidity existing at the time of the qualifying SE;
- new co-morbidity or trauma;
- study drug;
- other (specify).

### 11.2.7. Pharmacogenetic Samples

If a subject's LAR consents to pharmacogenetic sampling, a blood sample for genetic research will be collected at Visit 1 in order to avoid the possible introduction of bias through the exclusion of patients who may withdraw from study due to an AE (a subject population that may be of specific interest for subsequent genetic analysis). If for any reason a sample cannot be taken prior to treatment, a sample can be drawn at any point prior to completion with the restriction that no more than one genetic sample be taken per subject.

The objective of this research is to collect and store blood samples for possible DNA extraction and exploratory research into how genes or specific genetic variation may influence response (i.e. distribution, safety, tolerability, and efficacy) to SAGE-547. Specific genetic variations of interest include but are not limited to: classes of metabolizing enzymes (e.g. Cytochrome P450 supra-family genes), genes encoding enzymes involved in the production and metabolism of allopregnanolone (e.g. AKR1C4 (3 $\alpha$ -hydroxysteroid dehydrogenase)), genes associated with the GABA receptor (e.g. GABRA1-A6, GABRB1-B3, GABRD, GABRE, GABRG1-3) and genes associated with the production and degradation of GABA.

Future research may suggest other genes or gene categories as candidates for influencing not only response to SAGE-547 but also susceptibility to disorders for which SAGE-547 is being evaluated. Thus, the genetic research may involve study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.

#### 11.2.7.1. Biological Sampling and Coding Procedures (Pharmacogenetics)

To ensure patient confidentiality, utmost care will be taken in the coding and storage of pharmacogenetic samples.

*Extraction and coding:* DNA will be extracted from the blood sample and the DNA sample will be assigned a unique number replacing information from sampling tube. The assigned DNA number will be used to identify the sample and its corresponding information within Sage Therapeutics or at any designated contract laboratory for the purpose of sequencing of other DNA specific analysis. No personal details sufficient for individual identification will be available to any person (internal or external to Sage Therapeutics) working with the DNA.

*Genotype/Phenotype Analysis:* Samples and data from genetic analysis will be coded. The link between subject enrollment / randomization code and DNA number will be maintained and stored in a secure environment with restricted access. The established link will be used to identify relevant DNA samples for analysis, facilitated correlation of genotype results with clinical data, allow regulatory audit, and to trace samples for destruction in case of withdrawal of consent.

#### 11.2.7.2. Retention of Biological Samples for Pharmacogenetic Analysis

Extracted DNA is a finite research that is destroyed in the process of being analyzed. Primary blood samples from which DNA can be extracted will be stored and used until no further analyses are possible, a maximum storage period of 25 years from time of last subject last visit has been reached, or an individual or LAR withdraws his/her or their consent.

## 11.2.8. Other Outcomes

### 11.2.8.1. Pharmacokinetic Data

Formal plasma and urine analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS)). In addition, all samples will be analyzed for important SAGE-547 metabolites (if and when these are identified) and Captisol® concentrations.

#### Plasma Analysis

Plasma will be collected to assay for SAGE-547 concentrations at the following time points relative to the start of each infusion of study drug:

- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion.
- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open label SAGE-547 study drug infusion.
- All samples will also be analyzed for plasma concentrations of important metabolites of SAGE-547 if and when these are identified.
- All samples will also be analyzed for plasma concentrations of Captisol®.

The plasma samples will be drawn from the arm contralateral to that used for drug administration. Drawing samples from peripheral arterial or venous lines or from a central line is permissible. PK collection times should be adhered to as strictly as possible. The allowed time window for all samples is: pre-dose in the two hours prior to starting the infusion of study drug; samples up to and including 1h, +/- 5 minutes; subsequent samples, +/- 15 minutes. Subject-specific PK kits for sampling including instructions on collection and processing methods, and storage and shipping conditions, will be provided separately. To maintain the blind, all subjects will have samples taken as outlined above: subjects receiving SAGE-547 will have all samples analyzed for all analytes. Subjects on placebo may have samples analyzed to investigate endogenous allopregnanolone and metabolite concentrations, as well as Captisol® concentrations; experience with the plasma concentration data will determine if and which placebo samples are analyzed.

Each blood sample will be 3 ml in volume for subjects weighing 30 kg or more, and 2 ml in volume for subjects weighing less than 30 kg. Separate aliquots will be obtained from each sample to service the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum blood draw for PK analysis for a subject having two infusions of study drug will be 99 ml (66 ml for subjects weighing less than 30 kg).

Plasma PK parameters for SAGE-547 will be calculated where appropriate (e.g.,  $C_{max}$ ,  $C_{min}$ ,  $t_{max}$ ,  $AUC_{last}$ ,  $AUC_{\infty}$ ,  $CL_s$ ). In addition, similar PK parameters will be calculated for Captisol®. PK parameters for important metabolites of SAGE-547 may be calculated. An evaluation will be made



of the feasibility of adopting a population-PK approach to assess drug-drug-interactions with SAGE-547 as victim of AEDs.

In addition, the Visit 9 sample may be analyzed for plasma concentrations of third-line agents.

#### Other Analysis

If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations.

Full details of all pharmacokinetic analyses will be described in the Pharmacokinetic Analysis Plan.

#### **11.2.8.2. Correlation of QT/QTc Changes and Plasma Concentrations of SAGE-547**

An analysis will be performed to determine whether there is any correlation between changes in QT/QTc interval and plasma concentrations of SAGE-547, in order to investigate any effect that SAGE-547 may have on QT/QTc interval.

#### **11.2.8.3. Pharmacoeconomic Data**

At Visit 12 or Visit 12R, the following information will be collected: number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital. If the subject dies before Visit 12 or Visit 12R, data will be collected up to the date of death. The definition of “hospital” is the institution that the subject was initially treated in. If the subject is transferred to another hospital, that hospital would be the “discharge destination from the hospital” and the “number of days in hospital” would be the number of days in the initial treating hospital.

For those subjects discharged from hospital before Visit 12/12R, the following questions will be asked:

- On what study day was the subject discharged from hospital?
- What type of facility was the subject discharged to (another hospital, a rehabilitation center, a supported care facility, home, other)?
- How many days did the subject stay in this facility?

The following questions will be answered regarding the stay in the ICU and hospital:

- Was the subject still in the ICU at the end of Visit 10/10R?
- If the FOUR Score was  $\geq 12$  at Visit 10/10R and the subject was in the ICU at Visit 10/10R, what was the reason for the subject not being discharged from the ICU (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, other)?
- Was the subject still an in-patient in the hospital at the end of Visit 12/12R?
- If the FOUR Score was  $\geq 15$  at Visit 12/12R and the subject was in the hospital at Visit 12/12R, what was the reason for the subject not being discharged from the hospital (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, unsuitable home circumstances, other)?

#### **11.2.8.4. STESS**

The STESS will be assessed during Visit 1 in order to assess the severity of the status epilepticus.

#### **11.2.8.5. FOUR Score**

The Full Outline of UnResponsiveness or FOUR Score is designed to assess conscious level and unlike other scores, is suitable for subjects who are intubated. It assesses four domains of neurological function (eye responses, motor responses, brainstem reflexes, and breathing pattern).

The FOUR Score will be collected at the following time points relative to each infusion of study drug (the initial blinded infusion and the second open-label infusion if this is administered):

- baseline, +24, +48, +72, +96, +120, +144, +168, and +192 hours (all +/- 2 hours) after the start of the infusion, and at Visit 11/11R and Visit 12/12R.

#### **11.2.8.6. Glasgow Outcome Scale (GOS)**

The GOS is a relatively common assessment scale used to standardize descriptions of the objective degree of recovery from brain injury such as cerebral trauma, or in this case SRSE. It was first used in 1975 ([Jennett and Bond 1975](#)) and allows a prediction of the long-term course of rehabilitation to return to work and everyday life. The scale classifies subjects into 5 groups:

- Death
- Persistent vegetative state
- Severe disability
- Moderate disability
- Good recovery

The GOS will be assessed at Visit 12 or Visit 12R.

#### **11.2.8.7. Supervision Rating Scale (SRS)**

The Supervision Rating (SRS) measures the level of supervision that a patient/subject receives from caregivers. The SRS rates level of supervision on a 13-point ordinal scale that can optionally be grouped into five ranked categories (Independent, Overnight Supervision, Part-Time Supervision, Full-Time Indirect Supervision, and Full-Time Direct Supervision). The SRS was designed to be rated by a clinician based on interviews with the subject and an informant who has observed at first hand the level of supervision received by the subject ([Boake 2000](#)). Scoring is a one-step procedure in which the clinician assigns the rating that is closest to the subject's level. Ratings are based on the level of supervision received, not on how much supervision a subject is judged or predicted to need.

The SRS will be assessed at Visit 1 and Visit 12 or Visit 12R. The Visit 1 assessment will be a retrospective assessment of the supervision required by the subject immediately prior to the admission that included the index episode of status epilepticus.

#### **11.2.8.8. Modified Rankin Scale – 9Q (mRS-9Q)**

The Modified Rankin Scale (mRS) is a commonly used scale to determine disability and functional dependence due to neurological insult such as stroke in adults. The 7-point scale (0 – 6) denotes functional capacity from no symptoms (0) to severe disability (5) and death (6). The Modified

Rankin Scale – 9Q is a shortened version consisting of 9 questions that reliably determines the mRS score and was developed to both simplify the assessment and expand the rater base to non- medically trained personnel (Patel, Rao et al. 2012). The assessment is a web-based tool in the public domain with automatic score calculation and error checking found at [www.modifiedrankin.com](http://www.modifiedrankin.com).

The mRS will be assessed at Visit 1 and at Visit 12 or Visit 12R. The baseline assessment will be a retrospective assessment of the disability and dependence of the subject immediately prior to the admission that included the index episode of status epilepticus.

## 12. STUDY PROCEDURES

The study procedures listed below by study day reflect the required data collection times for this protocol. When a time window is necessary, this is specified below. If no time window is specified, the test may be performed at any time within the specified 24-hour period.

### 12.1. Visit 1 (V2-≤30h)

The baseline period will be up to approximately 84 hours prior to starting blinded study treatment and should include the assessments/procedures listed below and summarized in [Table 1 and Table 2 \(for retreatment\)](#), the Schedules of Events.

- Informed consent
- Eligibility checklist
- Verification of inclusion/exclusion criteria.
- Demographic information and medical history obtained by proxy and confirmed by the subject when possible.
- SE and wean history
- Blood will be collected from female subjects 17 years to 55 years for a serum pregnancy test unless they are known to be pre-menstrual or post-menopausal or to have had a hysterectomy.
- Blood and urine samples collected for clinical laboratory testing.
- Pharmacogenetic sample will be collected from consenting/eligible subjects.
- Vital signs
- Height
- Weight
- An ECG reading taken.
- Administration of the STESS.
- Administration of the FOUR Score.
- Administration of SRS.
- Administration of the mRS-9Q assessment.
- Assessment of the CGI scale.
- Evaluation of epilepsy status.
- Administration of continuous IV third-line agents.
- Perform EEG.
- Recording of adverse events.
- Recording of previous and concomitant anti-epileptic drugs.
- Recording of previous and concomitant third-line agents.
- Recording of concomitant pressors.

- Recording of other concomitant medications, procedures, and treatments.

## **12.2. Visit 2 (V3-≤54h)**

- Recording of adverse events.
- Recording of concomitant anti-epileptic drugs.
- Recording of concomitant third-line agents.
- Recording of concomitant pressors.
- Recording of other concomitant medications, procedures, and treatments.
- Wean of continuous third-line agent:
  - If wean is successful, subject is followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (these subjects are Qualifying Wean Success subjects or QWS subjects);
  - If wean is not successful, there is ongoing intravenous administration of at least one continuous IV third-line agent and EEG is performed and the subject is randomized.

## **12.3. SAGE-547 Treatment Period**

### **12.3.1. Visit 3/3R (0-24 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs will be recorded at:
  - 0, +30, +60 minutes (+/-15 minutes) and +2, +4, +8 (+/- 30 minutes) and +24 hours (+/- 2 hours) after the start of the infusion
- ECG readings will be recorded immediately after PK sampling at:
  - 0 (pre-dose) and at +0.5, +1, +3, +6, +12, and +24 hours after the start of the blinded study drug infusion.
- A blood sample for PK analysis should be collected at the following time points (all +/- 15 minutes except where otherwise stated):
  - 0 (pre-dose, within two hours of the start of the infusion) and at +0.5, +1 (+/- 5 minutes), +3, +6, +12, and +24 hours after the start of the blinded study drug infusion.
- Completion of the FOUR Score
  - +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the end of the QW)
- Ongoing intravenous administration of a continuous IV third-line agent.
- Study drug administration in loading (Hour 0-1) and maintenance infusions (at completion of Hour 1).
- Recording of adverse events (QWS subjects also).

- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.3.2. Visit 4/4R (25-48 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +48 hours (+/- 2 hours) after the start of the infusion
- An ECG reading taken immediately after PK sampling:
  - +48 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +48 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +48 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent.
- Ongoing study drug maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.3.3. Visit 5/5R (49-72 hours)**

- Weight
- Vital signs should be recorded at:
  - +72 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +72 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +72 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +72 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.

- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.4. Visit 6/6R (73-96 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +96 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +96 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +96 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +96 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Perform EEG.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.5. Visit 7/7R (97-120 hours)**

- Weight
- Vital signs should be recorded at:
  - +120 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +120 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +120 hours (+/- 15 minutes) after the start of study drug infusion, immediately prior to the end of the maintenance infusion.

- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +120 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled. Complete wean by 120 hours if at all possible.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## 12.4. SAGE-547 Taper Period

### 12.4.1. Visit 8/8R (121-144 hours)

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +144 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after each PK sampling:
  - +128, +136 hours and +144 hours after the start of the study drug infusion
  - During the open-label retreatment phase of the study ECG readings at: +126, +132, +138 hours and +144 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected (+/- 15 minutes unless otherwise stated):
  - +128 (immediately prior to the end of the first taper step), +136 hours (+/- 5 minutes, immediately prior to the end of the second taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of study drug infusion.
  - During the open-label retreatment phase of the study PK blood draws at: +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 hours (+/- 5 minutes, immediately prior to the end of the third taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of the study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +144 hours (+/- 2 hours) after the start of the infusion
- Complete wean of third line agents by H144 if not completed by H120.
- Perform EEG.
- Taper of SAGE-547 infusion begins at hour 121.



- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## **12.5. Follow-up Period**

### **12.5.1. Visit 9/9R (145-168 hours)**

- Vital signs should be recorded at:
  - +168 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +152, +160 hours (+/- 2 hours) after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +152 and +160 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +168 hours (+/- 2 hours) after the start of the infusion
- Perform EEG.
- Assessment of the presence of physiologic brain activity using EEG.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.5.2. Visit 10/10R (169-192 hours)**

- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +192 hours (+/- 2 hours) after the start of the infusion
- At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine retreatment with higher dose of study drug. All patients for retreatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.
- Recording of adverse events (QWS subjects also).

- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.3. Visit 11/11R (Visit 3/3R + 14d (±2))**

- Blood samples collected for clinical laboratory testing (renal panel only).
- Completion of the FOUR Score (QWS subjects also).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.4. Visit 12/12R (Visit 3/3R + 21d (±2))**

All assessments also performed for QWS subjects.

- Completion of the FOUR Score.
- Administration of the GOS.
- Administration of the SRS.
- Administration of the mRS-9Q assessment.
- Evaluation of epilepsy status (see [Section 11.1.2.2](#) for details).
- Assessment of the CGI Scale.
- Recording of adverse events.
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications.
- Collection of pharmacoeconomic data.
- Mortality will be assessed throughout the study period.

## **13. STATISTICS**

### **13.1. Statistical Plan**

Complete details for the analysis and reporting of data from this study will be contained in the Statistical Analysis Plan (SAP).

#### **13.1.1. Interim Analysis**

When approximately 50% of subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### 13.1.2. Study Populations

The **Safety Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to actual treatment. This analysis population will be used for all safety analyses.

The **Intent to Treat Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to randomized treatment. This analysis population will be used for all efficacy analyses.

The **Modified Intent to Treat Population** is defined as all subjects who:

1. complete their initial course of blinded SAGE-547 or placebo treatment unless the non-completion was due a drug-related adverse event; and
2. have at least one attempt to wean from third-line agents prior to the end of blinded study treatment infusion unless the failure to wean was because seizures were not controlled.

Subjects will be classified according to randomized treatment. This analysis population will be used for sensitivity analyses of the primary endpoint and select secondary efficacy endpoints.

Narratives will be prepared for all subjects who do not complete the infusion of blinded study medication or were not subjected to any wean attempts. Narratives will include details of the cause of SE, the comorbid conditions, the adverse event(s), and reasons for non-completion of the infusion or failure to attempt weaning. This blinded narrative will be reviewed by the medical monitors and the patient adjudicated as MITT eligible or ineligible. Acceptable reasons for defining a subject as MITT ineligible include death or withdrawal of consent due to progression of the underlying cause of SE or comorbid conditions, unless the cause of death or progression of disease were thought by the investigator, sponsor, or DSMB to be related to study drug.

The **Per-Protocol (PP) Population** is defined as a subset of the MITT population but will exclude data from all subjects with significant protocol violations or deviations. Subjects will be classified according to actual treatment received. This data set will be used for sensitivity analyses to examine the robustness of results for the primary and key secondary efficacy endpoints.

The **Pharmacokinetics Population** is defined as all subjects who at least had an infusion of blinded SAGE-547 initiated and have at least one pharmacokinetic sample collected.

The **Pharmacogenetic Population** is defined all subjects who consent to being included in the pharmacogenetic assessment and provide a pharmacogenetic sample.

Summary statistics of all data collected will be presented for subjects who were QW successes.

### 13.1.3. General Aspects

Tabular displays of descriptive statistics will be provided for all variables. Summary tables will include n, mean, mean, standard deviation, minimum and maximum for continuous variable and frequency and percentage for categorical variables.

### 13.1.4. Analysis of Primary Endpoint

The analysis of response to treatment (see Section 11.1.1 for definition of primary endpoint) between SAGE-547 treated subjects and placebo treated subjects will be performed on the ITT population using a Cochran-Mantel-Haenszel (CMH) test with variables for treatment, concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to

randomization (one vs two or more). The CMH general association statistic and its associated p-value will be presented. The comparison of treatment response rates will be conducted at the 5% level of significance. To confirm the CMH results, a permutation test will also be conducted.

An additional analysis of the primary endpoint will also be performed on the MITT population. In addition sensitivity analyses of the primary endpoint will be performed using the ITT population based on:

- the number of third-line agents (one, two, or three) subjects were administered post-randomization; and
- which third line agent was the subject of the first TW.

### **13.1.5. Analysis of Secondary Efficacy Endpoints**

Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section (Section 6). Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. The analysis of the secondary endpoints will also be performed on the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

### **13.1.6. Analysis of Other Endpoints**

Safety and “Other” endpoints will only be summarized by treatment group.

Summaries of safety endpoints will be based on the overall Safety Population.

### **13.1.7. Epilepsy and SRSE Status**

Diagnosis of epilepsy and recurrence of RSE or SRSE will be documented as the percentage of subjects by time point and overall. Kaplan-Meier curves may be plotted if sufficient data are available.

Utilization of AEDs during follow-up and during recurrence will be summarized.

### **13.1.8. Questionnaires**

The data collected from each questionnaire will be interpreted according to the standard methodology for that questionnaire. There will be no adjustment for missing values.

### **13.1.9. Pharmacokinetic Data Analysis**

Details of the pharmacokinetic data analysis will be described in detail in a separate Pharmacokinetic Analysis Plan.

### **13.1.10. Pharmacogenetic Data Analysis**

Any genotype data generated in this study will be stored within a secured database within Sage Therapeutics and / or a third party contracted to work with Sage Therapeutics to analyze the samples. Because the number of subjects agreeing to participate in the genetic research component of the study is unknown, it is not possible to establish, a priori, whether sufficient samples will be obtained to support formal statistical evaluation of data. As a consequence a Pharmacogenetic Analysis Plan will only be prepared where appropriate and the results obtained from any genetic research will be reported in a report separate from the main study CSR.

### **13.1.11. Retreated Subjects**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are retreated with SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo.

### **13.1.12. EEG-Responders**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who are classified as EEG-responders/non-responders based on the independent assessment of the PAEEG. Summaries will be derived for the two randomized treatment groups.

### **13.1.13. QT/QTc Assessment**

An analysis of the correlation between changes in QT/QTc intervals and SAGE-547 plasma levels will be performed to investigate if there is a potential effect that SAGE-547 may have on QT/QTc interval. A detailed description of the QT/QTc assessment will be included in the SAP.

### **13.1.14. Quantitative EEG**

The six EEG records for each subject may be subjected to exploratory quantitative EEG analysis, the details of which will be included in the EEG Analysis Plan. In summary the following comparisons may be made, SAGE-547 versus placebo: the QWEEG versus the TWEEG (main analysis); the CEEG versus PAEEG (subsidiary analysis); and TAEEG versus PAEEG (exploratory analysis).

## **13.2. Determination of Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between treatment groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

### **13.3. Statistical Analysis Plan**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

## **14. ADVERSE EVENTS**

The safety procedures in this study will be detailed in a Safety Management Plan, which will be agreed and signed before the first subject is randomized in the study. Section 14.1 summarizes Investigator responsibilities regarding the identification and documentation of AEs, the classification of AEs for relationship to study drug and severity, and the reporting of AE information to the Sponsor and the IRB.

[Section 14.2](#) summarizes Sponsor/Medical Monitor Responsibilities regarding monitoring of AE data and reporting relevant safety information to FDA.

[Section 14.3](#) lists important AE definitions.

### **14.1. Investigator Responsibilities**

#### **14.1.1. Identification and Documentation of Adverse Events by Investigator**

Subjects will be evaluated and questioned generally (if possible) to identify AEs during the course of the study. AEs will be collected from the signature of the consent form through Visit 12/12R. Adverse events that occur prior to completion of screening will be captured on the Medical History eCRF. Adverse events that occur after completion of screening will be recorded on the Adverse Event eCRF.

All AEs revealed by observation, other diagnostic procedures, or spontaneously reported by the subject and/or in response to an open question from study personnel will be recorded on the Adverse Event Form. Any clinically significant deterioration in laboratory assessments or other clinical findings are considered an AE and must be recorded on the Adverse Event Form, unless otherwise stated. AE information recorded will be entered into the database on an ongoing basis.

AEs with a relationship considered related to study drug (probable, possible) should be followed until the event is resolved or the Investigator determines the event is stable or no longer clinically significant. AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

For SAEs, an electronic Serious Adverse Event eCRF must be completed with as much information as possible and submitted in the time frame described below in [Section 14.1.3](#). When new significant information is obtained as well as when the outcome of an event is known, the electronic SAE eCRF should be updated within 24 hours. If the subject was an outpatient at the time of the SAE and was re-hospitalized due to the SAE, a copy of relevant hospital records (e.g., admission report, laboratory test results, discharge summary, etc.) may be requested to be included as part of the subject medical file.

All SAEs will be followed until resolved or until a stable status has been achieved.

**14.1.2. Adverse Event Classification****14.1.2.1. Relationship to Investigational Drug**

None:	No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state.
Possible:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject, but this is not known for sure.
Probable:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

**14.1.2.2. Severity**

Mild	Discomfort noticed, but no disruption to daily activity.  For subjects that are unconscious, this may be a slight or minor change in a lab result or clinical sign or symptom that does not require immediate corrective action.
Moderate	Discomfort sufficient to reduce or affect normal daily activity, but is not hazardous to health; prescription drug therapy may be employed to treat the AE.  For subjects that are unconscious, this may be a clinically meaningful change that may require immediate corrective action.
Severe	Inability to work or perform normal daily activity and represented a definite hazard to health; prescription drug therapy and/or hospitalization may be employed to treat the AE.  For unconscious subjects, this may be a significant clinical change that requires immediate corrective action.

**14.1.2.3. Action Taken with Investigational Drug**

None	Study medication was continued without change.
Discontinued	Study medication was terminated.
Dose adjusted	Study medication dose/infusion rate was changed and then continued per protocol.
Interrupted	Study medication was interrupted and then continued per protocol.
Unknown	The action taken with regard to study medication is unknown.
Not applicable	Administration of study medication was not ongoing.



**14.1.2.4. Assessment of Outcome**

Ongoing	At the end of the study, the event has not resolved or stabilized.
Ongoing and stable	The event is ongoing but has stabilized and is unlikely to change
Resolved	The event has resolved or the subject recovered without sequelae.
Resolved with sequelae	The event has at least one secondary outcome that may result in permanent disability and/or functional limitation.
Unknown	The status of the event is unknown.
Death	The subject has expired.

**14.1.3. Investigator Reporting to Sponsor and Sponsor Emergency Contact**

All new SAEs that come to the Investigator and/or Sponsor's notice during the course of the study (up to and including the last study visit) must be reported by the Investigator on the designated electronic report form within 24 hours of the point in time when the Investigator becomes aware of the SAE. As additional information becomes available, the designated electronic report form must be updated within 24 hours.

Investigators must report any SAE, whether or not considered drug related. The report must include an assessment of whether there is a reasonable possibility that the drug caused the event.

In a medical emergency (ie, an event that requires immediate attention regarding the treatment of a subject, operation of the clinical study, and/or the use of investigational drug), study site staff will apply appropriate medical intervention according to current standards of care, and contact the Medical Monitor.

**14.1.4. Medical Monitor and Emergency Contact Information**

[REDACTED], MD  
[REDACTED]

**14.1.5. SAE Reporting Contact Information**

Contact information and reporting instructions are provided in the Safety Management Plan.

**14.1.6. Reporting to Institutional Review Boards (IRBs)**

It is the responsibility of the Investigator to promptly notify the institution's IRB of all serious and unexpected suspected adverse reactions (see [Section 14.3](#) for definitions).

## **14.2. Sponsor/Medical Monitor Responsibilities**

### **14.2.1. Monitoring of Adverse Event Data**

The Medical Monitor will review any newly reported adverse events in an ongoing basis. If the aggregate assessment indicates that an event is occurring more frequently than would normally be expected in this population, or as previously observed, and the sponsor believes that the events are causally related to the administration of SAGE-547, the Sponsor will then report that information in an IND safety report.

### **14.2.2. Data Safety Monitoring Board**

An independent DSMB will monitor the clinical, PK and PD data for safety signals throughout the study and will be asked to assess the placebo response rate at the time of the interim analysis to determine final sample size. In order to perform their monitoring function the DSMB will have access to un-blinded safety data as necessary.

The composition and procedures for the board will be described in a separate DSMB Charter.

### **14.2.3. Reporting to FDA**

The Sponsor must report in an IND safety report any suspected adverse reaction to study treatment that is both serious and unexpected (21 CFR 312.32(c)(1)(i)). Before submitting an IND safety report, the Sponsor will ensure the event meets all three of the definitions: (1) suspected adverse reaction, (2) serious, (3) unexpected. If the AE does not meet all three of the definitions, it should not be submitted as an IND safety report. The Sponsor should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the adverse event and, therefore, that the event meets the definition of a suspected adverse reaction.

If there is a serious and unexpected suspected adverse reaction, the Sponsor will notify the appropriate regulatory agency(ies) and all appropriate parties on an expedited basis. In addition, Sponsors must submit expedited reports of an increased rate of occurrence or severity of serious suspected adverse reactions over that listed in the protocol or Investigational Brochure.

SUSARs will be unblinded prior to reporting to FDA. Unless it is necessary to unblind for the safety of the patient, the investigator will not be informed of the unblinding of the subject.

Under 21 CFR 312.32, Sponsors should identify in the protocol SAEs that it does not plan to report individually in an expedited manner, because they are known consequences of the disease or otherwise common in the study population. Given the grave condition and prognosis of SRSE being studied, individual occurrences of seizures or seizure activity will not be reported expeditiously in this study. Regardless of which events are reported in an expedited manner, all adverse events will be closely monitored throughout the study.

## **14.3. Adverse Event Definitions**

### **14.3.1. Adverse Event**

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

### **14.3.2. Suspected Adverse Reaction**

Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

### **14.3.3. Life-Threatening**

An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

### **14.3.4. Serious**

An AE or suspected adverse reaction is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE – see definition above
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disability
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

### **14.3.5. Unexpected**

An AE or suspected adverse reaction is considered “unexpected”:

- If it is not listed in the Investigational Brochure or is not listed at the specificity or severity that has been observed, or
- If an Investigational Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigational Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigational Brochure listed only cerebral vascular accidents.

“Unexpected,” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigational Brochure as occurring with a class of drugs or as anticipated from

the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

#### **14.4. Emergency Identification of Study Medication**

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject's treatment in the study via the IVRS; this normally requires prior approval by the medical monitor. However, if the subject is at immediate risk and the Investigator believes that immediate knowledge of the study treatment will alter medical management, discussion with the medical monitor may take place after unblinding. The Investigator will not unblind the medical monitor during that discussion. The process of unblinding will ensure that only the investigator is unblinded; the medical monitor, study management team, and data management team will not be made aware of the treatment allocation of an individual subject. All cases of emergency unblinding will be fully documented in a way that does not unblind the medical monitor, study management team, and data management team.

### **15. STUDY ADMINISTRATIVE CONSIDERATIONS**

#### **15.1. Quality Control and Quality Assurance**

The Investigators and institutions will permit trial related monitoring, audits, IRB review, and regulatory inspections as requested by FDA, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed informed consent forms, etc.) in addition to case report forms.

Quality assurance and quality control systems with written standard operating procedures (SOPs) will be followed to ensure this trial will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The site's dedicated study monitor will arrange to visit the Investigator at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be identified and resolved. The study monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality assurance officers named by Sage Therapeutics or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements, made by the Sponsor with the Investigator/institution and any other parties involved with the clinical trial, will be in writing in a separate agreement.

## **15.2. Data Handling and Recordkeeping**

### **15.2.1. Data Handling**

Procedures for data handling (including electronic data) used in this protocol will be documented in a Data Management Plan.

### **15.2.2. Case Report Form Completion**

eCRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of demographics, study drug administration, study procedures, AEs, questionnaire completion, efficacy assessments and subject status, including survival.

The Investigator will maintain copies of the eCRFs at the study site. For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate eCRF.

### **15.2.3. Retention of Study Records**

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval and until there are no pending or contemplated marketing applications or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to an appropriate person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

## **15.3. Confidentiality**

To maintain subject privacy, all eCRFs, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available trial registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by Sage Therapeutics to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

#### **15.4. Publication Policy**

All information concerning SAGE-547 is considered confidential and shall remain the sole property of Sage Therapeutics. The Investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval from Sage Therapeutics. No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between Sage Therapeutics and the Investigator.

#### **15.5. Protocol Amendments**

Changes to the conduct of the study should be prepared as a protocol amendment by the Sponsor. Protocol amendments should receive written IRB/IEC approval prior to implementation at the investigative site, except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the trial (eg, change of monitor, telephone numbers). In this case, Sage Therapeutics will amend and implement the protocol change and subsequently notify the regulatory authorities and the Investigative sites who will notify the respective IRB, as appropriate.

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**APPENDIX 1. APPENDIX 1: FOUR SCORE****FOUR score****Full Outline of UnResponsiveness****Eye response**

- E4: eyelids open or opened, tracking, or blinking to command
- E3: eyelids open but not tracking
- E2: eyelids closed but open to loud voice
- E1: eyelids closed but open to pain
- E0: eyelids remain closed with pain

**Motor response**

- M4: thumbs-up, fist or peace sign
- M3: localizing to pain
- M2: flexion response to pain
- M1: extension response to pain
- M0: no response to pain or generalized myoclonus status

**Brainstem reflexes**

- B4: pupil and corneal reflexes present
- B3: one pupil wide and fixed
- B2: pupil or corneal reflexes absent
- B1: pupil and corneal reflexes absent
- B0: absent pupil, corneal and cough reflex

**Respiration pattern**

- R4: not intubated, regular breathing pattern
- R3: not intubated, Cheyne-Stokes breathing pattern
- R2: not intubated, irregular breathing
- R1: breathes above ventilatory rate
- R0: breathes at ventilator rate or apnea

Reference ([Iyer, Hoel et al. 2009](#)).

**APPENDIX 2. GLASGOW OUTCOME SCALE (GOS)****GLASGOW  
OUTCOME  
SCALE**

Patient Name: \_\_\_\_\_  
 Rater Name: \_\_\_\_\_  
 Date: \_\_\_\_\_

*Note:* The scale presented here is based on the original article by Jennett and Bond. It has become common practice in clinical trial administration, however, to use a modified version that places the scores in reverse order (i.e., "good recovery" = 1, "moderate disability" =2, etc.).

Score	Description
1	DEATH
2	PERSISTENT VEGETATIVE STATE Patient exhibits no <i>obvious cortical</i> function.
3	SEVERE DISABILITY (Conscious but disabled). Patient depends upon others for daily support due to mental or physical disability or both.
4	MODERATE DISABILITY (Disabled but independent). Patient is independent as far as daily life is concerned. The disabilities found include varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes.
5	GOOD RECOVERY Resumption of normal activities even though there may be minor neurological or psychological deficits.

**TOTAL (1-5):** \_\_\_\_\_

Reference ([Jennett and Bond 1975](#)).

## APPENDIX 3. SUPERVISION RATING SCALE (SRS)

### SUPERVISION RATING SCALE (SRS)

**Instructions:** Circle the rating that is closest to the amount of supervision that the patient *actually receives*. "Supervision" means that someone is responsible for being with the patient.

<u>Rating</u>	<u>Description</u>
<b>Level 1: INDEPENDENT</b>	
1	The patient lives alone or independently. Other persons can live with the patient, but they cannot take responsibility for supervision (for example, a child or elderly person).
2	The patient is unsupervised overnight. The patient lives with one or more persons who <i>could</i> be responsible for supervision (for example, a spouse or roommate), but they are <i>all</i> sometimes absent overnight.
<b>Level 2: OVERNIGHT SUPERVISION</b>	
3	The patient is only supervised overnight. One or more supervising persons are always present overnight but they are <i>all</i> sometimes absent for the rest of the day.
<b>Level 3: PART-TIME SUPERVISION</b>	
4	The patient is supervised overnight and part-time during waking hours, but is allowed on independent outings. One or more supervising persons are always present overnight and are also present during part of waking hours every day. However, the patient is sometimes allowed to leave the residence without being accompanied by someone who is responsible for supervision.
5	The patient is supervised overnight and part-time during waking hours, but is unsupervised during working hours. Supervising persons are <i>all</i> sometimes absent for enough time for them to work full-time outside the home.
6	The patient is supervised overnight and during most waking hours. Supervising persons are <i>all</i> sometimes absent for periods longer than one hour, but less than the time needed to hold a full-time job away from home.
7	The patient is supervised overnight and during almost all waking hours. Supervising persons are <i>all</i> sometimes absent for periods shorter than one hour.
<b>Level 4: FULL-TIME INDIRECT SUPERVISION</b>	
8	The patient is under full-time indirect supervision. At least one supervising person is <i>always</i> present, but the supervising person does not check on the patient more than once every 30 minutes.
9	Same as #8 plus requires overnight safety precautions (for example, a deadbolt on outside door).
<b>Level 5: FULL-TIME DIRECT SUPERVISION</b>	
10	The patient is under full-time direct supervision. At least one supervising person is always present and the supervising person checks on the patient more than once every thirty minutes.
11	The patient lives in a setting in which the exits are physically controlled by others (for example, a locked ward).
12	Same as #11 plus a supervising person is designated to provide full-time line-of-sight supervision (for example, an escape watch or suicide watch).
13	The patient is in physical restraints.

3/12/93

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## APPENDIX 4. MODIFIED RANKIN SCALE – LEVEL OF FUNCTION SURVEY (mRS-9Q)

1. Do you have any symptoms that are bothering you? (For example, trouble with reading or writing, trouble speaking, problems with vision, numbness, weakness, balance trouble, or problems with swallowing?)	YES	<input type="radio"/>	NO	<input type="radio"/>
2. Are you able to do the same work as before?	YES	<input type="radio"/>	NO	<input type="radio"/>
3. Are you able to keep up with your hobbies?	YES	<input type="radio"/>	NO	<input type="radio"/>
4. Have you maintained your ties to friends and family?	YES	<input type="radio"/>	NO	<input type="radio"/>
5. Do you need help making a simple meal, doing household chores, or balancing a checkbook?	YES	<input type="radio"/>	NO	<input type="radio"/>
6. Do you need help with shopping or traveling close to home?	YES	<input type="radio"/>	NO	<input type="radio"/>
7. Do you need another person to help you walk?	YES	<input type="radio"/>	NO	<input type="radio"/>
8. Do you need help with eating, going to the toilet, or bathing?	YES	<input type="radio"/>	NO	<input type="radio"/>
9. Do you stay in bed most of the day and need constant nursing care?	YES	<input type="radio"/>	NO	<input type="radio"/>

## APPENDIX 5. CLINICAL GLOBAL IMPRESSION (CGI)

### Clinical Global Impression (CGI)

#### 1. Severity of illness

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- |                             |   |
|-----------------------------|---|
| 0 = Not assessed            | 4 = Moderately ill                        |
| 1 = Normal, not at all ill  | 5 = Markedly ill                          |
| 2 = Borderline mentally ill | 6 = Severely ill                          |
| 3 = Mildly ill              | 7 = Among the most extremely ill patients |

#### 2. Global improvement: Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.

Compared to his condition at admission to the project, how much has he changed?

- |                        |                     |
|------------------------|---------------------|
| 0 = Not assessed       | 4 = No change       |
| 1 = Very much improved | 5 = Minimally worse |
| 2 = Much improved      | 6 = Much worse      |
| 3 = Minimally improved | 7 = Very much worse |

#### 3. Efficacy index: Rate this item on the basis of drug effect only.

Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.

EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

Therapeutic effect		Side effects			
		None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
<b>Marked</b>	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
<b>Moderate</b>	Decided improvement. Partial remission of symptoms	05	06	07	08
<b>Minimal</b>	Slight improvement which doesn't alter status of care of patient	09	10	11	12
<b>Unchanged or worse</b>		13	14	15	16
Not assessed = 00					

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

**APPENDIX 6. STATUS EPILEPTICUS SEVERITY SCORE (STESS)**

Outcome Predictor	Feature	Score
Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type (prior to first treatment)	Simple-partial, complex-parial, absence, myoclonic (complicating idiopathic generalized epilepsy)	0
	Generalized-convulsive	1
	Nonconvulsive status epilepticus in coma	2
Age	< 65 years	0
	≥ 65 years	2
History of previous seizures	Yes	0
	No or unknown	1
Summed Total		

**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY  
TO EVALUATE THE EFFICACY AND SAFETY OF SAGE-547 INJECTION  
IN THE TREATMENT OF SUBJECTS WITH SUPER-REFRACTORY  
STATUS EPILEPTICUS**

**PROTOCOL NUMBER: 547-SSE-301**

**IND NUMBER: 117901**

**EudraCT Number: 2015-002142-31**

Product: SAGE-547 Injection (allopregnanolone)

Sponsor Contact: [REDACTED], MD

[REDACTED]  
Sage Therapeutics  
215 First Street  
Cambridge, MA 02142  
[REDACTED]

Medical Monitor: [REDACTED], MD

Date of Protocol: 09 March 2015

Date of Amendment One 27 May 2015

**Confidentiality Statement**

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

**PROTOCOL NUMBER: 547-SSE-301**

Sponsor [REDACTED]:

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]:

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

CRO [REDACTED]:

[REDACTED]



## 1. SIGNATURE PAGE

Title of Protocol:

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus

Protocol No: 547-SSE-301

### Sponsor Approval

[Redacted Signature]  
[Redacted Name], MD

08 Jun 2015

Date (dd/mmm/yyyy)

Sage Therapeutics

### Investigator Agreement

By signing this page I attest that I have read and understand the contents of Clinical Protocol 547-SSE-301 and any current amendments. I agree to adhere to the design, conduct, and reporting requirements of the study as stated in the clinical protocol and to my obligations to the Sponsor as described in the protocol and executed contracts between myself, my Institution, and the Sponsor. I also agree to adhere to any subsequent amendments to the clinical protocol.

Investigator's Signature: \_\_\_\_\_

Investigator's Name: \_\_\_\_\_

Institution: \_\_\_\_\_

Date: \_\_\_\_\_

## 2. SYNOPSIS

<b>Name of Sponsor:</b> Sage Therapeutics 215 First Street Cambridge, MA 02142		
<b>Protocol No.</b> 547-SSE-301	<b>Phase:</b> 3	
<b>Name of Investigational Product:</b> SAGE-547 Injection		
<b>Name of Active Ingredient:</b> Allopregnanolone		
<b>Title of the Protocol:</b> A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus		
<b>Dosing Regimen: SAGE-547 or Placebo Dosing Schedule</b>		
<b>Hour</b>	<b>Type and Duration of SAGE-547 Infusions</b>	<b>Dose</b>
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	90 µg/kg/h
H121 – H128	8 hour taper	65 µg/kg/h
H129 – H136	8 hour taper	45 µg/kg/h
H137 – H144	8 hour taper	25 µg/kg/h
<b>Dosing Regimen: SAGE-547 Open Label Dosing Schedule</b>		
<b>Hour</b>	<b>Type and Duration of SAGE-547 Infusion</b>	<b>Dose</b>
H1	One hour loading infusion	300 µg/kg/h
H2 –H120	119 hour maintenance infusion	150 µg/kg/h
H121 – H126	6 hour taper	125 µg/kg/h
H127 – H132	6 hour taper	95 µg/kg/h
H133 – H138	6 hour taper	65 µg/kg/h
H139 – H144	6 hour taper	35 µg/kg/h
<b>Study Sites</b> Up to 150 sites in the USA, Europe, and Canada.		
<b>Number of Subjects</b>		

The study will randomize 140 subjects at up to 150 sites.

### Study Population

Subjects will be aged two years or more, in SRSE<sup>1</sup> (as defined in the Inclusion Criteria [Section 8.1](#)), and being managed in an intensive care setting.

### Duration of Subject Involvement

Individual subject participation will be up to 30 days.

### Study Design

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

Patients will follow one of three paths to entry to the study. The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst suppression with a third-line agent. These subjects will be consented for the study after admission to the intensive care unit, but before any third-line agents are administered for burst suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their legally authorized representative (LAR). Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours. Once burst suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of study drug.

The second path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst suppression pattern on the EEG. These subjects may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of study drug.

The third path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst

<sup>1</sup> In this study, the term Super-Refractory Status Epilepticus or SRSE is equivalent to “Refractory Status Epilepticus (RSE) that has failed standard treatment” and the two terms are used interchangeably.

suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These subjects may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 treatment or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within six hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo).

The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that subjects, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as both the ability to wean the subject off all third-line agents before the end of the infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication infusion, and concurrent signs of physiologic brain activity as determined by EEG. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#) and [Table 2](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo will all subsequently be eligible to be administered SAGE-547 at the higher dose.

### Visit Schedule

The visit schedule and an overview of events at each visit is provided in [Table 1](#), [Table 2](#) and [Table 3](#) Schedule of Assessments.

**Study Objectives*****Primary objective:***

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult and pediatric subjects with SRSE, and for the response to endure at least 24 hours after the end of the SAGE-547 or placebo infusion (primary response).

***Secondary objectives:***

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in the Clinical Global Impression scale (CGI) between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

***Safety objectives:***

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

***Other objectives:***

1. To evaluate the impact of retreatment with a higher dose SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol<sup>®</sup> and identified SAGE-547 metabolite plasma concentrations;

3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;
6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS) (age  $\geq 17$  years).

## Endpoints

### *Primary endpoint:*

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### *Secondary endpoints:*

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### *Safety endpoints:*

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.

**Other endpoints:**

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who fail to respond to their randomized double blind treatment and are retreated with a higher dose of SAGE-547.
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol<sup>®</sup> and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS) (age  $\geq 17$  years).

**Inclusion Criteria**

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects two (2) years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst suppression pattern; or who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst suppression pattern.

**Exclusion Criteria**

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone or any excipients in SAGE-547.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy.
4. Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing underlying neurological disorder.

5. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis for whatever reason, but dialysis is not planned or non-continuous dialysis is planned (that would not adequately remove Captisol<sup>®</sup>);
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the opinion of the investigator, of less than 30 days;
  - e. a do not resuscitate (DNR) order.
6. Subjects who are being administered more than three third-line agents concomitantly or in whom the qualifying wean cannot be completed within 24 hours, or who are being administered a third-line agent for other indications such as management of raised intra-cranial pressure that would preclude weaning according to this protocol.
7. Subjects with a living will that does not allow heroic measures.
8. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
9. Subjects who have been enrolled in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not withdraw or complete and then re-enroll).

### Pharmacogenetic Research

In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### Statistical Analysis

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

### Interim Analysis

When approximately 50% of the subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### Analysis of Primary Endpoint

The analysis of response to treatment between SAGE-547 treated subjects and placebo treated subjects will be performed using a Cochran-Mantel-Haenszel test with variables for treatment, concomitant



pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). In this analysis, a treatment responder is a subject who is successfully weaned off all third-line agents and blinded study medication prior to the end of study treatment infusion and remains off third-line agents for at least 24 hours following cessation of the blinded study medication, and who has concurrent signs of physiologic brain activity as determined by EEG. The analysis will be based on the ITT Population. The comparison of treatment response rates will be conducted at the 5% level of significance.

### **Analysis of Secondary Efficacy Endpoints**

The primary analysis will be repeated for the MITT population. Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section. Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. Secondary analyses will be repeated for the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from Baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third-line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

Summaries of safety endpoints will be based on the overall Safety Population which is defined as all subjects who at least initiated the infusion with blinded study treatment.

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are retreated with SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo. Summary statistics will be presented for subjects who were QW successes.

### **Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

**Table 1: Schedule of Assessments for Protocol 547-SSE-301: One Infusion of Study Drug (blinded)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical/SE/Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X		X	X	X	X	X	X				
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X		X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X		X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X		X	X		X		X		X		
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X			
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>o</sup>											X
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV 3rd-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>p</sup>				
EEG	X	X				X		X	X			
Randomization		X										
Study Drug Administration <sup>q</sup>			X	X	X	X	X	X				
TW Outcome & Retreat Decision										X <sup>r</sup>		
Physiologic Brain Activity									X			
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

**Table 2: Schedule of Assessments for Protocol 547-SSE-301: Two Infusions of Study Drug (one blinded, one open-label)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V3R
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	0-24h
Eligibility Checklist	X										S
Informed Consent <sup>a</sup>	X										E
Inclusion/Exclusion Criteria	X										E
Demography <sup>b</sup>	X										
Medical and SE and Wean History <sup>c</sup>	X										T
Height	X										A
Weight <sup>d</sup>	X		X	X	X	X	X	X			B
Serum Pregnancy Test <sup>e</sup>	X										L
Hematology <sup>f</sup>	X		X	X		X		X		X <sup>g</sup>	E
Serum Chemistry and GFR	X		X	X		X		X		X	
Urinalysis <sup>h</sup>	X		X	X		X		X		X	E
Pharmacogenetic sample	X										X
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X	T
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X	E
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X		N
STESS	X										I
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	O
Glasgow Outcome Score (GOS)											N
Supervision Rating Scale (SRS)	X <sup>o</sup>										
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>										
Epilepsy Status	X										N
Clinical Global Impression (CGI)	X										E
Continuous IV Third-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>p</sup>			X
EEG	X	X				X		X	X		T
Randomization		X									
Study Drug Administration <sup>q</sup>			X	X	X	X	X	X			
TW Outcome and Retreat Decision										X <sup>r</sup>	P
Physiologic Brain Activity									X		
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	A
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	G
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	E
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X	
Pharmacoeconomic Data											
Mortality											

Table 2 continued

	V3R	V4R	V5R	V6R	V7R	V8R	V9R	V10R	V11R	V12R
	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3R+14d (±2d)	V3R+21d (±2d)
Weight <sup>d</sup>	X	X	X	X	X	X				
Serum Pregnancy Test <sup>e</sup>										
Hematology <sup>f</sup>	X	X		X		X		X <sup>g</sup>		
Serum Chemistry and GFR	X	X		X		X		X	X	
Urinalysis <sup>h</sup>	X	X		X		X		X		
Vital Signs <sup>i</sup>	X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>	X	X	X	X	X	X	X			
STESS										
FOUR Score <sup>m</sup>	X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)										X
Supervision Rating Scale (SRS)										X
Modified Rankin Score (mRS) <sup>n</sup>										X
Epilepsy Status										X
Clinical Global Impression Scale (CGI)										X
Continuous IV Third-Line Agent(s)	X	X	Wean	Wean	Wean	Wean <sup>p</sup>				
EEG			X			X	X			
Randomization										
Study Drug Administration <sup>q</sup>	X	X	X	X	X	X				
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures, and Treatments	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data										X
Mortality										X

**Table 3: Schedule of Assessments for Protocol 547-SSE-301: Qualifying Wean Successes**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2-≤30h	V3-≤54h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical and SE and Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X											
Serum Pregnancy Test <sup>c</sup>	X											
Hematology <sup>f</sup>	X											
Serum Chemistry and GFR <sup>f</sup>	X											
Urinalysis <sup>h</sup>	X											
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X											
ECG <sup>j</sup>	X											
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>o</sup>											X
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV Third-Line Agent(s)	X	Wean										
EEG	X	X										
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications, Procedures and Treatments	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data												X
Mortality												X

<sup>a</sup> Written informed consent by proxy (LAR) will be obtained prior to starting any study-related procedures not considered standard of care.

<sup>b</sup> Demographic information will be obtained by proxy and confirmed by the subject when possible.

<sup>c</sup> Medical history will be obtained by proxy and confirmed by the subject when possible. All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Dosing changes with the third-line agent(s) that constitute a wean attempt will be marked as such on the CRF, and the start/stop dates and times of all wean attempts prior to V3 will be recorded, as well as the outcome of the wean attempt.

- <sup>d</sup> Weight will be collected at Screening (V1) and once during each 24 hour period of the initial study drug infusion period (V3-V8) and second infusion period (V3R-V8R, if applicable). Daily weight will be used to determine the appropriate infusion rate of each dose.
- <sup>e</sup> Serum pregnancy test for females aged 10 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy. .
- <sup>f</sup> Blood samples will be taken for hematology and serum chemistry and GFR calculation at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will document whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.
- <sup>g</sup> Blood samples will be taken at V11 or V11R for serum chemistry (renal panel only).
- <sup>h</sup> Urine samples will be taken for urinalysis and NAG at V1, at 24, 48, 96, 144 and 192 hours ( $\pm 2$  hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will add a comment about whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.
- <sup>i</sup> Vital signs will be recorded at the following time points relative to the start of each infusion of study drug: Screening (V1), at 0, 30, 60 minutes ( $\pm 15$  minutes), at 2, 4, and 8 hours ( $\pm 30$  minutes), and at 24, 48, 72, 96, 120, 144, 168, and 192 hours ( $\pm 2$  hours).
- <sup>j</sup> ECG (12-lead) should be performed at Screening (V1) and at the following times relative to the start of study drug infusion. For the blinded (first) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 128, 136, 144, 152, 160, and 192 hours ( $\pm 2$  hours). For the open label SAGE-547 (second) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 126, 132, 138, 144, 152, 160, and 192 hours ( $\pm 2$  hours). Heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours.
- <sup>k</sup> Plasma will be collected to assay for study drug concentrations at the following time points relative to the start of each infusion of study drug: For the blinded (first) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion. For the open label SAGE-547 (second) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open label SAGE-547 study drug infusion. Pre-dose samples may be taken within two hours before starting the infusion of study drug; timepoints up to and including 1h will have a time window of  $\pm 5$  minutes; all other timepoints will have a window of  $\pm 15$  minutes.
- <sup>m</sup> FOUR Score assessments will be performed at Screening (V1), 24, 48, 72, 96, 120, 144, 168, and 192 hours (all  $\pm 2$  hours) relative to the start of each infusion of study drug, and at V11 or V11R, and at V12 or V12R.
- <sup>n</sup> Modified Rankin Score (mRS) applicable for subjects  $\geq 17$  years old only.
- <sup>o</sup> SRS at V1 will be a retrospective assessment of the supervision required by the subject immediately prior to admission that includes the index episode of the SE, and mRS at V1 will be a retrospective assessment of the disability and dependence of the subject immediately prior to admission that includes the index episode of the SE.
- <sup>p</sup> Target for complete wean of all continuous IV third-line agents by 144 hours at V8/V8R if not completed by 120 hours at V7/V7R.
- <sup>q</sup> Study drug infusion is intended for IV administration only with a dedicated peripheral IV line using Sage-approved IV administration bags and lines.
- <sup>r</sup> At V10 only a decision to re-treat at a higher dose of SAGE-547 will be made by the Investigator if the continuous IV third-line agent wean has failed or the third-line agent requires re-introduction during V9. Subjects who become eligible for re-treatment at a higher dose of SAGE-547 will discontinue the planned visit schedule at V10, then repeat V3 (V3R) and all applicable subsequent visits.
- <sup>s</sup> AEs will be collected from the time Informed Consent is obtained and prior to the start of study-specific screening procedures not considered standard of care. Collection of AEs will continue throughout the study from V1 through V12 or V12R.
- <sup>t</sup> Subjects may enter the study on AEDs and be administered AEDs during the study. All Concomitant AEDs must be recorded on the CRF with details including date and time of starting/stopping each AED, the route of administration, changes in doses, and frequency of administration. Details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the CRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.
- <sup>u</sup> All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Details will include the name of the drug, the start/stop dates and times, and, after consent, the doses with start/stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

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**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
AE	adverse event
AED	anti-epileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the time-concentration curve
AW	additional weans
BDZ	benzodiazepine
BIEEG	blinded infusion electroencephalogram
BUN	blood urea nitrogen
CBC	complete blood count
CEEG	consent electroencephalogram
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
C <sub>max</sub>	maximum plasma concentration
C <sub>min</sub>	minimum plasma concentration
CNS	central nervous system
CRF	case report form
CSR	clinical study report
CYP2C9	cytochrome P450 enzyme involved in drug metabolism
DNR	do not resuscitate
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EEG	electroencephalogram
EIND	Emergency Use Investigational New Drug Application
EP	European Pharmacopeia
ESETT	Established Status Epilepticus Treatment Trial
FDA	Food and Drug Administration
FOUR	Full Outline of UnResponsiveness
GABA	$\gamma$ -aminobutyric acid
GABA <sub>A</sub>	$\gamma$ -aminobutyric acid-gated chloride channel

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GOS	Glasgow Outcome Scale
H	hour
HPLC	high performance liquid chromatography
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent to Treat
IV	intravenous
IVRS	Interactive Voice Randomization System
LAR	legally authorized representative
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent to Treat
mRS-9Q	Modified Rankin Score - 9Q
MS/MS	tandem mass spectrometry
nM	nanomolar
NMDA	n-methyl-D-aspartic acid
OW	other weans
PAEEG	primary endpoint electroencephalogram
PD	pharmacodynamics
PK	pharmacokinetic
QOL	quality of life
QW	qualifying wean
QWEEG	qualifying wean electroencephalogram
RBC	red blood cell

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
RSE	refractory status epilepticus
SAE	serious adverse event
SAP	Statistical Analysis Plan
SE	status epilepticus
SOP	standard operating procedure
SRS	Severity Rating Scale
SRSE	Super-refractory status epilepticus
SSRI	Selective serotonin re-uptake inhibitors
STESS	Status Epilepticus Severity Score
SUSAR	Suspected Unexpected Serious Adverse Reactions
SWFI	Sterile Water for Injection
TAEED	taper electroencephalogram
T <sub>max</sub>	time at maximum plasma concentration
TW	terminal wean
TWEEG	terminal wean electroencephalogram
US	United States
USP	United States Pharmacopeia



### 3. INTRODUCTION AND RATIONALE

#### 3.1. Status Epilepticus

Status epilepticus (SE) is a life-threatening seizure condition in which the brain is in a state of persistent seizure triggered by neuronal hyperexcitability. The Neurocritical Care Society defines SE as one continuous unremitting seizure lasting longer than five minutes or recurrent seizures without regaining consciousness between seizures for greater than five minutes (Brophy, Bell et al. 2012). Common causes of SE include preexisting epilepsy, cerebrovascular disease (in adults), electrolyte and metabolic disturbances, anoxia, encephalopathies, head trauma, high fever (in children, especially in the first year of life) and drug or substance intoxication. SE is associated with substantial morbidity and mortality.

##### 3.1.1. Epidemiology of SE

Geography, sex, age, and race influence the epidemiology of SE, whose incidence has a bimodal distribution, peaking in infants/young children and the elderly (Hauser 1990; DeLorenzo, Pellock et al. 1995; Wu, Shek et al. 2002). The incidence of SE in the elderly population is at least twice that in the general population. Concurrent medical conditions often exist in the elderly population, which can complicate therapy and worsen the prognosis of SE (Chapman, Smith et al. 2001).

The annual incidence of SE in the US is generally quoted to be within the range of 18/100,000 to 61/100,000, based on a 19-year retrospective study in Rochester, Minnesota (Hesdorffer, Logroscino et al. 1998) and a 2-year prospective study in Richmond, Virginia (DeLorenzo, Pellock et al. 1995), respectively. Two studies from Europe give annual incidences of a similar magnitude, ranging between 9.9/100,000 and 15.8/100,000 (Coeytaux, Jallon et al. 2000; Knake, Rosenow et al. 2001). It is thus estimated that in the United States each year there are as many as 150,000 cases of SE (DeLorenzo, Pellock et al. 1995).

#### 3.2. Refractory SE

When a patient begins to seize, the emergency medical technician will administer a first-line intravenous (IV) benzodiazepine (BDZ), such as diazepam, lorazepam or midazolam (Silbergleit, Durkalski et al. 2012), which is done either at the scene of the seizure or in the ambulance. If this is unsuccessful at abating the seizure, additional doses of the first-line therapy will be administered in the emergency room. Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line therapy, which is an IV anti-epileptic drug (AED) such as phenytoin or valproic acid (Novy, Logroscino et al. 2010; Shorvon 2011; Hocker, Britton et al. 2013).

Approximately 20-30% of patients refractory to first-line treatment will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to approximately 70-80% of patients who receive second-line therapy refractory to that therapy.

If a patient's SE continues after administration of BDZs and AEDs, the subject is diagnosed as having refractory status epilepticus (RSE), which must be treated quickly to terminate the seizure activity, maintain the patient's airway, and prevent cerebral damage. RSE patients are immediately admitted to the Intensive Care Unit (ICU) and placed in a

medically-induced coma to stop all seizure-related activity. The drugs used to induce coma are continuously-infused IV agents, commonly propofol, midazolam, or pentobarbital, referred to as third-line agents (Brophy, Bell et al. 2012).

The RSE patient is continually monitored using electroencephalography (EEG) to ensure burst suppression is achieved. Burst suppression is a pattern of brain waves seen on an EEG, characterized by periods of activity alternating with periods of little or no activity in the brain, informing medical personnel of the effectiveness of the medically-induced coma. The goal of burst suppression is to allow the brain and corresponding neuronal tissue to restore function and reset to normal pre-seizure levels.

### **3.2.1. Epidemiology of RSE**

Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line AED therapy. In turn, approximately 20 – 30% of these patients treated with AEDs will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to 28% of the total estimated SE patient population refractory to second-line therapy. Based on the previously-cited estimated incidence in the US, this means that there are up to 42,000 incident cases of RSE in the USA, annually (DeLorenzo, Pellock et al. 1995).

### **3.3. Super-refractory SE**

After 24 hours of burst suppression, the patient is weaned off of the third-line therapy. If the weaning is unsuccessful (neuronal activity has not returned to normal), the third-line agent is re-administered or a different third-line agent is started, and the patient is considered to be in super-refractory status epilepticus (SRSE) (Chapman, Smith et al. 2001; Shorvon 2011; Brophy, Bell et al. 2012). SAGE-547 is being developed as an adjunct to third-line therapy in patients in RSE who have failed standard treatment. In this protocol, the term “RSE that has failed standard treatment” is deemed to be equivalent to the term “SRSE” and the two may be used interchangeably.

#### **3.3.1. Epidemiology of SRSE**

The incidence of SRSE is very poorly understood, mainly because the diagnostic codes used for SE do not generally differentiate its nature as responding or refractory to treatment. Based on the variable reporting of outcomes data, the incident cases of SRSE could represent between one and two-thirds of the RSE patients (Novy, Logroscino et al. 2010; Ferlisi and Shorvon 2012; Hocker, Britton et al. 2013; Sutter, Marsch et al. 2013). More detailed epidemiology studies are needed to better elucidate the proportion of RSE patients whose condition becomes super-refractory. A recent review of ICU discharge data in the USA suggests an annual incidence of approximately 35,000, based on patients who required at least three days in the ICU for SE [Sage data on file].

#### **3.3.2. Outcomes of SRSE**

SE has varying degrees of mortality depending on the underlying etiologies. Table 4 outlines the acute mortality in patients with SE by etiology (Neligan and Shorvon 2010). The mortality rate of SRSE is estimated to be 30% to 50% using current standard of care.

The causes of death from SE (and therefore SRSE) are heterogeneous, resulting from neuronal cell death, complications of underlying medical conditions, or adverse effects of the current standard treatments. Prognosis worsens and mortality increases with longer duration of SE, i.e.

with SE that develops into RSE or SRSE (Neligan and Shorvon 2010), and with longer duration of medically-induced coma (Ferlisi and Shorvon 2012). There is an obvious unmet medical need to improve upon the current standard of care treatment regimens.

Morbidity is high and survivors have outcomes ranging from poor function to vegetative state (Shorvon 2011). Approximately one third of patients with RSE and SRSE will recover, but with chronic neurologic or other deficits (Neligan and Shorvon 2010; Hocker, Britton et al. 2013). In all, it is estimated that less than 25-30% of all SRSE patients have a favorable functional outcome.

**Table 4: Approximate Mortality of Status Epilepticus in Different Etiologies**

Underlying Etiology	Associated Acute Mortality in Patients with SE (%)
Drug reduction/withdrawal, poor AED compliance, or low AED levels	0-10
Cerebrovascular Disease	20-60
Metabolic Disorders	10-35
Acute CNS Infection	0-30
Anoxia	60-100
Alcohol Abuse	0-10
Head Trauma	0-25
Drug Overdose/Toxicity	10-25
Brain Tumors	0-20
Cryptogenic/Idiopathic	5-20

### 3.3.3. Unmet Medical Need in Super-refractory Status Epilepticus

Treatment approaches for SRSE consist of diagnosis and treatment of underlying medical conditions, adding and changing anti-seizure drugs, and repeated attempts at weaning from IV anesthetic agents. Treatment of SRSE has three aims:

- to prevent excitotoxicity, which begins within 24 hours of SE onset;
- to prevent cerebral damage by initiating neuroprotective burst suppression;
- to prevent the complications of extended periods of anesthesia or unconsciousness (Shorvon 2011).

Currently, there are no therapies that have been specifically approved for RSE or SRSE. The primary drugs used to induce coma are continuously infused IV anesthetics such as propofol, midazolam, or pentobarbital, known as third-line agents. Use of these drugs to control SRSE has only been studied in small retrospective reviews or small prospective studies without controls (Hocker, Britton et al. 2013) therefore there is no agreement on which drug is optimal nor on an optimal dosing regimen for the treatments that are used.

The most common adverse effect of the third-line agents is hemodynamic instability; in addition, they are not universally effective, with breakthrough seizures and withdrawal seizures requiring

dose adjustments and changes in third-line agent(s). The drug thought to be most effective in SRSE, pentobarbital, is also associated with the most toxic adverse effect profile, comprising decreased blood pressure and cardiorespiratory collapse (Claassen, Hirsch et al. 2002). The ability to wean patients successfully off the third-line agents as quickly as possible is therefore paramount, and an adjunct to SRSE treatment that enhances the success of the third-line agents and supports their successful weaning in a short timeframe would be an important addition to the therapeutic armamentarium. Preliminary clinical data show that SAGE-547 has been a successful adjunct to third-line therapy in this regard.

### 3.4. SAGE-547 Injection

Allopregnanolone is an endogenous, naturally occurring neuroactive steroid formed in the corpus luteum of the ovary, adrenal cortex and central nervous system (CNS) (Holzbauer, Birmingham et al. 1985; Paul and Purdy 1992; Ottander, Poromaa et al. 2005). It is a metabolite of progesterone created by the actions of 5- $\alpha$  reductase and 3- $\alpha$  hydroxy-steroid dehydrogenase. Allopregnanolone is a potent positive allosteric modulator of both synaptic and extra-synaptic GABA<sub>A</sub> receptors.

SAGE-547 Injection (allopregnanolone aqueous formulation in Captisol<sup>®</sup>) is being developed for the treatment of patients in RSE who have not responded to standard treatment. SAGE-547 Injection is a solution of 5 mg/mL allopregnanolone in Sterile Water for Injection (SWFI), USP and 250 mg/mL betadex sulfobutyl-ether sodium, NF. It is further diluted with Sterile Water for Injection, USP (SWFI) in IV bags to achieve an allopregnanolone concentration of approximately 1.67 mg/mL in an approximately isotonic solution and will be administered intravenously.

#### 3.4.1. Scientific Rationale for SAGE-547 in SRSE

Ineffective recruitment of inhibitory neurotransmission, together with excessive neuronal excitation, likely plays a role in the initiation and propagation of the electrical disturbance occurring in SE. GABA ( $\gamma$ -aminobutyric acid), the major inhibitory neurotransmitter in the central nervous system (CNS), is released from GABAergic neurons and binds to several types of GABA receptors (GABA<sub>A</sub>, GABA<sub>B</sub>, and GABA<sub>C</sub>) on target neurons. GABA<sub>A</sub> receptors are macromolecular proteins that form a chloride ion channel complex and contain specific binding sites for GABA and a number of allosteric regulators, including barbiturates, benzodiazepines, and some anesthetic agents. GABA receptor-mediated inhibition contributes significantly to the normal termination of a seizure (Kapur and Macdonald 1997). SAGE-547 is a positive allosteric modulator of the GABA<sub>A</sub> receptor.

The importance of terminating seizure activity as soon as possible is underpinned by a growing body of evidence from research and clinical observation that SE becomes more difficult to control as its duration increases. It has been postulated that this occurs due to a mechanistic shift from inadequate GABAergic inhibitory receptor-mediated transmission to excessive N-methyl-D-aspartic acid (NMDA) excitatory receptor-mediated transmission (Kapur and Macdonald 1997). As prolonged epileptiform bursting results in a reduction of GABA<sub>A</sub>-mediated synaptic inhibition, antiepileptic treatments which rely on enhancing intrasynaptic GABA<sub>A</sub> neurotransmission become less effective the longer SE continues.

Furthermore, the constitutive process of synaptic GABA<sub>A</sub> receptor internalization is accelerated by the increased neuronal activity associated with seizures. These findings suggest that the rate of GABA<sub>A</sub> receptor internalization is regulated by neuronal activity, and its acceleration contributes to the reduction of inhibitory transmission observed during prolonged seizures (Kapur and

[Macdonald 1997](#)). Of note is that SAGE-547 binds to extrasynaptic as well as intrasynaptic GABA<sub>A</sub> receptors; extrasynaptic receptors remain active with ongoing seizure activity, resulting in a putative mode of action for SAGE-547 in SRSE.

Status epilepticus induces cerebral damage that includes neuronal cell necrosis, gliosis, and network reorganization. The major cause of cell death in cerebral damage is excitotoxicity, which is initiated by glutaminergic receptor over-activation, causing calcium to flood the cell, thereby leading to apoptosis and necrosis. This process is initiated within a few hours of the start of seizure activity, and provides the medical imperative to terminate SE as quickly as possible. To prevent the consequences of the excitotoxicity cascade, it is recommended that anesthesia be initiated within 1-2 hours of onset of seizures at doses designed to induce EEG burst suppression ([Shorvon and Ferlisi 2011](#)).

### **3.4.2. SAGE-547 Clinical Program in the Treatment of SRSE**

The current SAGE-547 development program includes:

- an ongoing Phase 2 open-label trial, Study 547-SSE-201;
- this proposed Phase 3 randomized, double-blind, placebo-controlled trial, Study 547-SSE-301;
- a planned open-label, expanded access protocol, Study 547-SSE-302;
- a number of EINDs for SAGE-547 in patients with SRSE.

The designs of these studies are all similar, with a five to six day infusion of SAGE-547 (or placebo), during which time attempts are made to wean the subject off all third-line agents. In the Phase 3 studies, those subjects who cannot be weaned off third-line agents while being administered SAGE-547 (or placebo) will be eligible for a second open-label infusion of SAGE-547 at a higher dose, which is also being employed for the latter patients being enrolled in the Phase 2 study. Follow up of subjects is for 21 – 30 days after the first infusion of study medication.

### **3.4.3. Data from the SAGE-547 Development Program**

The data from 30 subjects included in the on-going clinical evaluation of SAGE-547 for the treatment of adults and children with SRSE clearly offers preliminary evidence that SAGE-547 could provide substantial and clinically significant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate. These subjects comprise 20 from the ongoing Phase 2 trial (71% success rate in 12/17 evaluable subjects) and 10 subjects who received EIND treatments (78% success rate in 7/9 evaluable subjects).

Successful therapy of SRSE has been defined as “the SE is completely controlled by the therapy, without breakthrough of withdrawal seizures, or discontinuation due to side effects or death during therapy,” ([Ferlisi and Shorvon 2012](#)). By this definition, which is in accord with the efficacy assessments used in the overall clinical evaluation of SAGE-547, 19 of the 26 (73%) subjects with SRSE who completed the SAGE-547 infusion were treatment successes. As data collection is ongoing, this information is preliminary and subject to change upon further monitoring.

Published reports on RSE and SRSE have stated mortality rate ranges from 35% to 65%. The underlying etiologies of SE in the 547-SAGE-201 study and EINDs are heterogeneous, and each

one conveys a different risk of mortality and longer term morbidity. However, the death rate in subjects who have received SAGE-547, 6 out of 30 (20%) subjects, appears to be lower than the published rates. None of the deaths were considered related to SAGE-547: brain tumor, organophosphate toxicity, respiratory failure, respiratory arrest due to ventilator support withdrawal, and breast cancer.

In the Phase 2 study, 20 SAEs (15 non-fatal) have been reported in 13 (65%) subjects, and of these 3 events in 2 subjects (10%) were considered by the investigator to be related to SAGE-547: pulmonary emboli and tracheostomy dehiscence/infection. The Sponsor did not consider these events to be related to SAGE-547, rather to the underlying disease states. Four of the 20 subjects (20%) experienced AEs considered possibly related to SAGE-547 by the investigator, namely moderate myopathy and severe pulmonary emboli in 1 subject, moderate tracheostomy dehiscence and tracheostomy infection in 1 subject, moderate thrombocytosis in 1 subject and moderate BUN, ALT and AST elevation in 1 subject.

Review of the most current safety data from 547-SAGE-201 reveals that there were changes in serum chemistry, hematology, and urinalysis during the study, but that none of those changes were assessed as related to SAGE-547. There were also no SAGE-547-related changes to vital signs.

Despite the heterogeneity in the underlying causes of SE, the ages of the subject, comorbidities, which normally complicate the treatment of SE, and the fact that all subjects had failed current standard of care treatment, a large majority of subjects had a successful therapy outcome, with discontinuation of all third-line agents and resolution of SE.

Refer to the Investigational Brochure for further information on the pre-clinical and clinical data supporting the use of SAGE-547 in SRSE.

### **3.5. Study Rationale - SAGE-547 in SRSE**

#### **3.5.1. Justification for the Control Group**

Although SAGE-547 has demonstrated extremely promising activity in subjects with SRSE, both in the Phase 2 study and during the EINDs, these have been open-label investigations with no control data for comparison. Generally in the literature there are few data describing the success rates of wean attempts of third-line agents, and few comparative data on the effectiveness of the three main third-line agents, propofol, pentobarbital, and midazolam.

Several options for a control group in Study 547-SSE-301 were considered:

- No control group was thought to be unacceptable since there are no reliable published data on success rates in this population that could be used for broad comparisons;
- An active control was considered but found to be impractical since none of the third-line agents are approved for their use in SRSE, no standardized dosing regimens or treatment guidelines have been adopted for the management of SRSE, and clinicians were unlikely to agree which of the available third-line agents would be reserved for the active control arm;
- Historical controls were considered but abandoned because of the practical difficulties of obtaining high quality data, the lack of ability to prospectively match cases, and a suspicion that clinical practice in the standard of care of SRSE is evolving, mandating the use of prospective, concurrent control data;

- Comparison to standard of care alone was considered as a feasible design. However, in a field where no widely adopted treatment guidelines exist, there was a concern that knowledge of the treatment group (SAGE-547 plus standard of care versus standard of care alone) would alter the behavior of the investigators such that they could be more aggressive with weaning in the SAGE-547 group;
- Placebo control is not without its challenges since the preliminary efficacy data for SAGE-547 show that the compound exerts central pharmacological effects and is associated with positive outcomes in around 70% of patients. There is therefore a potential ethical concern about administering placebo to desperately ill patients who have often exhausted all treatment options for SRSE. This concern has been addressed in two ways: firstly all patients receive current standard of care; secondly, all subjects who fail to be weaned from their third-line agents at the end of the blinded infusion of study drug will be administered open-label SAGE-547 without un-blinding their initial treatment allocation, so treatment with the investigational product is not denied, but delayed about a week in the setting of ongoing receipt of full current standard of care.

It was therefore decided that a blinded, placebo-controlled design was appropriate for Study 547-SSE-301.

### **3.5.2. Justification for the Dose Regimen**

The standard dose regimen has been studied in 19 subjects in the 547-SSE-201 Phase 2 trial; the average peak plasma concentration of SAGE-547 at the end of the loading dose was approximately 144 ng/ml. The average plasma concentration during the maintenance infusion was approximately 70 ng/ml. At these concentrations, there were no clear safety signals although two-thirds of subjects experienced an SAE and there were four deaths, all related to the underlying comorbid conditions. The standard dosing regimen was associated with an approximate 70% successful treatment outcome. For these reasons, the standard dosing regimen has been adopted for the initial SAGE-547 infusion to be compared in a blinded fashion to placebo.

In the 547-SSE-201 trial, three subjects have thus far received the higher dose regimen. This dose regimen has also been well tolerated. The average peak plasma concentrations at the end of the loading dose for both dosing regimens will be in the same range, as the loading dose is the same for both regimens. The average plasma concentrations observed during the higher maintenance dose are 102 ng/ml (n=2). The rationale for adopting the higher dose regimen as the open-label infusion of SAGE-547 for subjects who are retreated in this 547-SSE-301 trial is that those who fail on the standard SAGE-547 dose regimen are afforded the opportunity to have access to a higher dose. The justification to also administer the higher dose regimen to failures on placebo is that the regimen has thus far been well tolerated, and this methodology preserves the blind for the initial infusion.

A five-day dosing regimen with SAGE-547 was investigated in the Phase 2 study, 547-SSE-201. There were some cases when weaning off all third-line agents was not possible within 48 hours, but weaning was completed after the end of the infusion of SAGE-547. For this reason, the duration of dosing with SAGE-547 has been increased from 120 hours (five days) in Phase 2 to 144 hours (six days) in this Phase 3 study.



### 3.5.3. Rationale for Genetic Testing Sub-study

Sage Therapeutics intends to perform genetic research in the SAGE-547 development program in order to explore how genetic variations may affect the metabolism and activity of SAGE-547. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials, and, possibly, to genetically-guided treatment strategies for optimizing decision making with respect to individual benefit:risk. Participation of subjects in genetic research as part of the overall clinical study is optional.

### 3.6. Benefit-Risk Evaluation of the Present Study

Previous reports of human administration of exogenous allopregnanolone indicate that for exposures in men and women up to 150 nM, the most commonly reported AEs were sedation (recorded as sleepiness or tiredness), feelings of intoxication (like alcohol), flushing, and mild headache (Timby, Balgord et al. 2006; van Broekhoven F, T et al. 2007). No SAEs were reported (Navarro, Kaddouz et al. 2003; Timby, Balgord et al. 2006; van Broekhoven F, T et al. 2007; Kask, Backstrom et al. 2008; Kask, Backstrom et al. 2009; Timby, Hedstrom et al. 2011a). In view of the reduced consciousness and sedation of study subjects at entry into this protocol, none of these previously-reported events are likely to impact subjects in this study.

To date, in the SAGE-547 Phase 2 study and the EIND subjects, a majority of subjects demonstrated a successful therapy outcome (>70%). The majority in the clinical trial (65%) have also experienced SAEs, but none has been considered related to SAGE-547 by the Sponsor (SAEs in 2 subjects (10%) were considered possibly related by Investigator). Five deaths have been reported in 30 subjects (20%), all related to the underlying cause of SRSE and not related to SAGE-547 – this is in the context of published mortality rates between 35% and 65%. These preliminary data suggest that SAGE-547 has the potential to provide clinically relevant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate.

The underlying etiologies of SE are heterogeneous, and each one conveys a different risk of mortality. Subjects who survive SRSE still have a high risk of severe morbidity (Neligan and Shorvon 2010). The subjects treated with SAGE-547 in Study 547-SSE-201, are heterogeneous in factors such as age and etiology of SE, factors that usually complicate treatment and can increase morbidity and mortality. Even with this heterogeneity, the preliminary efficacy and safety data for SAGE-547 are very encouraging, and the mortality rate suggests that the risk to benefit assessment of this treatment rests on the side of benefit.



## **4. ETHICS**

### **4.1. Institutional Review Board or Independent Ethics Committee**

This protocol will be reviewed and approved by the Institutional Review Board (IRB) where the study is conducted. The IRB will meet all FDA requirements governing IRBs (CFR, Title 21, Part 56).

### **4.2. Ethical Conduct of the Study**

The Sponsor, the Medical Monitor, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable ICH and GCP guidelines, and must also conduct the study in accordance with local regulations.

### **4.3. Subject Information and Informed Consent**

Subjects prospectively enrolled in this study will be unable to give consent. Therefore, consent will be given by proxy by a legally authorized representative (LAR). Written informed consent is required for each subject prior to any testing under this protocol not considered standard of care, including screening tests and evaluations. Should a subject gain the ability to sufficiently comprehend the situation and consent during the course of the study, written informed consent or verbal assent will be documented as required or recommended by the institution's IRB.

The form of consent to be obtained will depend on the condition of the subject as determined by the Principal Investigator. The informed consent form (ICF), as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50.

It is the responsibility of the Investigator to obtain consent and to provide the subject's LAR with a copy of the signed and dated informed consent form. The informed consent form for subject participation must also be available as part of the subject file for review by the site's dedicated study monitor or any authorized auditor of the Sponsor or regulatory authorities.

All ICFs used in this study must be approved by the appropriate IRB and by the Sponsor. The ICF must not be altered without the prior agreement of the relevant IRB and the Sponsor.

### **4.4. Ethical and Regulatory Considerations for Pharmacogenetic Sub-study**

#### **4.4.1. Informed Consent for Pharmacogenetics**

The genetic component of this study is optional and subjects may participate in other components of the main study without having to agree to participate in the genetic component. If subject chooses to participate in the genetic component of the study, the subject or LAR must sign and date a specific consent form for the genetic component of the study in addition to the main study consent form. The principal investigator(s) is responsible for ensuring that consent is freely given and that the subject understands that they may discontinue from the genetic aspect of the study independent of their decision to remain within or withdrawal from the main study.

#### **4.4.2. Subject Data Protection Relative to Pharmacogenomics**

Sage Therapeutics will not provide individual genotype results to subjects, their family members, their general physician, their employer or any insurance company unless required to do so by law. While extra precautions will be taken to preserve confidentiality and to prevent genetic data from being linked to an individual's identity outside of a restricted access site, in certain exceptional situations (e.g. in case of a medical emergency or as a consequence of a specific regulatory need), certain individuals may see both genetic data and the personal identifiers of a subject; however in all cases a subject's medical information and genetic files will remain physically separated.

### **5. STUDY OBJECTIVES**

#### **5.1. Primary Objective**

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult and pediatric subjects with SRSE, and for the response to endure at least 24 hours after cessation of the SAGE-547 or placebo infusion (primary response).

#### **5.2. Secondary Objectives**

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in Clinical Global Impression Scale between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

#### **5.3. Safety Objectives**

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;

- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, temperature, and weight);
- d. ECG parameters;
- e. Mortality.

## **5.4. Other Objectives**

1. To evaluate the impact of retreatment with a higher dose of SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol<sup>®</sup> and identified SAGE-547 metabolite plasma concentrations;
3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;
6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS) (age  $\geq 17$  years).

## **6. ENDPOINTS**

### **6.1. Primary Endpoint**

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### **6.2. Secondary Endpoints**

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) and to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;

6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### **6.3. Safety Endpoints**

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, temperature, and weight);
4. ECG parameters;
5. Mortality.

### **6.4. Other Endpoints**

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who fail to respond to their randomized double blind treatment and are retreated with a higher dose of SAGE-547;
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol<sup>®</sup> and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS) (age  $\geq 17$  years).

## **7. INVESTIGATIONAL PLAN**

### **7.1. Overview of Study Design**

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

Figure 1 provides an overview of the study design and Figure 2 gives the details of treatment and follow-up on the active treatment arm. Patients will follow one of three paths to entry to the study. The first path is for patients who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst suppression with a third-line agent. These patients will be consented for the study after admission to the intensive care unit, but before any third-line agents are administered for burst suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental

incapacity from the status epilepticus, and so consent will be obtained from their LAR. Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours. Once burst suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of study drug.

The second path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst suppression pattern on the EEG. These patients may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of study drug.

The third path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These patients may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo. Burst suppression must be maintained for the first 12 hours of the infusion of study drug.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within six hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. Randomization will be stratified by concomitant pentobarbital use (yes or no) and number of previous third line agent wean attempts prior to randomization (one vs two or more).

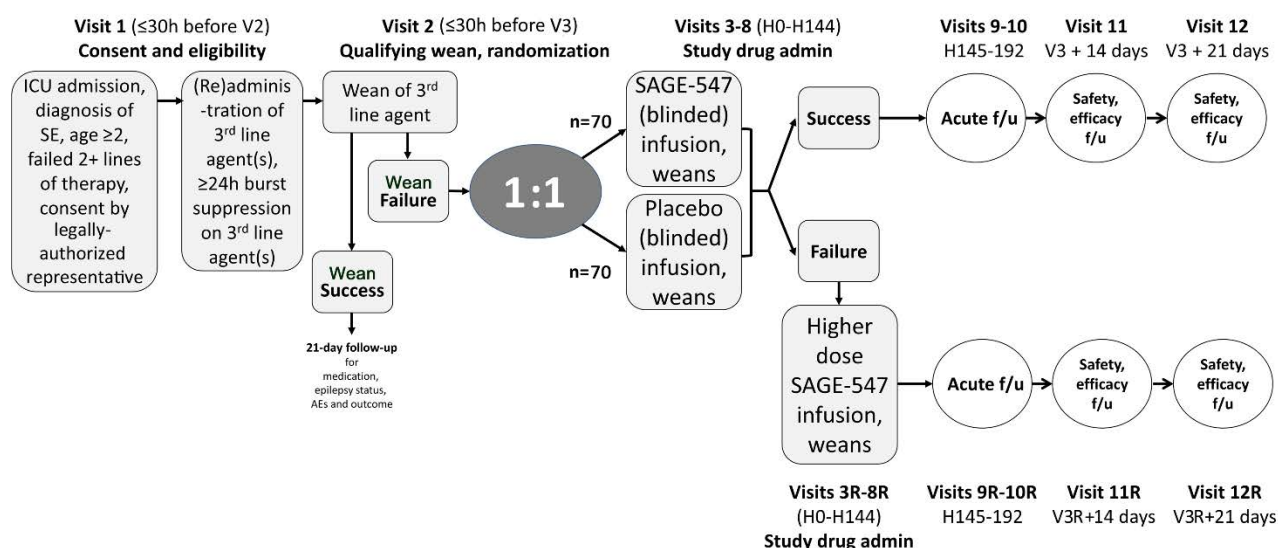
The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as the ability to wean the subject off all third-line agents before the end of the first infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication. Subjects must also have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) at the end of the primary endpoint assessment period as determined by EEG in order to be deemed a success. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#), [Table 2](#) and [Table 3](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. Eligibility for retreatment must be confirmed in writing by the medical monitor prior to the open-label infusion starting. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo will all subsequently be eligible to be administered SAGE-547 at the higher dose.

**Figure 1: Study Design**



## 7.2. Trial Conduct

This study will be conducted according to the principles of the World Medical Association Declaration of Helsinki and most recent amendment (2008), and in compliance with the protocol

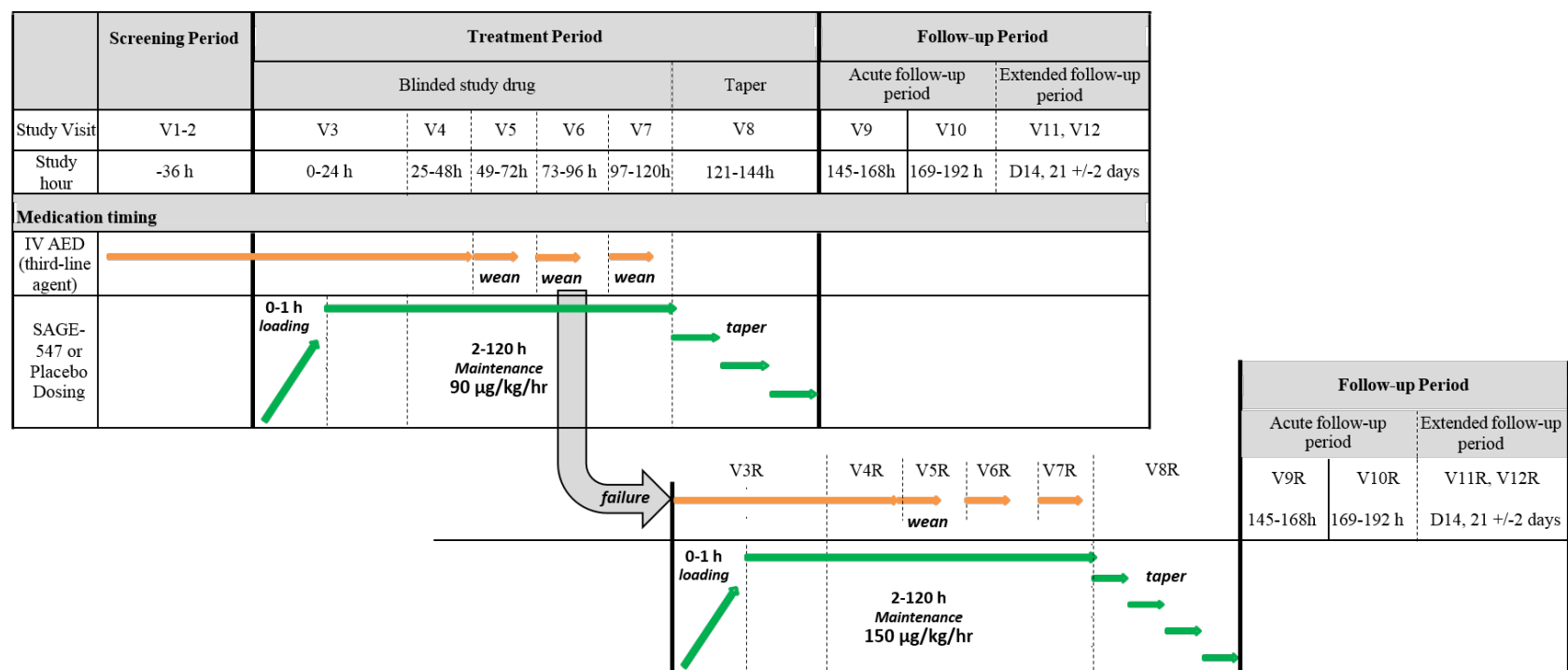
approved by the IRBs/Independent Ethics Committees (IECs), and in accordance with ICH Guidelines on GCP standards.

### **7.3. Blinding and Randomization**

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo). Details of the dynamic randomization process will be included in the SAP.

The randomized portion of the study will be blinded, with the two treatment products (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

The second infusion of SAGE-547 will be administered on an open label basis to subjects who failed the primary endpoint wean.

**Figure 2: Details of Treatment Administration and Follow-up**



## 8. SELECTION AND WITHDRAWAL OF SUBJECTS

The study will randomize 140 patients at up to 150 sites. All subjects deemed eligible to enroll must have written Medical Monitor approval on a case-by-case basis prior to undertaking the qualifying wean.

### 8.1. Inclusion Criteria

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects two (2) years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; *or* who have previously failed one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst suppression pattern; *or* who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst suppression pattern.

### 8.2. Exclusion Criteria

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy.
4. Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing underlying neurological disorder.
5. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis but for whatever reason, dialysis is not planned or non-continuous dialysis planned (that would not adequately remove Captisol<sup>®</sup>);
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the experience of the investigator, is less than 30 days;
  - e. a do not resuscitate (DNR) order.

6. Subjects who are being administered more than three third-line agents concomitantly or for whom the qualifying wean cannot be completed within 24 hours or who are being administered a third-line agent for indications such as raised intra-cranial pressure that would preclude weaning according to this protocol.
7. Subjects with a living will that does not allow heroic measure.
8. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
9. Subjects who have been enrolled in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not withdraw or complete and then re-enroll).

### **8.3. Selection and Consent of Subjects for Pharmacogenetic Substudy**

All subjects will be asked to participate in pharmacogenetic research; however, participation in research is voluntary and a subject can decide to decline his/her participation without penalty or loss of benefit. Participation or lack thereof will not be a cause for exclusion from any aspect of the main study. In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **8.4. Subject Withdrawal / Study Termination**

#### **8.4.1. Withdrawal/Discontinuation of Individual Subjects**

The reasons for study drug discontinuation and/or subject withdrawal from the study must be recorded in the subject's electronic case report form (eCRF). The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject has been discontinued/withdrawn due to an AE.

##### **8.4.1.1. Withdrawal from the Study**

Subjects or their LAR may withdraw subjects from the study at any time for any reason without compromising the subject's medical care. The Investigator will also withdraw subjects upon the request of Sage Therapeutics or upon termination of the study.

Subjects who withdraw from the study prior to Visit 10 (or 10R) should complete the procedures scheduled for the day of study drug taper (hour 121-144; Visit8/8R) on the day of their withdrawal, including the SAGE-547 taper schedule, with the addition of the mortality assessment from Visit 12/12R. Subjects who withdraw from the study after Visit 10/10R should undergo study procedures as outlined for Visit 12/12R on the day of their withdrawal. In all cases, the reason for subject withdrawal will be recorded in the eCRF.

Withdrawal of subjects for any reason should be discussed with the Medical Monitor.

##### **8.4.1.2. Discontinuation of Study Drug**

If it is necessary to discontinue the study drug earlier than planned, subjects should continue to be followed per protocol to capture safety and efficacy assessments for the duration of the study period.

The investigator may withdraw the subject from the study drug for the following reasons:

- Upon subject's or LAR's request
- The subject or LAR is unwilling or unable to adhere to the protocol-specified visits
- The subject experiences an intolerable adverse event
- During the course of the study, the subject develops symptoms or conditions listed in the exclusion criteria.
- Other medical reason, at the discretion of the Investigator and/or the Medical Monitor

Subjects who discontinue the study due to an AE considered related to study drug should be followed until the event is resolved, considered stable, or the Investigator determines the event is no longer clinically significant. Study drug discontinuation due to AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

#### **8.4.2. Study Termination**

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of AEs or other findings suggesting unacceptable risk to subjects, administrative or operational reasons. In the event of study termination, Sage Therapeutics will provide written notification to the Investigator. Investigational sites must promptly notify their IRB and initiate withdrawal procedures for participating subjects.

## **9. INVESTIGATIONAL PRODUCT**

### **9.1. Identity of Investigational Product**

SAGE-547 Injection (allopregnanolone)

### **9.2. Clinical Supplies**

#### **9.2.1. SAGE-547**

Adequate supplies of SAGE-547 Injection and materials for intravenous administration will be provided to each site.

SAGE-547 Injection is a clear, colorless sterile solution of allopregnanolone intended for intravenous injection. SAGE-547 Injection is an aqueous solution of 5 mg/mL allopregnanolone in 250 mg/mL Captisol® (betadex sulfobutyl-ether sodium, NF). It is presented either un-buffered or buffered with 10 mM citrate at a pH of 6.0 in either 20 mL or 50 mL vials. SAGE-547 is further diluted according to the Pharmacy Manual to achieve an approximately isotonic solution and will be administered intravenously.

No preservatives are included in the drug product, which is intended to be used as a single-use vial. All inactive components (excipients) used in the formulation are compendial grade and conform to current USP/EP, and include sodium citrate, citric acid and betadex sulfobutyl-ether sodium (Captisol®).

**9.2.2. Placebo**

Placebo will be identical to SAGE-547 and presented in identical vials. Placebo will be manufactured in a similar way to SAGE-547 and comprises all excipients but no SAGE-547.

**9.2.3. Blinding**

The vials of SAGE-547 and placebo will be identical in every way so that they are indistinguishable by the pharmacist, investigator, anyone treating or managing the patient, the monitors, and the sponsor. In this way the first infusion of study drug administered to each patient will be double-blind.

For the blinded study drug infusions, subject-specific dosing kits will be provided. These dosing kits will be pre-labelled with kit number for the first blinded infusion. For the second-infusion, open-label kits will be provided, which will require subject assignment by the pharmacy for reconciliation purposes. The study kits must be stored under refrigerated conditions (2-8 °C). IV administration bags and lines may be provided for the blinded and open-label infusions. Refer to the Pharmacy Manual for additional details.

The label for the SAGE-547 Injection vials will include standard product identification information according to the Code of Federal Regulations, 21CFR 312.6. All study labels will also contain the following statement:  
Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use.

**9.3. Preparation of SAGE-547 or Placebo Injection for Dosing**

The Pharmacy will be responsible for preparing the blinded and open-label study drug for subject dosing. The prepared admixture will be assigned a room temperature (20-25 °C) storage shelf life of 30 hours from time of compounding.

SAGE-547, which is hypertonic, will require dilution with SWFI to achieve an approximately isotonic solution according to the instructions provided in the Pharmacy Manual. Exactly the same procedures will be used to prepare the placebo admixture, so that all site staff remain blinded as to treatment allocation for the first infusion of study drug. SAGE-547 Injection is not intended to be administered to patients undiluted.

Refer to the Pharmacy Manual for specific instructions regarding infusion preparation.

**9.4. Administration and Accountability**

The Pharmacy will maintain accurate records of all investigational product supplies. Accurate records will be kept regarding the volume of SAGE-547 Injection or placebo used for each IV preparation, as well as the required infusion rate or rates, and the date and time of preparation. Reasons for departure from the expected dosing regimen must also be recorded. To satisfy regulatory requirements regarding drug accountability, all study medication will be reconciled in full. Refer to the Pharmacy Manual for additional details.

## 10. TREATMENT OF SUBJECTS

### 10.1. Dosing Schedule (Blinded Infusions)

SAGE-547 Injection or placebo will be administered according to the dosing schedules in [Table 5](#). The infusion rates to accomplish these  $\mu\text{g/kg/h}$  doses will be calculated according to the weight of the subject. The infusion rates will be applied to blinded study drug for the first infusion of study medication.

**Table 5: SAGE-547 or Placebo Dosing Schedule**

Hour	Type and Duration of Study Drug Infusion	Description
H1	One hour loading Infusion	300 $\mu\text{g/kg/h}$
H2 – H120	119 hour maintenance infusion	90 $\mu\text{g/kg/h}$
H121 – H128	8 hour taper	65 $\mu\text{g/kg/h}$
H129 – H136	8 hour taper	45 $\mu\text{g/kg/h}$
H137 – H144	8 hour taper	25 $\mu\text{g/kg/h}$

### 10.2. Dosing Schedule (Open-Label Infusions)

If a subject fails wean from third-line agent(s) or requires re-instatement of third-line therapy within 24 hours of discontinuing the initial infusion of study drug, SAGE-547 Injection will be re-administered according to the dosing schedule in Table 6. The infusion rates to accomplish these  $\mu\text{g/kg/h}$  doses will be calculated according to the weight of the subject. These infusion rates will be applied to SAGE-547 re-treatment for the open-label second infusions of study medication.

**Table 6: SAGE-547 Open Label Dosing Schedule**

Hour	Type and Duration of SAGE-547 Infusion	Description
H1	One hour loading Infusion	300 $\mu\text{g/kg/h}$
H2 – H120	119 hour maintenance infusion	150 $\mu\text{g/kg/h}$
H121 – H126	6 hour taper	125 $\mu\text{g/kg/h}$
H127 – H132	6 hour taper	95 $\mu\text{g/kg/h}$
H133 – H138	6 hour taper	65 $\mu\text{g/kg/h}$
H139 – H144	6 hour taper	35 $\mu\text{g/kg/h}$

### 10.3. Route of Administration

SAGE-547 Injection is intended for IV administration only. The compatibility of SAGE-547 with other drugs is unknown, and the product should be administered via a dedicated peripheral IV line using any Sage-supplied study-specific IV administration bags and lines. In order to preserve blinding, these instructions also apply to the blinded placebo infusions.

### 10.4. Treatment Period

The treatment period with double-blind SAGE-547 or placebo is six 24-hour periods (144 hours), which may encompass 6-7 calendar days. The retreatment period is of identical duration.

## **10.5. Concomitant Medications, Procedures and Treatments**

Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. All concomitant medications, procedures, and treatments should be documented throughout the study from Screening through Visit 12/12R and recorded on the eCRF.

SAGE-547 has demonstrated inhibitory effects on cytochrome P450 isoenzyme 2C9 (CYP2C9). Therefore, AEDs such as phenytoin and phenobarbital that are primarily metabolized by CYP2C9 should be closely monitored during SAGE-547 administration to ensure target exposures are maintained.

### **10.5.1. Concomitant AEDs**

Subjects may enter the study on AEDs, and be administered AEDs during the study. All of these must be recorded on the eCRF with details including date and time of starting and stopping each AED, the route of administration, changes in doses, and frequency of administration. In addition, details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the eCRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.

### **10.5.2. Concomitant Third-Line Agents**

All third-line agents (as defined in [Section 8](#)) administered since the diagnosis of SE will be recorded on the eCRF, whatever path the patient took for entry into the study. Details will include the name of the drug, the start and stop dates and times, and, after consent, the doses with start and stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

In addition, those changes in dose that constitute a wean attempt will be marked as such on the eCRF. In this way the start and stop dates and times of all wean attempts (see [Section 11](#) for definitions) will be recorded, as will the type of wean (QW, OW, or TW) and the outcome of the wean attempt (successful, failed and dose of this third-line agent increased or failed and this third-line agent stopped and another third-line agent started). Those wean attempts that occur after the TW up to and including Visit 12/12R will be marked “AW”.

Some third-line agents (such as propofol) are also used to induce sedation to facilitate a subject’s ability to tolerate the ventilator. For subjects requiring such sedation, propofol is the preferred agent unless there are contraindications. The eCRF will make clear from the indication for the third-line agent when it is being used for burst or seizure suppression and when it is being used as ventilator support or for another purpose. The investigator will add a note to the eCRF to justify that the doses used are appropriate for sedation and not for seizure or burst suppression. The doses used for ventilator support and other similar uses are usually much lower than those used for seizure or burst suppression, and use of these third-line agents for these other purposes does not constitute a wean failure under this protocol.

### **10.5.3. Concomitant Pressors**

The start and stop dates and times of all pressors will be recorded as well as the start and stop dates and times of all dose changes.

#### **10.5.4. Other Concomitant Medications**

All other concomitant medications must be recorded on the eCRF with details including date and time of starting and stopping, the route of administration, dose, and frequency of administration.

### **11. STUDY ASSESSMENTS**

#### **11.1. Efficacy Assessments**

##### **11.1.1. Primary Efficacy**

Success or failure will be determined, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo infusion and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the blinded (first) infusion of SAGE-547 or placebo. In addition, subjects must have evidence of physiologic brain activity (average EEG power at the end of Visit 9 of more than two microvolts) to be deemed to be successes. All subjects who fail to complete their infusion of randomized treatment or do not have at least one attempt during study treatment to wean off all third-line agents will be considered as “failures” for the primary endpoint.

##### **11.1.1.1. Weaning**

Third-line agents are anesthetic agents that are administered in order to reach a seizure or burst suppression EEG pattern. For the purposes of this study, third-line agents are defined as continuous intravenous infusions of pentobarbital, midazolam, propofol, and ketamine at maintenance doses alone or in combination sufficient to produce a burst suppression pattern on the EEG. The following are considered to be minimum maintenance doses of these agents that may be expected alone or in combination to achieve EEG burst suppression. If subjects are on lower doses than these and are not in EEG burst suppression for the 24 hours prior to the QW or the first 12 hours of the blinded study drug infusion, they will be considered to be screen failures/protocol violators and will exit the study.

- Pentobarbital: 1 mg/kg/hour
- Midazolam: 0.1 mg/kg/hour
- Propofol: 3 mg/kg/hour
- Ketamine 1.2 mg/kg/hour

The timing and nature of the third-line agent weans will be guided by the Clinical Standardization Guidelines for the study, and the clinical judgment of the investigator, and will always be primarily done in the best medical interests of the subject. Advice about weaning may be sought from the Clinical Standardization Team, a group of fellow investigators with experience of performing clinical trials in subjects with SRSE. The Clinical Standardization Team will be able to review EEGs in real time related to key study timepoints (qualifying wean, terminal wean, and the period after the end of the blinded study drug infusion) in order to provide advice about compliance with the Clinical Standardization Guidelines.

The following guidance for weaning applies to all weans of third-line agents undertaken during the study. These weans include the qualifying wean (QW); the terminal wean (TW), which is the

wean of the third-line agent if the subject is on only one third-line agent or the wean of the last third-line agent if the subject is on more than one third-line agent; the other weans (OW), which are the weans of the third-line agents other than the TW if the subject is on more than one third-line agent. The guidance also applies to additional weans (AW), which are the weans from third line agents that take place after the TW for the first blinded study drug infusion or the second open-label study drug infusion.

### **QW Guidance**

- Wean to be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace that third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Investigators should allow 24 hours to lapse after the end of a “successful” qualifying wean before finally declaring the QW a success. If a third-line agent needs to be re-instituted within that 24 hours, the QW is a failure, and the subject may then be randomized in the study.

### **OW Guidance**

- First OW should not begin before H49 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- If the subject is on two third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the TW. However the OW may be completed over a shorter or longer time period and may overlap if clinically indicated with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- If the subject is on three third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the wean of the second agent. The second agent should be weaned over 24 hours and that wean completed before starting the TW. However the OWs may be completed over a shorter or longer time period and may overlap if clinically indicated with each other and with the start of the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- All OWs should be completed before H96 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **TW Guidance**

- The TW is defined as the wean of the last third-line agent.



- If the subject is on one third-line agent, the TW should not begin before H49 and should begin no later than H97 after starting administration of study drug or starting the open-label infusion of SAGE-547. If the subject has had one or more OWs, the TW should ideally begin as soon as the last OW is complete but in any case not later than H97 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- The TW must be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace this third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.
- Every effort must be made to complete the TW before H120 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547, but the TW must be complete before H144 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

#### **AW Guidance**

- AWs will take place when medically indicated in the opinion of the investigator.
- Ideally the AW should take place over 24 hours, but completion may be over a shorter or longer time period than this. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.

#### **11.1.1.2. EEG**

Electroencephalographs (EEGs) that are representative of the intermittent or continuous EEG being used to support key investigator decisions will be collected at the following time points:

- A six-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst suppression for the second path to eligibility, and a variable pattern for the third path to eligibility.
- EEG will be performed to cover the qualifying wean (QWEEG). EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for the one hour after the end of the QW. The duration of the QWEEG will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s) or the decision to re-institute a third-line agent(s) at doses intended to induce burst suppression.
- EEG will be performed from three hours prior to the start of the blinded infusion to five hours after the start of the blinded infusion. This will be called the BIEEG. The intent of

this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG.

- EEG will be performed to cover the final or terminal wean of third-line agent (TWEEG). The TW is the wean of the final third-line agent during the blinded administration of study drug or the open-label infusion of SAGE-547; if the subject was on one third-line agent, the TW is the wean of that agent. If the subject was on three third-line agents, the TW is the wean of the third and final agent. EEG recording will start 30 minutes prior to the start of the TW, continue for up to 24 hours during the TW, and then continue for the one hour after the end of the TW. The duration of the TWEEG will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the final third-line agent or the decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity could not be managed using intermittent bolus doses of AEDs.
- EEG will be performed during the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 (TAEEG). The TAEEG is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the start of the taper (at Hour 119.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours during the taper, and then continue for the one hour after the end of the taper (to Hour 145 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547). The duration of the TAEEG will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity seen during the taper could not be managed using intermittent bolus doses of AEDs.
- EEG will be obtained to cover the end of the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 and the ensuing 24-hour period, during which the primary endpoint is assessed (PAEEG). The PAEEG is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the end of taper (at Hour 143.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours after the end of the blinded administration of study treatment or the open-label infusion of SAGE-547, and then continue for the one hour after the end of the 24-hour assessment period (to Hour 169 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547). The duration of the PAEEG will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity seen in the 24 hours following the end of the blinded administration of study treatment or the open-label infusion of SAGE-547 that could not be managed using intermittent bolus doses of AEDs.

In practice, most subjects are on continuous EEG monitoring or long periods of intermittent EEG monitoring. However, this protocol does not mandate continuous EEG monitoring and breaks from EEG monitoring to provide relief to the scalp from the irritating effects of the electrodes are advised, particularly in children, according to local practice. If a break in EEG monitoring is mandated by local practice guidelines at a time when one of the protocolled EEG segments is to be

collected, the break in EEG monitoring will take precedence, with the reason for missing the EEG reading noted on the eCRF. The EEGs obtained for the study are therefore part of the existing EEG record rather than being obtained de-novo at each timepoint. For timepoints where there might be some ambiguity, such as the TWEEG, the final EEG record is that of the final attempt to wean the last third-line agent, even if earlier attempts to wean that agent took place. In some cases (the TAEED and PAEEG, for instance), the EEG records will overlap, but different cuts are taken to service the different EEG record requirements.

The electronic EEG file will be de-identified, the date and time of the start and stop of the EEG and the subject number will be attached to the file, and the study time point will be indicated (CEEED, QWEEG, BIEEG, TWEEG, TAEED, and PAEEG). The PI will indicate on the eCRF what the EEG shows, as follows:

- For the CEEG, the PI will describe the EEG pattern that determined which path to eligibility the subject was on.
- For the QWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure on the qualifying wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the qualifying wean).
- For the BIEEG, the PI will note the date and time of the start of the EEG and the pattern seen on the EEG.
- For the TWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure on the terminal wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the terminal wean).
- For the TAEED, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst suppression before the end of the SAGE-547 infusion).
- For the PAEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst suppression in the 24 hours following the end of the SAGE-547 infusion).

A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm the PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period (average EEG power at the end of Visit 9 of more than two microvolts).

- All subjects will have the CEEG and QWEEG collected and stored, and the QWEEG read;
- Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;

- Those subjects randomized who are not retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read;
- Those subjects randomized who are retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion and the TWEEG, TAEED, and PAEEG related to the open-label study drug infusion collected and stored, and the QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read.

All EEG records may be subject to quantitative EEG analysis.

### **11.1.2. Secondary Efficacy**

#### **11.1.2.1. Clinical Global Impression Scale (CGI)**

The clinical global impression scales are often utilized in clinical trials to allow clinicians to integrate several sources of information into a single rating of the subject's condition. Both the CGI-Severity (Question 1, CGI-S) and the CGI-Improvement (Question 2, CGI-I) employ a 7-point Likert scale measuring severity of the disease state in the subject and improvement, respectively. All severity assessments after initiation of SAGE-547 treatment should consider the general state of the subject over the preceding week. The third question on the scale will not be employed in this trial, and where the scale states "mental illness", this means "physical illness" in this trial.

The CGI-S will be evaluated at Visit 1 and at the last visit, Visit 12 or 12R. The CGI-I will be evaluated at Visit 12 or 12R.

#### **11.1.2.2. Epilepsy Status**

At Visit 1, the diagnosis of epilepsy will be documented as a no/yes question. If there was a previous diagnosis of epilepsy, further details will be documented, including:

- Date of diagnosis;
- Details of anti-epileptic drugs currently being taken;
- Type of epilepsy;
- Seizure frequency in the past month.

Information about the current (index) episode of status epilepticus will be obtained at Visit 1:

- Date of onset
- Date of failure to respond to first line agent(s) and the name(s) of the agent(s)
- Date of failure to respond to second line agent(s) and the name(s) of the agent(s)
- Any previous treatment with third line agents and the response to those agents (details of the third line agent drugs and previous wean attempts will be recorded on the Third Line Agent Medication CRF)
- The cause of the index episode of status epilepticus
- If the subject was transferred from another hospital or from within the hospital, the reason for the transfer will be recorded (such as for study enrollment, due to lack of medical

options at original hospital or unit, due to lack of beds at the original hospital or unit, family request, other)

Previous (non-index) diagnosis of status epilepticus will be documented as a no/yes question. If SE did occur in the past, further information will be gathered, including:

- SE, RSE, or SRSE diagnosis, whichever was the most severe diagnosis for each episode;
- Cause;
- Treatment, including experimental treatments and need for intubation/ventilation;
- Dates of onset and duration if the episode of status epilepticus occurred in the past 12 months.

At Visit 12 or Visit 12R, the following information will be gathered:

- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of SE up to and including Visit 12 or Visit 12R;
- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of seizures (convulsive and non-convulsive) up to and including Visit 12 or Visit 12R;
- Number of separate episodes of SE after H144 at the end of Visit 8 or Visit 8R (no/yes); if yes,
  - SE, RSE, or SRSE diagnosis;
  - Cause;
  - Treatment, including experimental treatments and need for intubation/ventilation;
  - Dates of onset and duration.

Note that a separate episode of SE is defined as an episode of SE separated from other periods of status epilepticus by at least 24 hours.

- Diagnosis of epilepsy since Visit 11 or Visit 11R will be documented as a no/yes question. If a diagnosis of epilepsy has been made, further details will be documented, including:
  - Status as ongoing or new epilepsy since Visit 11 or Visit 11R after initiation of SAGE-547 treatment;
  - Details of anti-epileptic drugs currently being taken;
  - Type of epilepsy and seizure frequency in the past week.

## **11.2. Safety Assessments**

The safety and tolerability of SAGE-547 will be assessed using adverse events, clinical laboratory measures, vital signs, ECG intervals and morphology, and mortality. All safety assessments should be performed per hospital standard of care and will be collected periodically throughout the study according to [Table 1](#), [Table 2](#), and [Table 3](#) (Schedules of Assessments).

### **11.2.1. Adverse Events**

AEs will be collected after informed consent has been signed and prior to study-specific

screening procedures not considered standard of care, during subject preparation for SAGE-547 administration and through Visit 12 or Visit 12R. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™) coding system (current version). See [Section 14](#) for additional details.

### **11.2.2. Clinical Laboratory Tests**

Blood samples will be taken for hematology, and serum chemistry and GFR will be calculated at:

- Visit 1 and then at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.
- Blood samples will be taken at Visit 11 or Visit 11R for serum chemistry (renal panel only).

Urine samples (20 ml) will be taken for urinalysis and urine NAG analysis at:

- Visit 1 and at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.

These samples will be analyzed at a central laboratory; hour-to-hour medical decisions will be based on sampling for laboratory testing done outside the protocol as part of normal standard of care. GFR will be calculated using values from local laboratory tests.

Any out-of-range values will be flagged by the laboratory; the investigator will add a comment about whether the abnormality is clinically significant. Clinical significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

#### **11.2.2.1. Hematology and Serum Chemistry**

Hematology will include complete blood count (CBC) white blood cell count with differential, platelet count and red blood cell (RBC) count, hemoglobin and hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose.

#### **11.2.2.2. Pregnancy Test**

Females of child-bearing potential will be tested for pregnancy by serum pregnancy test at Visit 1. In this study, since an accurate history of menstruation in girls and menopause in older women may not be available at Visit 1, “child-bearing potential” is taken to mean any female aged 10 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy. Female subjects with a positive pregnancy test will be ineligible for study participation.

**11.2.2.3. Urinalysis**

Urinalysis will include assessment of protein, blood, leukocytes, glucose, ketones, urobilinogen, pH, and specific gravity.

**11.2.3. Vital Signs**

Blood pressure, heart rate, and temperature will be recorded at the following time points relative to the first infusion of study drug, and to the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547:

- Visit 1;
- At 0, +30, +60 minutes (+/-15 minutes) and +2, +4 and +8 hours (+/- 30 minutes) after the start of the infusion;
- At +24, +48, +72, +96, +120, +144, +168, and +192 hours (+/- 2 hours) after the start of the infusion.

**11.2.4. Weight and Height**

Weight and height will be measured at Visit 1 and weight will also be measured once during each 24 hour period of the first infusion of study drug, and of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547. These daily weights will be used to modify the dose of SAGE-547 if required.

**11.2.5. ECG**

12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours; at other times the allowed time window for ECGs is +/- 2 hours:

- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +128, +136, +144, +152, +160, and +192 hours after the start of the blinded (first) study drug infusion
- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +126, +132, +138, +144, +152, +160, and +192 hours after the start of the open-label (second) study drug

The heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm.

**11.2.6. Mortality**

Mortality will be recorded on the Visit 12 or Visit 12R case report form. If the subject has died, the following information will be collected:

- Date of death;
- Cause of death.

As accurate as possible cause of death will be collected, which will be further categorized as due to one of the following causes:

- SE;
- complications of long term intubation and third-line agent infusions;

- underlying cause of qualifying SE;
- co-morbidity existing at the time of the qualifying SE;
- new co-morbidity or trauma;
- study drug;
- other (specify).

### 11.2.7. Pharmacogenetic Samples

If a subject's LAR consents to pharmacogenetic sampling, a blood sample for genetic research will be collected at Visit 1 in order to avoid the possible introduction of bias through the exclusion of patients who may withdraw from study due to an AE (a subject population that may be of specific interest for subsequent genetic analysis). If for any reason a sample cannot be taken prior to treatment, a sample can be drawn at any point prior to completion with the restriction that no more than one genetic sample be taken per subject.

The objective of this research is to collect and store blood samples for possible DNA extraction and exploratory research into how genes or specific genetic variation may influence response (i.e. distribution, safety, tolerability, and efficacy) to SAGE-547. Specific genetic variations of interest include but are not limited to: classes of metabolizing enzymes (e.g. Cytochrome P450 supra-family genes), genes encoding enzymes involved in the production and metabolism of allopregnanolone (e.g. AKR1C4 (3a-hydroxysteroid dehydrogenase)), genes associated with the GABA receptor (e.g. GABRA1-A6, GABRB1-B3, GABRD, GABRE, GABRG1-3) and genes associated with the production and degradation of GABA.

Future research may suggest other genes or gene categories as candidates for influencing not only response to SAGE-547 but also susceptibility to disorders for which SAGE-547 is being evaluated. Thus, the genetic research may involve study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.

#### 11.2.7.1. Biological Sampling and Coding Procedures (Pharmacogenetics)

To ensure patient confidentiality, utmost care will be taken in the coding and storage of pharmacogenetic samples.

*Extraction and coding:* DNA will be extracted from the blood sample and the DNA sample will be assigned a unique number replacing information from sampling tube. The assigned DNA number will be used to identify the sample and its corresponding information within Sage Therapeutics or at any designated contract laboratory for the purpose of sequencing of other DNA specific analysis. No personal details sufficient for individual identification will be available to any person (internal or external to Sage Therapeutics) working with the DNA.

*Genotype/Phenotype Analysis:* Samples and data from genetic analysis will be coded. The link between subject enrollment / randomization code and DNA number will be maintained and stored in a secure environment with restricted access. The established link will be used to identify relevant DNA samples for analysis, facilitated correlation of genotype results with clinical data, allow regulatory audit, and to trace samples for destruction in case of withdrawal of consent.



### 11.2.7.2. Retention of Biological Samples for Pharmacogenetic Analysis

Extracted DNA is a finite research that is destroyed in the process of being analyzed. Primary blood samples from which DNA can be extracted will be stored and used until no further analyses are possible, a maximum storage period of 25 years from time of last subject last visit has been reached, or an individual or LAR withdrawals his/her or their consent.

### 11.2.8. Other Outcomes

#### 11.2.8.1. Pharmacokinetic Data

Formal plasma and urine analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS)). In addition, all samples will be analyzed for important SAGE-547 metabolites (if and when these are identified) and Captisol<sup>®</sup> concentrations.

#### Plasma Analysis

Plasma will be collected to assay for SAGE-547 concentrations at the following time points relative to the start of each infusion of study drug:

- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion.
- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open label SAGE-547 study drug infusion.
- All samples will also be analyzed for plasma concentrations of important metabolites of SAGE-547 if and when these are identified.
- All samples will also be analyzed for plasma concentrations of Captisol<sup>®</sup>.

The plasma samples will be drawn from the arm contralateral to that used for drug administration. Drawing samples from peripheral arterial or venous lines or from a central line is permissible. PK collection times should be adhered to as strictly as possible. The allowed time window for all samples is: pre-dose in the two hours prior to starting the infusion of study drug; samples up to and including 1h, +/- 5 minutes; subsequent samples, +/- 15 minutes. Subject-specific PK kits for sampling including instructions on collection and processing methods, and storage and shipping conditions, will be provided separately. To maintain the blind, all subjects will have samples taken as outlined above: subjects receiving SAGE-547 will have all samples analyzed for all analytes. Subjects on placebo may have samples analyzed to investigate endogenous allopregnanolone and metabolite concentrations, as well as Captisol<sup>®</sup> concentrations; experience with the plasma concentration data will determine if and which placebo samples are analyzed.

Each blood sample will be 3 ml in volume for adults and children weighing 30 kg or more, and 2 ml in volume for children weighing less than 30 kg. Separate aliquots will be obtained from

each sample to service the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum blood draw for PK analysis for a subject having two infusions of study drug will be 99 ml (66 ml for children weighing less than 30 kg).

Plasma PK parameters for SAGE-547 will be calculated where appropriate (e.g.,  $C_{max}$ ,  $C_{min}$ ,  $t_{max}$ ,  $AUC_{last}$ ,  $AUC_{\infty}$ ,  $CL_s$ ). In addition, similar PK parameters will be calculated for Captisol<sup>®</sup>. PK parameters for important metabolites of SAGE-547 may be calculated. An evaluation will be made of the feasibility of adopting a population-PK approach to assess drug-drug-interactions with SAGE-547 as victim of AEDs.

In addition, the Visit 9 sample may be analyzed for plasma concentrations of third-line agents.

### Other Analysis

If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations.

Full details of all pharmacokinetic analyses will be described in the Pharmacokinetic Analysis Plan.

### **11.2.8.2. Correlation of QT/QTc Changes and Plasma Concentrations of SAGE-547**

An analysis will be performed to determine whether there is any correlation between changes in QT/QTc interval and plasma concentrations of SAGE-547, in order to investigate any effect that SAGE-547 may have on QT/QTc interval.

### **11.2.8.3. Pharmacoeconomic Data**

At Visit 12 or Visit 12R, the following information will be collected: number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital. If the subject dies before Visit 12 or Visit 12R, data will be collected up to the date of death. The definition of “hospital” is the institution that the subject was initially treated in. If the subject is transferred to another hospital, that hospital would be the “discharge destination from the hospital” and the “number of days in hospital” would be the number of days in the initial treating hospital.

For those subjects discharged from hospital before Visit 12/12R, the following questions will be asked:

- On what study day was the subject discharged from hospital?
- What type of facility was the subject discharged to (another hospital, a rehabilitation center, a supported care facility, home, other)?
- How many days did the subject stay in this facility?

The following questions will be answered regarding the stay in the ICU and hospital:

- Was the subject still in the ICU at the end of Visit 10/10R?
- If the FOUR Score was  $\geq 12$  at Visit 10/10R and the subject was in the ICU at Visit 10/10R, what was the reason for the subject not being discharged from the ICU (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, other)?
- Was the subject still an in-patient in the hospital at the end of Visit 12/12R?

- If the FOUR Score was  $\geq 15$  at Visit 12/12R and the subject was in the hospital at Visit 12/12R, what was the reason for the subject not being discharged from the hospital (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, unsuitable home circumstances, other)?

#### **11.2.8.4. STESS**

The STESS will be assessed during Visit 1 in order to assess the severity of the status epilepticus.

#### **11.2.8.5. FOUR Score**

The Full Outline of UnResponsiveness or FOUR Score is designed to assess conscious level and unlike other scores, is suitable for subjects who are intubated. It assesses four domains of neurological function (eye responses, motor responses, brainstem reflexes, and breathing pattern).

The FOUR Score will be collected at the following time points relative to each infusion of study drug (the initial blinded infusion and the second open-label infusion if this is administered):

- baseline, +24, +48, +72, +96, +120, +144, +168, and +192 hours (all +/- 2 hours) after the start of the infusion, and at Visit 11/11R and Visit 12/12R.

#### **11.2.8.6. Glasgow Outcome Scale (GOS)**

The GOS is a relatively common assessment scale used to standardize descriptions of the objective degree of recovery from brain injury such as cerebral trauma, or in this case SRSE. It was first used in 1975 ([Jennett and Bond 1975](#)) and allows a prediction of the long-term course of rehabilitation to return to work and everyday life. The scale classifies subjects into 5 groups:

- Death
- Persistent vegetative state
- Severe disability
- Moderate disability
- Good recovery

The GOS will be assessed at Visit 12 or Visit 12R.

#### **11.2.8.7. Supervision Rating Scale (SRS)**

The Supervision Rating (SRS) measures the level of supervision that a patient/subject receives from caregivers. The SRS rates level of supervision on a 13-point ordinal scale that can optionally be grouped into five ranked categories (Independent, Overnight Supervision, Part-Time Supervision, Full-Time Indirect Supervision, and Full-Time Direct Supervision). The SRS was designed to be rated by a clinician based on interviews with the subject and an informant who has observed at first hand the level of supervision received by the subject ([Boake 2000](#)). Scoring is a one-step procedure in which the clinician assigns the rating that is closest to the subject's level. Ratings are based on the level of supervision received, not on how much supervision a subject is judged or predicted to need.

The SRS will be assessed at Visit 1 and Visit 12 or Visit 12R. The Visit 1 assessment will be a retrospective assessment of the supervision required by the subject immediately prior to the admission that included the index episode of status epilepticus.

**11.2.8.8. Modified Rankin Scale – 9Q (mRS-9Q)**

The Modified Rankin Scale (mRS) is a commonly used scale to determine disability and functional dependence due to neurological insult such as stroke in adults. The 7-point scale (0 – 6) denotes functional capacity from no symptoms (0) to severe disability (5) and death (6). The Modified Rankin Scale – 9Q is a shortened version consisting of 9 questions that reliably determines the mRS score and was developed to both simplify the assessment and expand the rater base to non- medically trained personnel ([Patel, Rao et al. 2012](#)). The assessment is a web-based tool in the public domain with automatic score calculation and error checking found at [www.modifiedrankin.com](http://www.modifiedrankin.com).

The mRS will be assessed at Visit 1 and at Visit 12 or Visit 12R in subjects  $\geq 17$  years of age. The baseline assessment will be a retrospective assessment of the disability and dependence of the subject immediately prior to the admission that included the index episode of status epilepticus.

## 12. STUDY PROCEDURES

The study procedures listed below by study day reflect the required data collection times for this protocol. When a time window is necessary, this is specified below. If no time window is specified, the test may be performed at any time within the specified 24-hour period.

### 12.1. Visit 1 (V2-≤30h)

The baseline period will be up to approximately 84 hours prior to starting blinded study treatment and should include the assessments/procedures listed below and summarized in [Table 1](#) and [Table 2 \(for retreatment\)](#), the Schedules of Events.

- Informed consent
- Eligibility checklist
- Verification of inclusion/exclusion criteria.
- Demographic information and medical history obtained by proxy and confirmed by the subject when possible.
- SE and wean history
- Blood will be collected from female subjects 10 years to 55 years for a serum pregnancy test unless they are known to be pre-menstrual or post-menopausal or to have had a hysterectomy.
- Blood and urine samples collected for clinical laboratory testing.
- Pharmacogenetic sample will be collected from consenting/eligible subjects.
- Vital signs
- Height
- Weight
- An ECG reading taken.
- Administration of the STESS.
- Administration of the FOUR Score.
- Administration of SRS.
- Administration of the mRS-9Q assessment.
- Assessment of the CGI scale.
- Evaluation of epilepsy status.
- Administration of continuous IV third-line agents.
- Perform EEG.
- Recording of adverse events.
- Recording of previous and concomitant anti-epileptic drugs.

- Recording of previous and concomitant third-line agents.
- Recording of concomitant pressors.
- Recording of other concomitant medications, procedures, and treatments.

## **12.2. Visit 2 (V3-≤54h)**

- Recording of adverse events.
- Recording of concomitant anti-epileptic drugs.
- Recording of concomitant third-line agents.
- Recording of concomitant pressors.
- Recording of other concomitant medications, procedures, and treatments.
- Wean of continuous third-line agent:
  - If wean is successful, subject is followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (these subjects are Qualifying Wean Success subjects or QWS subjects);
  - If wean is not successful, there is ongoing intravenous administration of at least one continuous IV third-line agent and EEG is performed and the subject is randomized.

## **12.3. SAGE-547 Treatment Period**

### **12.3.1. Visit 3/3R (0-24 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs will be recorded at:
  - 0, +30, +60 minutes (+/-15 minutes) and +2, +4, +8 (+/- 30 minutes) and +24 hours (+/- 2 hours) after the start of the infusion
- ECG readings will be recorded immediately after PK sampling at:
  - 0 (pre-dose) and at +0.5, +1, +3, +6, +12, and +24 hours after the start of the blinded study drug infusion.
- A blood sample for PK analysis should be collected at the following time points (all +/- 15 minutes except where otherwise stated):
  - 0 (pre-dose, within two hours of the start of the infusion) and at +0.5, +1 (+/- 5 minutes), +3, +6, +12, and +24 hours after the start of the blinded study drug infusion.
- Completion of the FOUR Score
  - +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the end of the QW)

- Ongoing intravenous administration of a continuous IV third-line agent.
- Study drug administration in loading (Hour 0-1) and maintenance infusions (at completion of Hour 1).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.3.2. Visit 4/4R (25-48 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +48 hours (+/- 2 hours) after the start of the infusion
- An ECG reading taken immediately after PK sampling:
  - +48 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +48 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +48 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent.
- Ongoing study drug maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.3.3. Visit 5/5R (49-72 hours)**

- Weight
- Vital signs should be recorded at:
  - +72 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +72 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +72 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):

- +72 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.4. Visit 6/6R (73-96 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +96 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +96 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +96 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +96 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled.
- Perform EEG.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.5. Visit 7/7R (97-120 hours)**

- Weight
- Vital signs should be recorded at:
  - +120 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:



- +120 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +120 hours (+/- 15 minutes) after the start of study drug infusion, immediately prior to the end of the maintenance infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +120 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is adequately controlled. Complete wean by 120 hours if at all possible.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## **12.4. SAGE-547 Taper Period**

### **12.4.1. Visit 8/8R (121-144 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +144 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after each PK sampling:
  - +128, +136 hours and +144 hours after the start of the study drug infusion
  - During the open-label retreatment phase of the study ECG readings at: +126, +132, +138 hours and +144 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected (+/- 15 minutes unless otherwise stated):
  - +128 (immediately prior to the end of the first taper step), +136 hours (+/- 5 minutes, immediately prior to the end of the second taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of study drug infusion.
  - During the open-label retreatment phase of the study PK blood draws at: +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 hours (+/- 5 minutes, immediately prior to the end of the third taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of the study drug infusion.

- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +144 hours (+/- 2 hours) after the start of the infusion
- Complete wean of third line agents by H144 if not completed by H120.
- Perform EEG.
- Taper of SAGE-547 infusion begins at hour 121.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## **12.5. Follow-up Period**

### **12.5.1. Visit 9/9R (145-168 hours)**

- Vital signs should be recorded at:
  - +168 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +152, +160 hours (+/- 2 hours) after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +152 and +160 hours (+/- 15 minutes) after the start of study drug infusion.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +168 hours (+/- 2 hours) after the start of the infusion
- Perform EEG.
- Assessment of the presence of physiologic brain activity using EEG.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.5.2. Visit 10/10R (169-192 hours)**

- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):

- +192 hours (+/- 2 hours) after the start of the infusion
- At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine retreatment with higher dose of study drug. All patients for retreatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.3. Visit 11/11R (Visit 3/3R + 14d (±2))**

- Blood samples collected for clinical laboratory testing (renal panel only).
- Completion of the FOUR Score (QWS subjects also).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.4. Visit 12/12R (Visit 3/3R + 21d (±2))**

All assessments also performed for QWS subjects.

- Completion of the FOUR Score.
- Administration of the GOS.
- Administration of the SRS.
- Administration of the mRS-9Q assessment.
- Evaluation of epilepsy status (see [Section 11.1.2.2](#) for details).
- Assessment of the CGI Scale.
- Recording of adverse events.
- Recording of concomitant medications, procedures, and treatments, including anti-epileptic drugs, third-line agents, pressors and other medications.
- Collection of pharmacoeconomic data.
- Mortality will be assessed throughout the study period.

## **13. STATISTICS**

### **13.1. Statistical Plan**

Complete details for the analysis and reporting of data from this study will be contained in the Statistical Analysis Plan (SAP).

### 13.1.1. Interim Analysis

When approximately 50% of subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### 13.1.2. Study Populations

The **Safety Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to actual treatment. This analysis population will be used for all safety analyses.

The **Intent to Treat Population** is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to randomized treatment. This analysis population will be used for all efficacy analyses.

The **Modified Intent to Treat Population** is defined as all subjects who:

1. complete their initial course of blinded SAGE-547 or placebo treatment unless the non-completion was due a drug-related adverse event; and
2. have at least one attempt to wean from third-line agents prior to the end of blinded study treatment infusion unless the failure to wean was because seizures were not controlled.

Subjects will be classified according to randomized treatment. This analysis population will be used for sensitivity analyses of the primary endpoint and select secondary efficacy endpoints.

Narratives will be prepared for all subjects who do not complete the infusion of blinded study medication or were not subjected to any wean attempts. Narratives will include details of the cause of SE, the comorbid conditions, the adverse event(s), and reasons for non-completion of the infusion or failure to attempt weaning. This blinded narrative will be reviewed by the medical monitors and the patient adjudicated as MITT eligible or ineligible. Acceptable reasons for defining a subject as MITT ineligible include death or withdrawal of consent due to progression of the underlying cause of SE or comorbid conditions, unless the cause of death or progression of disease were thought by the investigator, sponsor, or DSMB to be related to study drug.

The **Per-Protocol (PP) Population** is defined as a subset of the MITT population but will exclude data from all subjects with significant protocol violations or deviations. Subjects will be classified according to actual treatment received. This data set will be used for sensitivity analyses to examine the robustness of results for the primary and key secondary efficacy endpoints.

The **Pharmacokinetics Population** is defined as all subjects who at least had an infusion of blinded SAGE-547 initiated and have at least one pharmacokinetic sample collected.

The **Pharmacogenetic Population** is defined all subjects who consent to being included in the pharmacogenetic assessment and provide a pharmacogenetic sample.

Summary statistics of all data collected will be presented for subjects who were QW successes.

### **13.1.3. General Aspects**

Tabular displays of descriptive statistics will be provided for all variables. Summary tables will include n, mean, mean, standard deviation, minimum and maximum for continuous variable and frequency and percentage for categorical variables.

### **13.1.4. Analysis of Primary Endpoint**

The analysis of response to treatment (see Section 11.1.1 for definition of primary endpoint) between SAGE-547 treated subjects and placebo treated subjects will be performed on the ITT population using a Cochran-Mantel-Haenszel (CMH) test with variables for treatment, concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). The CMH general association statistic and its associated p-value will be presented. The comparison of treatment response rates will be conducted at the 5% level of significance. To confirm the CMH results, a permutation test will also be conducted.

An additional analysis of the primary endpoint will also be performed on the MITT population. In addition sensitivity analyses of the primary endpoint will be performed using the ITT population based on:

- the number of third-line agents (one, two, or three) subjects were administered post-randomization; and
- which third line agent was the subject of the first TW.

### **13.1.5. Analysis of Secondary Efficacy Endpoints**

Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the ITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section ([Section 6](#)). Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. The analysis of the secondary endpoints will also be performed on the MITT population. Summary statistics will be provided for all endpoints. Categorical endpoints (change from baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

### **13.1.6. Analysis of Other Endpoints**

Safety and “Other” endpoints will only be summarized by treatment group.

Summaries of safety endpoints will be based on the overall Safety Population.

**13.1.7. Epilepsy and SRSE Status**

Diagnosis of epilepsy and recurrence of RSE or SRSE will be documented as the percentage of subjects by time point and overall. Kaplan-Meier curves may be plotted if sufficient data are available.

Utilization of AEDs during follow-up and during recurrence will be summarized.

**13.1.8. Questionnaires**

The data collected from each questionnaire will be interpreted according to the standard methodology for that questionnaire. There will be no adjustment for missing values.

**13.1.9. Pharmacokinetic Data Analysis**

Details of the pharmacokinetic data analysis will be described in detail in a separate Pharmacokinetic Analysis Plan.

**13.1.10. Pharmacogenetic Data Analysis**

Any genotype data generated in this study will be stored within a secured database within Sage Therapeutics and / or a third party contracted to work with Sage Therapeutics to analyze the samples. Because the number of subjects agreeing to participate in the genetic research component of the study is unknown, it is not possible to establish, a priori, whether sufficient samples will be obtained to support formal statistical evaluation of data. As a consequence a Pharmacogenetic Analysis Plan will only be prepared where appropriate and the results obtained from any genetic research will be reported in a report separate from the main study CSR.

**13.1.11. Retreated Subjects**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are retreated with SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo.

**13.1.12. EEG-Responders**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who are classified as EEG-responders/non-responders based on the independent assessment of the PAEEG. Summaries will be derived for the two randomized treatment groups.

**13.1.13. QT/QTc Assessment**

An analysis of the correlation between changes in QT/QTc intervals and SAGE-547 plasma levels will be performed to investigate if there is a potential effect that SAGE-547 may have on QT/QTc interval. A detailed description of the QT/QTc assessment will be included in the SAP.

**13.1.14. Quantitative EEG**

The six EEG records for each subject may be subjected to exploratory quantitative EEG analysis, the details of which will be included in the EEG Analysis Plan. In summary the following comparisons may be made, SAGE-547 versus placebo: the QWEEG versus the TWEEG (main analysis); the CEEG versus PAEEG (subsidiary analysis); and TAEEG versus PAEEG (exploratory analysis).

### **13.2. Determination of Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between treatment groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

### **13.3. Statistical Analysis Plan**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.

## **14. ADVERSE EVENTS**

The safety procedures in this study will be detailed in a Safety Management Plan, which will be agreed and signed before the first subject is randomized in the study. Section 14.1 summarizes Investigator responsibilities regarding the identification and documentation of AEs, the classification of AEs for relationship to study drug and severity, and the reporting of AE information to the Sponsor and the IRB.

[Section 14.2](#) summarizes Sponsor/Medical Monitor Responsibilities regarding monitoring of AE data and reporting relevant safety information to FDA.

[Section 14.3](#) lists important AE definitions.

### **14.1. Investigator Responsibilities**

#### **14.1.1. Identification and Documentation of Adverse Events by Investigator**

Subjects will be evaluated and questioned generally (if possible) to identify AEs during the course of the study. AEs will be collected from the signature of the consent form through Visit 12/12R. Adverse events that occur prior to completion of screening will be captured on the Medical History eCRF. Adverse events that occur after completion of screening will be recorded on the Adverse Event eCRF.

All AEs revealed by observation, other diagnostic procedures, or spontaneously reported by the subject and/or in response to an open question from study personnel will be recorded on the Adverse Event Form. Any clinically significant deterioration in laboratory assessments or other clinical findings are considered an AE and must be recorded on the Adverse Event Form, unless otherwise stated. AE information recorded will be entered into the database on an ongoing basis.

AEs with a relationship considered related to study drug (probable, possible) should be followed until the event is resolved or the Investigator determines the event is stable or no longer clinically significant. AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

For SAEs, an electronic Serious Adverse Event eCRF must be completed with as much information as possible and submitted in the time frame described below in [Section 14.1.3](#). When new significant information is obtained as well as when the outcome of an event is known, the electronic SAE eCRF should be updated within 24 hours. If the subject was an outpatient at the time of the SAE and was re-hospitalized due to the SAE, a copy of relevant hospital records (e.g., admission report, laboratory test results, discharge summary, etc.) may be requested to be included as part of the subject medical file.

All SAEs will be followed until resolved or until a stable status has been achieved.



**14.1.2. Adverse Event Classification****14.1.2.1. Relationship to Investigational Drug**

None:	No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state.
Possible:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject, but this is not known for sure.
Probable:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

**14.1.2.2. Severity**

Mild	Discomfort noticed, but no disruption to daily activity.  For subjects that are unconscious, this may be a slight or minor change in a lab result or clinical sign or symptom that does not require immediate corrective action.
Moderate	Discomfort sufficient to reduce or affect normal daily activity, but is not hazardous to health; prescription drug therapy may be employed to treat the AE.  For subjects that are unconscious, this may be a clinically meaningful change that may require immediate corrective action.
Severe	Inability to work or perform normal daily activity and represented a definite hazard to health; prescription drug therapy and/or hospitalization may be employed to treat the AE.  For unconscious subjects, this may be a significant clinical change that requires immediate corrective action.

**14.1.2.3. Action Taken with Investigational Drug**

None	Study medication was continued without change.
Discontinued	Study medication was terminated.
Dose adjusted	Study medication dose/infusion rate was changed and then continued per protocol.
Interrupted	Study medication was interrupted and then continued per protocol.
Unknown	The action taken with regard to study medication is unknown.
Not applicable	Administration of study medication was not ongoing.

**14.1.2.4. Assessment of Outcome**

Ongoing	At the end of the study, the event has not resolved or stabilized.
Ongoing and stable	The event is ongoing but has stabilized and is unlikely to change
Resolved	The event has resolved or the subject recovered without sequelae.
Resolved with sequelae	The event has at least one secondary outcome that may result in permanent disability and/or functional limitation.
Unknown	The status of the event is unknown.
Death	The subject has expired.

**14.1.3. Investigator Reporting to Sponsor and Sponsor Emergency Contact**

All new SAEs that come to the Investigator and/or Sponsor's notice during the course of the study (up to and including the last study visit) must be reported by the Investigator on the designated electronic report form within 24 hours of the point in time when the Investigator becomes aware of the SAE. As additional information becomes available, the designated electronic report form must be updated within 24 hours.

Investigators must report any SAE, whether or not considered drug related. The report must include an assessment of whether there is a reasonable possibility that the drug caused the event.

In a medical emergency (ie, an event that requires immediate attention regarding the treatment of a subject, operation of the clinical study, and/or the use of investigational drug), study site staff will apply appropriate medical intervention according to current standards of care, and contact the Medical Monitor.

**14.1.4. Medical Monitor and Emergency Contact Information**

[REDACTED], MD  
[REDACTED]

**14.1.5. SAE Reporting Contact Information**

Contact information and reporting instructions are provided in the Safety Management Plan.

**14.1.6. Reporting to Institutional Review Boards (IRBs)**

It is the responsibility of the Investigator to promptly notify the institution's IRB of all serious and unexpected suspected adverse reactions (see [Section 14.3](#) for definitions).

## **14.2. Sponsor/Medical Monitor Responsibilities**

### **14.2.1. Monitoring of Adverse Event Data**

The Medical Monitor will review any newly reported adverse events in an ongoing basis. If the aggregate assessment indicates that an event is occurring more frequently than would normally be expected in this population, or as previously observed, and the sponsor believes that the events are causally related to the administration of SAGE-547, the Sponsor will then report that information in an IND safety report.

### **14.2.2. Data Safety Monitoring Board**

An independent DSMB will monitor the clinical, PK and PD data for safety signals throughout the study and will be asked to assess the placebo response rate at the time of the interim analysis to determine final sample size. In order to perform their monitoring function the DSMB will have access to un-blinded safety data as necessary.

The composition and procedures for the board will be described in a separate DSMB Charter.

### **14.2.3. Reporting to FDA**

The Sponsor must report in an IND safety report any suspected adverse reaction to study treatment that is both serious and unexpected (21 CFR 312.32(c)(1)(i)). Before submitting an IND safety report, the Sponsor will ensure the event meets all three of the definitions: (1) suspected adverse reaction, (2) serious, (3) unexpected. If the AE does not meet all three of the definitions, it should not be submitted as an IND safety report. The Sponsor should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the adverse event and, therefore, that the event meets the definition of a suspected adverse reaction.

If there is a serious and unexpected suspected adverse reaction, the Sponsor will notify the appropriate regulatory agency(ies) and all appropriate parties on an expedited basis. In addition, Sponsors must submit expedited reports of an increased rate of occurrence or severity of serious suspected adverse reactions over that listed in the protocol or Investigational Brochure.

SUSARs will be unblinded prior to reporting to FDA. Unless it is necessary to unblind for the safety of the patient, the investigator will not be informed of the unblinding of the subject.

Under 21 CFR 312.32, Sponsors should identify in the protocol SAEs that it does not plan to report individually in an expedited manner, because they are known consequences of the disease or otherwise common in the study population. Given the grave condition and prognosis of SRSE being studied, individual occurrences of seizures or seizure activity will not be reported expeditiously in this study. Regardless of which events are reported in an expedited manner, all adverse events will be closely monitored throughout the study.

## **14.3. Adverse Event Definitions**

### **14.3.1. Adverse Event**

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

### **14.3.2. Suspected Adverse Reaction**

Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

### **14.3.3. Life-Threatening**

An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

### **14.3.4. Serious**

An AE or suspected adverse reaction is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE – see definition above
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disability
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

### **14.3.5. Unexpected**

An AE or suspected adverse reaction is considered “unexpected”:

- If it is not listed in the Investigational Brochure or is not listed at the specificity or severity that has been observed, or
- If an Investigational Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigational Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigational Brochure listed only cerebral vascular accidents.

“Unexpected,” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigational Brochure as occurring with a class of drugs or as anticipated from

the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

#### **14.4. Emergency Identification of Study Medication**

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject's treatment in the study via the IVRS; this normally requires prior approval by the medical monitor. However, if the subject is at immediate risk and the Investigator believes that immediate knowledge of the study treatment will alter medical management, discussion with the medical monitor may take place after unblinding. The Investigator will not unblind the medical monitor during that discussion. The process of unblinding will ensure that only the investigator is unblinded; the medical monitor, study management team, and data management team will not be made aware of the treatment allocation of an individual subject. All cases of emergency unblinding will be fully documented in a way that does not unblind the medical monitor, study management team, and data management team.

### **15. STUDY ADMINISTRATIVE CONSIDERATIONS**

#### **15.1. Quality Control and Quality Assurance**

The Investigators and institutions will permit trial related monitoring, audits, IRB review, and regulatory inspections as requested by FDA, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed informed consent forms, etc.) in addition to case report forms.

Quality assurance and quality control systems with written standard operating procedures (SOPs) will be followed to ensure this trial will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The site's dedicated study monitor will arrange to visit the Investigator at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be identified and resolved. The study monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality assurance officers named by Sage Therapeutics or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements, made by the Sponsor with the Investigator/institution and any other parties involved with the clinical trial, will be in writing in a separate agreement.

## **15.2. Data Handling and Recordkeeping**

### **15.2.1. Data Handling**

Procedures for data handling (including electronic data) used in this protocol will be documented in a Data Management Plan.

### **15.2.2. Case Report Form Completion**

eCRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of demographics, study drug administration, study procedures, AEs, questionnaire completion, efficacy assessments and subject status, including survival.

The Investigator will maintain copies of the eCRFs at the study site. For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate eCRF.

### **15.2.3. Retention of Study Records**

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval and until there are no pending or contemplated marketing applications or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to an appropriate person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

## **15.3. Confidentiality**

To maintain subject privacy, all eCRFs, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available trial registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by Sage Therapeutics to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

#### **15.4. Publication Policy**

All information concerning SAGE-547 is considered confidential and shall remain the sole property of Sage Therapeutics. The Investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval from Sage Therapeutics. No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between Sage Therapeutics and the Investigator.

#### **15.5. Protocol Amendments**

Changes to the conduct of the study should be prepared as a protocol amendment by the Sponsor. Protocol amendments should receive written IRB/IEC approval prior to implementation at the investigative site, except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the trial (eg, change of monitor, telephone numbers). In this case, Sage Therapeutics will amend and implement the protocol change and subsequently notify the regulatory authorities and the Investigative sites who will notify the respective IRB, as appropriate.

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**APPENDIX 1. APPENDIX 1: FOUR SCORE****FOUR score****Full Outline of UnResponsiveness****Eye response**

- E4: eyelids open or opened, tracking, or blinking to command
- E3: eyelids open but not tracking
- E2: eyelids closed but open to loud voice
- E1: eyelids closed but open to pain
- E0: eyelids remain closed with pain

**Motor response**

- M4: thumbs-up, fist or peace sign
- M3: localizing to pain
- M2: flexion response to pain
- M1: extension response to pain
- M0: no response to pain or generalized myoclonus status

**Brainstem reflexes**

- B4: pupil and corneal reflexes present
- B3: one pupil wide and fixed
- B2: pupil or corneal reflexes absent
- B1: pupil and corneal reflexes absent
- B0: absent pupil, corneal and cough reflex

**Respiration pattern**

- R4: not intubated, regular breathing pattern
- R3: not intubated, Cheyne-Stokes breathing pattern
- R2: not intubated, irregular breathing
- R1: breathes above ventilatory rate
- R0: breathes at ventilator rate or apnea

Reference ([Iyer, Hoel et al. 2009](#)).

**APPENDIX 2. GLASGOW OUTCOME SCALE (GOS)****GLASGOW  
OUTCOME  
SCALE**

Patient Name: \_\_\_\_\_

Rater Name: \_\_\_\_\_

Date: \_\_\_\_\_

*Note:* The scale presented here is based on the original article by Jennett and Bond. It has become common practice in clinical trial administration, however, to use a modified version that places the scores in reverse order (i.e., "good recovery" = 1, "moderate disability" =2, etc.).

Score	Description
1	DEATH
2	PERSISTENT VEGETATIVE STATE Patient exhibits no <i>obvious cortical</i> function.
3	SEVERE DISABILITY (Conscious but disabled). Patient depends upon others for daily support due to mental or physical disability or both.
4	MODERATE DISABILITY (Disabled but independent). Patient is independent as far as daily life is concerned. The disabilities found include varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes.
5	GOOD RECOVERY Resumption of normal activities even though there may be minor neurological or psychological deficits.

TOTAL (1-5): \_\_\_\_\_

Reference ([Jennett and Bond 1975](#)).

## APPENDIX 3. SUPERVISION RATING SCALE (SRS)

### SUPERVISION RATING SCALE (SRS)

**Instructions:** Circle the rating that is closest to the amount of supervision that the patient *actually receives*. "Supervision" means that someone is responsible for being with the patient.

<u>Rating</u>	<u>Description</u>
<u>Level 1: INDEPENDENT</u>	
1	The patient lives alone or independently. Other persons can live with the patient, but they cannot take responsibility for supervision (for example, a child or elderly person).
2	The patient is unsupervised overnight. The patient lives with one or more persons who <i>could</i> be responsible for supervision (for example, a spouse or roommate), but they are <i>all</i> sometimes absent overnight.
<u>Level 2: OVERNIGHT SUPERVISION</u>	
3	The patient is only supervised overnight. One or more supervising persons are always present overnight but they are <i>all</i> sometimes absent for the rest of the day.
<u>Level 3: PART-TIME SUPERVISION</u>	
4	The patient is supervised overnight and part-time during waking hours, but is allowed on independent outings. One or more supervising persons are always present overnight and are also present during part of waking hours every day. However, the patient is sometimes allowed to leave the residence without being accompanied by someone who is responsible for supervision.
5	The patient is supervised overnight and part-time during waking hours, but is unsupervised during working hours. Supervising persons are <i>all</i> sometimes absent for enough time for them to work full-time outside the home.
6	The patient is supervised overnight and during most waking hours. Supervising persons are <i>all</i> sometimes absent for periods longer than one hour, but less than the time needed to hold a full-time job away from home.
7	The patient is supervised overnight and during almost all waking hours. Supervising persons are <i>all</i> sometimes absent for periods shorter than one hour.
<u>Level 4: FULL-TIME INDIRECT SUPERVISION</u>	
8	The patient is under full-time indirect supervision. At least one supervising person is <i>always</i> present, but the supervising person does not check on the patient more than once every 30 minutes.
9	Same as #8 plus requires overnight safety precautions (for example, a deadbolt on outside door).
<u>Level 5: FULL-TIME DIRECT SUPERVISION</u>	
10	The patient is under full-time direct supervision. At least one supervising person is always present and the supervising person checks on the patient more than once every thirty minutes.
11	The patient lives in a setting in which the exits are physically controlled by others (for example, a locked ward).
12	Same as #11 plus a supervising person is designated to provide full-time line-of-sight supervision (for example, an escape watch or suicide watch).
13	The patient is in physical restraints.

3/12/93

Corwin Boake, Ph.D., TIRR, 1333 Moursund, Houston, TX 77030-3405, 713/799-6990

#### APPENDIX 4. MODIFIED RANKIN SCALE – LEVEL OF FUNCTION SURVEY (mRS-9Q)

1. Do you have any symptoms that are bothering you? (For example, trouble with reading or writing, trouble speaking, problems with vision, numbness, weakness, balance trouble, or problems with swallowing?)	YES	<input type="radio"/>	NO	<input type="radio"/>
2. Are you able to do the same work as before?	YES	<input type="radio"/>	NO	<input type="radio"/>
3. Are you able to keep up with your hobbies?	YES	<input type="radio"/>	NO	<input type="radio"/>
4. Have you maintained your ties to friends and family?	YES	<input type="radio"/>	NO	<input type="radio"/>
5. Do you need help making a simple meal, doing household chores, or balancing a checkbook?	YES	<input type="radio"/>	NO	<input type="radio"/>
6. Do you need help with shopping or traveling close to home?	YES	<input type="radio"/>	NO	<input type="radio"/>
7. Do you need another person to help you walk?	YES	<input type="radio"/>	NO	<input type="radio"/>
8. Do you need help with eating, going to the toilet, or bathing?	YES	<input type="radio"/>	NO	<input type="radio"/>
9. Do you stay in bed most of the day and need constant nursing care?	YES	<input type="radio"/>	NO	<input type="radio"/>

## APPENDIX 5. CLINICAL GLOBAL IMPRESSION (CGI)

### Clinical Global Impression (CGI)

#### 1. Severity of illness

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- |                             |   |
|-----------------------------|---|
| 0 = Not assessed            | 4 = Moderately ill                        |
| 1 = Normal, not at all ill  | 5 = Markedly ill                          |
| 2 = Borderline mentally ill | 6 = Severely ill                          |
| 3 = Mildly ill              | 7 = Among the most extremely ill patients |

#### 2. Global improvement: Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.

Compared to his condition at admission to the project, how much has he changed?

- |                        |                     |
|------------------------|---------------------|
| 0 = Not assessed       | 4 = No change       |
| 1 = Very much improved | 5 = Minimally worse |
| 2 = Much improved      | 6 = Much worse      |
| 3 = Minimally improved | 7 = Very much worse |

#### 3. Efficacy index: Rate this item on the basis of **drug effect only**.

Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.

EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

#### Therapeutic effect

#### Side effects

		None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
<b>Marked</b>	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
<b>Moderate</b>	Decided improvement. Partial remission of symptoms	05	06	07	08
<b>Minimal</b>	Slight improvement which doesn't alter status of care of patient	09	10	11	12
<b>Unchanged or worse</b>		13	14	15	16
Not assessed = 00					

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

**APPENDIX 6. STATUS EPILEPTICUS SEVERITY SCORE (STESS)**

Outcome Predictor	Feature	Score
Consciousness	Alert or somnolent/confused	0
	Stuporous or comatose	1
Worst seizure type (prior to first treatment)	Simple-partial, complex-parial, absence, myoclonic (complicating idiopathic generalized epilepsy)	0
	Generalized-convulsive	1
	Nonconvulsive status epilepticus in coma	2
Age	< 65 years	0
	≥ 65 years	2
History of previous seizures	Yes	0
	No or unknown	1
Summed Total		

**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY  
TO EVALUATE THE EFFICACY AND SAFETY OF SAGE-547 INJECTION  
IN THE TREATMENT OF SUBJECTS WITH SUPER-REFRACTORY  
STATUS EPILEPTICUS**

**PROTOCOL NUMBER: 547-SSE-301**

**IND NUMBER: 117901**

Product: SAGE-547 Injection (allopregnanolone)

Sponsor Contact: [REDACTED], MD

[REDACTED]  
Sage Therapeutics  
215 First Street  
Cambridge, MA 02142

Medical Monitor: [REDACTED], MD

Date of Protocol: 09 March 2015

**Confidentiality Statement**

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.



**PROTOCOL NUMBER: 547-SSE-301**

Sponsor [REDACTED]:

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

Sponsor [REDACTED]:

[REDACTED]

[REDACTED]

Sage Therapeutics

215 First Street, Cambridge, MA 02142

[REDACTED]

CRO [REDACTED]:

[REDACTED]

## 1. SIGNATURE PAGE

Title of Protocol:

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus

Protocol No: 547-SSE-301

### Sponsor Approval

\_\_\_\_\_  
[Redacted Signature] MD  
[Redacted Title]

10 March 2015

Date (dd/mmm/yyyy)

Sage Therapeutics

### Investigator Agreement

By signing this page I attest that I have read and understand the contents of Clinical Protocol 547-SSE-301 and any current amendments. I agree to adhere to the design, conduct, and reporting requirements of the study as stated in the clinical protocol and to my obligations to the Sponsor as described in the protocol and executed contracts between myself, my Institution, and the Sponsor. I also agree to adhere to any subsequent amendments to the clinical protocol.

Investigator's Signature: \_\_\_\_\_

Investigator's Name: \_\_\_\_\_

Institution: \_\_\_\_\_

Date: \_\_\_\_\_

## 2. SYNOPSIS

<b>Name of Sponsor:</b> Sage Therapeutics 215 First Street Cambridge, MA 02142		
<b>Protocol No.</b> 547-SSE-301		<b>Phase:</b> 3
<b>Name of Investigational Product:</b> SAGE-547 Injection		
<b>Name of Active Ingredient:</b> Allopregnanolone		
<b>Title of the Protocol:</b> A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SAGE-547 Injection in the Treatment of Subjects with Super-Refractory Status Epilepticus		
<b>Dosing Regimen: SAGE-547 or Placebo Dosing Schedule</b>		
<b>Hour</b>	<b>Type and Duration of SAGE-547 Infusions</b>	<b>Dose</b>
H1	One hour loading Infusion	300 µg/kg/h
H2 – H120	119 hour maintenance infusion	90 µg/kg/h
H121 – H128	8 hour taper	65 µg/kg/h
H129 – H136	8 hour taper	45 µg/kg/h
H137 – H144	8 hour taper	25 µg/kg/h
<b>Dosing Regimen: SAGE-547 Open Label Dosing Schedule</b>		
<b>Hour</b>	<b>Type and Duration of SAGE-547 Infusion</b>	<b>Dose</b>
H1	One hour loading infusion	300 µg/kg/h
H2 –H120	119 hour maintenance infusion	150 µg/kg/h
H121 – H126	6 hour taper	125 µg/kg/h
H127 – H132	6 hour taper	95 µg/kg/h
H133 – H138	6 hour taper	65 µg/kg/h
H139 – H144	6 hour taper	35 µg/kg/h
<b>Study Sites</b> Up to 150 sites in the USA and Canada.		
<b>Number of Subjects</b>		

The study will randomize 140 subjects at up to 150 sites.

### Study Population

Subjects will be aged two years or more, in SRSE<sup>1</sup> (as defined in the Inclusion Criteria [Section 8.1](#)), and being managed in an intensive care setting.

### Duration of Subject Involvement

Individual subject participation will be up to 30 days.

### Study Design

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

Patients will follow one of three paths to entry to the study. The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst suppression with a third-line agent. These subjects will be consented for the study after admission to the intensive care unit, but before any third-line agents are administered for burst suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their legally authorized representative (LAR). Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours. Once burst suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo.

The second path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst suppression pattern on the EEG. These subjects may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo.

The third path to entry to the study is for subjects who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These subjects may have had one or more previous unsuccessful weans. It is common practice to stop all third-

<sup>1</sup> In this study, the term Super-Refractory Status Epilepticus or SRSE is equivalent to "Refractory Status Epilepticus (RSE) that has failed standard treatment" and the two terms are used interchangeably.

line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 treatment or placebo.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within six hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo).

The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that subjects, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as both the ability to wean the subject off all third-line agents before the end of the infusion of blinded study medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication infusion, and concurrent signs of physiologic brain activity as determined by EEG. Details of the assessments and time points are provided in the schedule of assessments ([Table 1](#) and [Table 2](#)).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo will all subsequently be eligible to be administered SAGE-547 at the higher dose.

### Visit Schedule

The visit schedule and an overview of events at each visit is provided in [Table 1](#), [Table 2](#) and [Table 3](#) Schedule of Assessments.

### Study Objectives

#### *Primary objective:*

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult and pediatric subjects with

SRSE, and for the response to endure at least 24 hours after the end of the SAGE-547 or placebo infusion (primary response).

***Secondary objectives:***

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in the Clinical Global Impression scale (CGI) between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

***Safety objectives:***

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, respiratory rate, temperature, oxygen saturation, weight);
- d. ECG parameters;
- e. Mortality.

***Other objectives:***

1. To evaluate the impact of retreatment with a higher dose SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol<sup>®</sup> and identified SAGE-547 metabolite plasma concentrations;
3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital;

5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;
6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS) (age  $\geq 18$  years).

## Endpoints

### ***Primary endpoint:***

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### ***Secondary endpoints:***

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### ***Safety endpoints:***

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, respiratory rate, temperature, oxygen saturation, weight);
4. ECG parameters;
5. Mortality.

### ***Other endpoints:***

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who fail to respond to their randomized double blind treatment and are retreated with a higher dose of SAGE-547.
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of

Captisol<sup>®</sup> and identified SAGE-547 metabolite plasma concentrations;

3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS) (age  $\geq 18$  years).

### **Inclusion Criteria**

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects two (2) years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;

Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; *or* who have previously failed one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst suppression pattern; *or* who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst suppression pattern.

### **Exclusion Criteria**

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone or any excipients in SAGE-547.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy.
4. Children (subjects aged less than 18 years) with an encephalopathy due to an underlying progressive neurological disorder.
5. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis for whatever reason, but dialysis is not planned or non-continuous dialysis is planned (that would not adequately remove Captisol<sup>®</sup>);
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;



- c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the opinion of the investigator, of less than 30 days;
  - e. a do not resuscitate (DNR) order.
6. Subjects who are being administered more than three third-line agents concomitantly or in whom the qualifying wean cannot be completed within 24 hours, or who are being administered a third-line agent for other indications such as management of raised intra-cranial pressure that would preclude weaning according to this protocol.
  7. Subjects with a living will that does not allow heroic measures.
  8. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
  9. Subjects who have been enrolled in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not withdraw or complete and then re-enroll).

### **Pharmacogenetic Research**

In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **Statistical Analysis**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. All deviations from or changes to the SAP following database lock will be described in detail in the SAP and will be summarized in the final clinical study report.

### **Interim Analysis**

When approximately 50% of the subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

### **Analysis of Primary Endpoint**

The analysis of response to treatment between SAGE-547 treated subjects and placebo treated subjects will be performed using a Cochran-Mantel-Haenszel test with variables for treatment, concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). In this analysis, a treatment responder is a subject who is successfully weaned off all third-line agents and blinded study medication prior to the end of study treatment infusion and remains off third-line agents for at least 24 hours following cessation of the blinded study medication, and who has concurrent signs of physiologic brain activity as determined by EEG. The analysis will be based on the MITT Population. The comparison of treatment response rates will be conducted at the 5% level of

significance.

### **Analysis of Secondary Efficacy Endpoints**

Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the MITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section. Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. Summary statistics will be provided for all endpoints. Categorical endpoints (change from Baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with variables for treatment, concomitant pentobarbital use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third-line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

Summaries of safety endpoints will be based on the overall Safety Population which is defined as all subjects who at least initiated the infusion with blinded study treatment.

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are retreated with SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo. Summary statistics will be presented for subjects who were QW successes.

### **Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 63 subjects randomized to SAGE-547 and 63 subjects randomized to placebo, there would be 90% power for detecting a significant difference between groups at a 5% level of significance. Randomization will be stratified by concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

**Table 1: Schedule of Assessments for Protocol 547-SSE-301: One Infusion of Study Drug (blinded)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2- ≤30h	V3- ≤30h	0-24h	25h- 48h	49h- 72h	73h- 96h	97h- 120h	121h- 144h	145h- 168h	169h- 192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical and SE and Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X		X	X	X	X	X	X				
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X		X	X		X		X		X		
Serum Chemistry and GFR <sup>f</sup>	X		X	X		X		X		X	X <sup>g</sup>	
Urinalysis <sup>h</sup>	X		X	X		X		X		X		
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X			
Urine Sampling (PK) (first 70 pts) <sup>l</sup>			X	X	X	X	X	X	X			
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>o</sup>											X
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV Third-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>p</sup>				
EEG	X	X				X		X	X			
Randomization		X										
Study Drug Administration <sup>q</sup>			X	X	X	X	X	X				

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2- ≤30h	V3- ≤30h	0-24h	25h- 48h	49h- 72h	73h- 96h	97h- 120h	121h- 144h	145h- 168h	169h- 192h	V3+14d (±2d)	V3+21d (±2d)
<b>TW Outcome and Retreat Decision</b>										X <sup>r</sup>		
<b>Physiologic Brain Activity</b>										X		
<b>Adverse Events<sup>s</sup></b>	X	X	X	X	X	X	X	X	X	X	X	X
<b>Concomitant Anti-Epileptic Drugs<sup>t</sup></b>	X	X	X	X	X	X	X	X	X	X	X	X
<b>Concomitant Third-Line Agents<sup>u</sup></b>	X	X	X	X	X	X	X	X	X	X	X	X
<b>Concomitant Pressors</b>	X	X	X	X	X	X	X	X	X	X	X	X
<b>Other Concomitant Medications</b>	X	X	X	X	X	X	X	X	X	X	X	X
<b>Pharmacoeconomic Data</b>												X
<b>Mortality</b>												X

**Table 2: Schedule of Assessments for Protocol 547-SSE-301: Two Infusions of Study Drug (one blinded, one open-label)**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V3R
	V2- ≤30h	V3- ≤30h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	0-24h
Eligibility Checklist	X										S
Informed Consent <sup>a</sup>	X										E
Inclusion/Exclusion Criteria	X										E
Demography <sup>b</sup>	X										
Medical and SE and Wean History <sup>c</sup>	X										T
Height	X										A
Weight <sup>d</sup>	X		X	X	X	X	X	X			B
Serum Pregnancy Test <sup>e</sup>	X										L
Hematology <sup>f</sup>	X		X	X		X		X		X <sup>g</sup>	E
Serum Chemistry and GFR	X		X	X		X		X		X	
Urinalysis <sup>h</sup>	X		X	X		X		X		X	E
Pharmacogenetic sample	X										X
Vital Signs <sup>i</sup>	X		X	X	X	X	X	X	X	X	T
ECG <sup>j</sup>	X		X	X	X	X	X	X	X	X	E
Plasma Sampling (PK) <sup>k</sup>			X	X	X	X	X	X	X		N
Urine Sampling (PK) (first 70 pts) <sup>l</sup>			X	X	X	X	X	X	X		S
STESS	X										I
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	O
Glasgow Outcome Score (GOS)											N
Supervision Rating Scale (SRS)	X <sup>o</sup>										
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>										
Epilepsy Status	X										N
Clinical Global Impression (CGI)	X										E
Continuous IV Third-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean <sup>p</sup>			X
EEG	X	X				X		X	X		T
Randomization		X									
Study Drug Administration <sup>q</sup>			X	X	X	X	X	X			

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V3R
	V2- ≤30h	V3- ≤30h	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	0-24h
<b>TW Outcome and Retreat Decision</b>										X <sup>r</sup>	<b>P</b>
<b>Physiologic Brain Activity</b>										X	
<b>Adverse Events<sup>s</sup></b>	X	X	X	X	X	X	X	X	X	X	<b>A</b>
<b>Concomitant Anti-Epileptic Drugs<sup>t</sup></b>	X	X	X	X	X	X	X	X	X	X	<b>G</b>
<b>Concomitant Third-Line Agents<sup>u</sup></b>	X	X	X	X	X	X	X	X	X	X	<b>E</b>
<b>Concomitant Pressors</b>	X	X	X	X	X	X	X	X	X	X	
<b>Other Concomitant Medications</b>	X	X	X	X	X	X	X	X	X	X	
<b>Pharmacoeconomic Data</b>											
<b>Mortality</b>											

Table 2 continued

	V3R	V4R	V5R	V6R	V7R	V8R	V9R	V10R	V11R	V12R
	0-24h	25h-48h	49h-72h	73h-96h	97h-120h	121h-144h	145h-168h	169h-192h	V3R+14d (±2d)	V3R+21d (±2d)
Weight <sup>d</sup>	X	X	X	X	X	X				
Serum Pregnancy Test <sup>e</sup>										
Hematology <sup>f</sup>	X	X		X		X		X <sup>g</sup>		
Serum Chemistry and GFR	X	X		X		X		X	X	
Urinalysis <sup>h</sup>	X	X		X		X		X		
Vital Signs <sup>i</sup>	X	X	X	X	X	X	X	X		
ECG <sup>j</sup>	X	X	X	X	X	X	X	X		
Plasma Sampling (PK) <sup>k</sup>	X	X	X	X	X	X	X			
Urine Sampling (PK) (first 70 pts) <sup>l</sup>										
STESS										
FOUR Score <sup>m</sup>	X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)										X
Supervision Rating Scale (SRS)										X
Modified Rankin Score (mRS) <sup>n</sup>										X
Epilepsy Status										X
Clinical Global Impression Scale (CGI)										X
Continuous IV Third-Line Agent(s)	X	X	Wean	Wean	Wean	Wean <sup>p</sup>				
EEG			X			X	X			
Randomization										
Study Drug Administration <sup>q</sup>	X	X	X	X	X	X				
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors	X	X	X	X	X	X	X	X	X	X
Other Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Pharmacoeconomic Data										X
Mortality										X

**Table 3: Schedule of Assessments for Protocol 547-SSE-301: Qualifying Wean Successes**

	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2- ≤30h	V3- ≤30h	0-24h	25h- 48h	49h- 72h	73h- 96h	97h- 120h	121h- 144h	145h- 168h	169h- 192h	V3+14d (±2d)	V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent <sup>a</sup>	X											
Inclusion/Exclusion Criteria	X											
Demography <sup>b</sup>	X											
Medical and SE and Wean History <sup>c</sup>	X											
Height	X											
Weight <sup>d</sup>	X											
Serum Pregnancy Test <sup>e</sup>	X											
Hematology <sup>f</sup>	X											
Serum Chemistry and GFR <sup>f</sup>	X											
Urinalysis <sup>h</sup>	X											
Pharmacogenetic sample	X											
Vital Signs <sup>i</sup>	X											
ECG <sup>j</sup>	X											
STESS	X											
FOUR Score <sup>m</sup>	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X <sup>o</sup>											X
Modified Rankin Score (mRS) <sup>n</sup>	X <sup>o</sup>											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV Third-Line Agent(s)	X	Wean										
EEG	X	X										
Adverse Events <sup>s</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs <sup>t</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents <sup>u</sup>	X	X	X	X	X	X	X	X	X	X	X	X



	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	V2- ≤30h	V3- ≤30h	0-24h	25h- 48h	49h- 72h	73h- 96h	97h- 120h	121h- 144h	145h- 168h	169h- 192h	V3+14d (±2d)	V3+21d (±2d)
<b>Concomitant Pressors</b>	X	X	X	X	X	X	X	X	X	X	X	X
<b>Other Concomitant Medications</b>	X	X	X	X	X	X	X	X	X	X	X	X
<b>Pharmacoeconomic Data</b>												X
<b>Mortality</b>												X

<sup>a</sup> Written informed consent by proxy (LAR) will be obtained prior to starting any study-related procedures not considered standard of care.

<sup>b</sup> Demographic information will be obtained by proxy and confirmed by the subject when possible.

<sup>c</sup> Medical history will be obtained by proxy and confirmed by the subject when possible. All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Dosing changes with the third-line agent(s) that constitute a wean attempt will be marked as such on the CRF, and the start/stop dates and times of all wean attempts prior to V3 will be recorded, as well as the outcome of the wean attempt.

<sup>d</sup> Weight will be collected at Screening (V1) and once during each 24 hour period of the initial study drug infusion period (V3-V8) and second infusion period (V3R-V8R, if applicable). Daily weight will be used to determine the appropriate infusion rate of each dose.

<sup>e</sup> Serum pregnancy test for females aged 12 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy. .

<sup>f</sup> Blood samples will be taken for hematology and serum chemistry and GFR calculation at V1, at 24, 48, 96, 144 and 192 hours (± 2 hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will document whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

<sup>g</sup> Blood samples will be taken at V11 or V11R for serum chemistry (renal panel only).

<sup>h</sup> Urine samples will be taken for urinalysis at V1, at 24, 48, 96, 144 and 192 hours (± 2 hours) relative to the start of each infusion of study drug. Any out-of-range values will be flagged and the investigator will add a comment about whether the abnormality is clinically significant. Clinically significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

<sup>i</sup> Vital signs will be recorded at the following time points relative to the start of each infusion of study drug: Screening (V1), at 0, 30, 60 minutes (± 15 minutes), at 2, 4, and 8 hours (± 30 minutes), and at 24, 48, 72, 96, 120, 144, 168, and 192 hours (± 2 hours). Respiratory rate does not need to be collected if the subject is mechanically ventilated at the time of vital sign assessment.

<sup>j</sup> ECG (12-lead) should be performed at Screening (V1) and at the following times relative to the start of study drug infusion. For the blinded (first) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 128, 136, 144, 152, 160, and 192 hours (± 2 hours). For the open label SAGE-547 (second) study drug infusion: Pre-dose (V3/V3R), at 0.5, 1, 3, 6, 12, 24, 48, 72, 96, 120, 126, 132, 138, 144, 152, 160, and 192 hours (± 2 hours). Heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours.

<sup>k</sup> Plasma will be collected to assay for study drug concentrations at the following time points relative to the start of each infusion of study drug: For the blinded (first) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion. For the open label SAGE-547 (second) study drug infusion: • pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open label SAGE-547 study drug infusion. All timepoints have a time window of +/- 5 minutes.

<sup>l</sup> In the first 70 patients enrolled in the study, all urine voided in each 24-hour period during and after the blinded and open-label study drug infusion will be collected, pooled, and the volume measured. A 20 mL sample will be taken from each pooled urine collection.

<sup>m</sup> FOUR Score assessments will be performed at Screening (V1), 24, 48, 72, 96, 120, 144, 168, and 192 hours (all  $\pm$  2 hours) relative to the start of each infusion of study drug, and at V11 or V11R, and at V12 or V12R.

<sup>n</sup> Modified Rankin Score (mRS) applicable for subjects  $\geq$ 18 years old only.

<sup>o</sup> SRS at V1 will be a retrospective assessment of the supervision required by the subject immediately prior to admission that includes the index episode of the SE, and mRS at V1 will be a retrospective assessment of the disability and dependence of the subject immediately prior to admission that includes the index episode of the SE.

<sup>p</sup> Target for complete wean of all continuous IV third-line agents by 144 hours at V8/V8R if not completed by 120 hours at V7/V7R.

<sup>q</sup> Study drug infusion is intended for IV administration only with a dedicated peripheral IV line using Sage-approved IV administration bags and lines.

<sup>r</sup> At V10 only a decision to re-treat at a higher dose of SAGE-547 will be made by the Investigator if the continuous IV third-line agent wean has failed or the third-line agent requires re-introduction during V9. Subjects who become eligible for re-treatment at a higher dose of SAGE-547 will discontinue the planned visit schedule at V10, then repeat V3 (V3R) and all applicable subsequent visits.

<sup>s</sup> AEs will be collected from the time Informed Consent is obtained and prior to the start of study-specific screening procedures not considered standard of care. Collection of AEs will continue throughout the study from V1 through V12 or V12R.

<sup>t</sup> Subjects may enter the study on AEDs and be administered AEDs during the study. All Concomitant AEDs must be recorded on the CRF with details including date and time of starting/stopping each AED, the route of administration, changes in doses, and frequency of administration. Details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the CRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.

<sup>u</sup> All third-line agents administered since the diagnosis of SE will be recorded on the CRF. Details will include the name of the drug, the start/stop dates and times, and the doses with start/stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

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**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
AE	adverse event
AED	anti-epileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the time-concentration curve
AW	additional weans
BDZ	benzodiazepine
BUN	blood urea nitrogen
CBC	complete blood count
CEEG	consent electroencephalogram
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
C <sub>max</sub>	maximum plasma concentration
C <sub>min</sub>	minimum plasma concentration
CNS	central nervous system
CRF	case report form
CSR	clinical study report
CYP2C9	cytochrome P450 enzyme involved in drug metabolism
DNR	do not resuscitate
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EEG	electroencephalogram
EIND	Emergency Use Investigational New Drug Application
EP	European Pharmacopeia
ESETT	Established Status Epilepticus Treatment Trial
FDA	Food and Drug Administration
FOUR	Full Outline of UnResponsiveness
GABA	$\gamma$ -aminobutyric acid
GABA <sub>A</sub>	$\gamma$ -aminobutyric acid-gated chloride channel
GCP	Good Clinical Practice

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
GFR	glomerular filtration rate
GOS	Glasgow Outcome Scale
H	hour
HPLC	high performance liquid chromatography
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
IV	intravenous
IVRS	Interactive Voice Randomization System
LAR	legally authorized representative
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent to Treat
mRS-9Q	Modified Rankin Score - 9Q
MS/MS	tandem mass spectrometry
nM	nanomolar
NMDA	n-methyl-D-aspartic acid
OW	other weans
PAEEG	primary endpoint electroencephalogram
PD	pharmacodynamics
PK	pharmacokinetic
QOL	quality of life
QW	qualifying wean
QWEEG	qualifying wean electroencephalogram
RBC	red blood cell
RSE	refractory status epilepticus
SAE	serious adverse event

<b>Abbreviation or Specialist Term</b>	<b>Explanation</b>
SAP	Statistical Analysis Plan
SE	status epilepticus
SOP	standard operating procedure
SRS	Severity Rating Scale
SRSE	Super-refractory status epilepticus
SSRI	Selective serotonin re-uptake inhibitors
STESS	Status Epilepticus Severity Score
SUSAR	Suspected Unexpected Serious Adverse Reactions
SWFI	Sterile Water for Injection
TAEEG	treatment electroencephalogram
T <sub>max</sub>	time at maximum plasma concentration
TW	terminal wean
TWEEG	terminal wean electroencephalogram
US	United States
USP	United States Pharmacopeia

### 3. INTRODUCTION AND RATIONALE

#### 3.1. Status Epilepticus

Status epilepticus (SE) is a life-threatening seizure condition in which the brain is in a state of persistent seizure triggered by neuronal hyperexcitability. The Neurocritical Care Society defines SE as one continuous unremitting seizure lasting longer than five minutes or recurrent seizures without regaining consciousness between seizures for greater than five minutes (Brophy, Bell et al. 2012). Common causes of SE include preexisting epilepsy, cerebrovascular disease (in adults), electrolyte and metabolic disturbances, anoxia, encephalopathies, head trauma, high fever (in children, especially in the first year of life) and drug or substance intoxication. SE is associated with substantial morbidity and mortality.

##### 3.1.1. Epidemiology of SE

Geography, sex, age, and race influence the epidemiology of SE, whose incidence has a bimodal distribution, peaking in infants/young children and the elderly (Hauser 1990; DeLorenzo, Pellock et al. 1995; Wu, Shek et al. 2002). The incidence of SE in the elderly population is at least twice that in the general population. Concurrent medical conditions often exist in the elderly population, which can complicate therapy and worsen the prognosis of SE (Chapman, Smith et al. 2001).

The annual incidence of SE in the US is generally quoted to be within the range of 18/100,000 to 61/100,000, based on a 19-year retrospective study in Rochester, Minnesota (Hesdorffer, Logroscino et al. 1998) and a 2-year prospective study in Richmond, Virginia (DeLorenzo, Pellock et al. 1995), respectively. Two studies from Europe give annual incidences of a similar magnitude, ranging between 9.9/100,000 and 15.8/100,000 (Coeytaux, Jallon et al. 2000; Knake, Rosenow et al. 2001). It is thus estimated that in the United States each year there are as many as 150,000 cases of SE (DeLorenzo, Pellock et al. 1995).

#### 3.2. Refractory SE

When a patient begins to seize, the emergency medical technician will administer a first-line intravenous (IV) benzodiazepine (BDZ), such as diazepam, lorazepam or midazolam (Silbergleit, Durkalski et al. 2012), which is done either at the scene of the seizure or in the ambulance. If this is unsuccessful at abating the seizure, additional doses of the first-line therapy will be administered in the emergency room. Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line therapy, which is an IV anti-epileptic drug (AED) such as phenytoin or valproic acid (Novy, Logroscino et al. 2010; Shorvon 2011; Hocker, Britton et al. 2013).

Approximately 20-30% of patients refractory to first-line treatment will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to approximately 70-80% of patients who receive second-line therapy refractory to that therapy.

If a patient's SE continues after administration of BDZs and AEDs, the subject is diagnosed as having refractory status epilepticus (RSE), which must be treated quickly to terminate the seizure activity, maintain the patient's airway, and prevent cerebral damage. RSE patients are immediately admitted to the Intensive Care Unit (ICU) and placed in a

medically-induced coma to stop all seizure-related activity. The drugs used to induce coma are continuously-infused IV agents, commonly propofol, midazolam, or pentobarbital, referred to as third-line agents (Brophy, Bell et al. 2012).

The RSE patient is continually monitored using electroencephalography (EEG) to ensure burst suppression is achieved. Burst suppression is a pattern of brain waves seen on an EEG, characterized by periods of activity alternating with periods of little or no activity in the brain, informing medical personnel of the effectiveness of the medically-induced coma. The goal of burst suppression is to allow the brain and corresponding neuronal tissue to restore function and reset to normal pre-seizure levels.

### **3.2.1. Epidemiology of RSE**

Of those patients on first-line therapy, approximately 35% will not respond and will require the administration of a second-line AED therapy. In turn, approximately 20 – 30% of these patients treated with AEDs will respond to the second-line agent (Novy, Logroscino et al. 2010), leaving up to 28% of the total estimated SE patient population refractory to second-line therapy. Based on the previously-cited estimated incidence in the US, this means that there are up to 42,000 incident cases of RSE in the USA, annually (DeLorenzo, Pellock et al. 1995).

### **3.3. Super-refractory SE**

After 24 hours of burst suppression, the patient is weaned off of the third-line therapy. If the weaning is unsuccessful (neuronal activity has not returned to normal), the third-line agent is re-administered or a different third-line agent is started, and the patient is considered to be in super-refractory status epilepticus (SRSE) (Chapman, Smith et al. 2001; Shorvon 2011; Brophy, Bell et al. 2012). SAGE-547 is being developed as an adjunct to third-line therapy in patients in RSE who have failed standard treatment. In this protocol, the term “RSE that has failed standard treatment” is deemed to be equivalent to the term “SRSE” and the two may be used interchangeably.

#### **3.3.1. Epidemiology of SRSE**

The incidence of SRSE is very poorly understood, mainly because the diagnostic codes used for SE do not generally differentiate its nature as responding or refractory to treatment. Based on the variable reporting of outcomes data, the incident cases of SRSE could represent between one and two-thirds of the RSE patients (Novy, Logroscino et al. 2010; Ferlisi and Shorvon 2012; Hocker, Britton et al. 2013; Sutter, Marsch et al. 2013). More detailed epidemiology studies are needed to better elucidate the proportion of RSE patients whose condition becomes super-refractory. A recent review of ICU discharge data in the USA suggests an annual incidence of approximately 35,000, based on patients who required at least three days in the ICU for SE [Sage data on file].

#### **3.3.2. Outcomes of SRSE**

SE has varying degrees of mortality depending on the underlying etiologies. Table 4 outlines the acute mortality in patients with SE by etiology (Neligan and Shorvon 2010). The mortality rate of SRSE is estimated to be 30% to 50% using current standard of care.

The causes of death from SE (and therefore SRSE) are heterogeneous, resulting from neuronal cell death, complications of underlying medical conditions, or adverse effects of the current standard treatments. Prognosis worsens and mortality increases with longer duration of SE, i.e.

with SE that develops into RSE or SRSE (Neligan and Shorvon 2010), and with longer duration of medically-induced coma (Ferlisi and Shorvon 2012). There is an obvious unmet medical need to improve upon the current standard of care treatment regimens.

Morbidity is high and survivors have outcomes ranging from poor function to vegetative state (Shorvon 2011). Approximately one third of patients with RSE and SRSE will recover, but with chronic neurologic or other deficits (Neligan and Shorvon 2010; Hocker, Britton et al. 2013). In all, it is estimated that less than 25-30% of all SRSE patients have a favorable functional outcome.

**Table 4: Approximate Mortality of Status Epilepticus in Different Etiologies**

Underlying Etiology	Associated Acute Mortality in Patients with SE (%)
Drug reduction/withdrawal, poor AED compliance, or low AED levels	0-10
Cerebrovascular Disease	20-60
Metabolic Disorders	10-35
Acute CNS Infection	0-30
Anoxia	60-100
Alcohol Abuse	0-10
Head Trauma	0-25
Drug Overdose/Toxicity	10-25
Brain Tumors	0-20
Cryptogenic/Idiopathic	5-20

### 3.3.3. Unmet Medical Need in Super-refractory Status Epilepticus

Treatment approaches for SRSE consist of diagnosis and treatment of underlying medical conditions, adding and changing anti-seizure drugs, and repeated attempts at weaning from IV anesthetic agents. Treatment of SRSE has three aims:

- to prevent excitotoxicity, which begins within 24 hours of SE onset;
- to prevent cerebral damage by initiating neuroprotective burst suppression;
- to prevent the complications of extended periods of anesthesia or unconsciousness (Shorvon 2011).

Currently, there are no therapies that have been specifically approved for RSE or SRSE. The primary drugs used to induce coma are continuously infused IV anesthetics such as propofol, midazolam, or pentobarbital, known as third-line agents. Use of these drugs to control SRSE has only been studied in small retrospective reviews or small prospective studies without controls (Hocker, Britton et al. 2013) therefore there is no agreement on which drug is optimal nor on an optimal dosing regimen for the treatments that are used.

The most common adverse effect of the third-line agents is hemodynamic instability; in addition, they are not universally effective, with breakthrough seizures and withdrawal seizures requiring

dose adjustments and changes in third-line agent(s). The drug thought to be most effective in SRSE, pentobarbital, is also associated with the most toxic adverse effect profile, comprising decreased blood pressure and cardiorespiratory collapse (Claassen, Hirsch et al. 2002). The ability to wean patients successfully off the third-line agents as quickly as possible is therefore paramount, and an adjunct to SRSE treatment that enhances the success of the third-line agents and supports their successful weaning in a short timeframe would be an important addition to the therapeutic armamentarium. Preliminary clinical data show that SAGE-547 has been a successful adjunct to third-line therapy in this regard.

### 3.4. SAGE-547 Injection

Allopregnanolone is an endogenous, naturally occurring neuroactive steroid formed in the corpus luteum of the ovary, adrenal cortex and central nervous system (CNS) (Holzbauer, Birmingham et al. 1985; Paul and Purdy 1992; Ottander, Poromaa et al. 2005). It is a metabolite of progesterone created by the actions of 5- $\alpha$  reductase and 3- $\alpha$  hydroxy-steroid dehydrogenase. Allopregnanolone is a potent positive allosteric modulator of both synaptic and extra-synaptic GABA<sub>A</sub> receptors.

SAGE-547 Injection (allopregnanolone aqueous formulation in Captisol<sup>®</sup>) is being developed for the treatment of patients in RSE who have not responded to standard treatment. SAGE-547 Injection is a solution of 5 mg/mL allopregnanolone in Sterile Water for Injection (SWFI), USP and 250 mg/mL betadex sulfobutyl-ether sodium, NF. It is further diluted with Sterile Water for Injection, USP (SWFI) in IV bags to achieve an allopregnanolone concentration of approximately 1.67 mg/mL in an approximately isotonic solution and will be administered intravenously.

#### 3.4.1. Scientific Rationale for SAGE-547 in SRSE

Ineffective recruitment of inhibitory neurotransmission, together with excessive neuronal excitation, likely plays a role in the initiation and propagation of the electrical disturbance occurring in SE. GABA ( $\gamma$ -aminobutyric acid), the major inhibitory neurotransmitter in the central nervous system (CNS), is released from GABAergic neurons and binds to several types of GABA receptors (GABA<sub>A</sub>, GABA<sub>B</sub>, and GABA<sub>C</sub>) on target neurons. GABA<sub>A</sub> receptors are macromolecular proteins that form a chloride ion channel complex and contain specific binding sites for GABA and a number of allosteric regulators, including barbiturates, benzodiazepines, and some anesthetic agents. GABA receptor-mediated inhibition contributes significantly to the normal termination of a seizure (Kapur and Macdonald 1997). SAGE-547 is a positive allosteric modulator of the GABA<sub>A</sub> receptor.

The importance of terminating seizure activity as soon as possible is underpinned by a growing body of evidence from research and clinical observation that SE becomes more difficult to control as its duration increases. It has been postulated that this occurs due to a mechanistic shift from inadequate GABAergic inhibitory receptor-mediated transmission to excessive N-methyl-D-aspartic acid (NMDA) excitatory receptor-mediated transmission (Kapur and Macdonald 1997). As prolonged epileptiform bursting results in a reduction of GABA<sub>A</sub>-mediated synaptic inhibition, antiepileptic treatments which rely on enhancing intrasynaptic GABA<sub>A</sub> neurotransmission become less effective the longer SE continues.

Furthermore, the constitutive process of synaptic GABA<sub>A</sub> receptor internalization is accelerated by the increased neuronal activity associated with seizures. These findings suggest that the rate of GABA<sub>A</sub> receptor internalization is regulated by neuronal activity, and its acceleration contributes to the reduction of inhibitory transmission observed during prolonged seizures (Kapur and



[Macdonald 1997](#)). Of note is that SAGE-547 binds to extrasynaptic as well as intrasynaptic GABA<sub>A</sub> receptors; extrasynaptic receptors remain active with ongoing seizure activity, resulting in a putative mode of action for SAGE-547 in SRSE.

Status epilepticus induces cerebral damage that includes neuronal cell necrosis, gliosis, and network reorganization. The major cause of cell death in cerebral damage is excitotoxicity, which is initiated by glutaminergic receptor over-activation, causing calcium to flood the cell, thereby leading to apoptosis and necrosis. This process is initiated within a few hours of the start of seizure activity, and provides the medical imperative to terminate SE as quickly as possible. To prevent the consequences of the excitotoxicity cascade, it is recommended that anesthesia be initiated within 1-2 hours of onset of seizures at doses designed to induce EEG burst suppression ([Shorvon and Ferlisi 2011](#)).

### **3.4.2. SAGE-547 Clinical Program in the Treatment of SRSE**

The current SAGE-547 development program includes:

- an ongoing Phase 2 open-label trial, Study 547-SSE-201;
- this proposed Phase 3 randomized, double-blind, placebo-controlled trial, Study 547-SSE-301;
- a planned open-label, expanded access protocol, Study 547-SSE-302;
- a number of EINDs for SAGE-547 in patients with SRSE.

The designs of these studies are all similar, with a five to six day infusion of SAGE-547 (or placebo), during which time attempts are made to wean the subject off all third-line agents. In the Phase 3 studies, those subjects who cannot be weaned off third-line agents while being administered SAGE-547 (or placebo) will be eligible for a second open-label infusion of SAGE-547 at a higher dose, which is also being employed for the latter patients being enrolled in the Phase 2 study. Follow up of subjects is for 21 – 30 days after the first infusion of study medication.

### **3.4.3. Data from the SAGE-547 Development Program**

The data from 30 subjects included in the on-going clinical evaluation of SAGE-547 for the treatment of adults and children with SRSE clearly offers preliminary evidence that SAGE-547 could provide substantial and clinically significant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate. These subjects comprise 20 from the ongoing Phase 2 trial (71% success rate in 12/17 evaluable subjects) and 10 subjects who received EIND treatments (78% success rate in 7/9 evaluable subjects).

Successful therapy of SRSE has been defined as “the SE is completely controlled by the therapy, without breakthrough of withdrawal seizures, or discontinuation due to side effects or death during therapy,” ([Ferlisi and Shorvon 2012](#)). By this definition, which is in accord with the efficacy assessments used in the overall clinical evaluation of SAGE-547, 19 of the 26 (73%) subjects with SRSE who completed the SAGE-547 infusion were treatment successes. As data collection is ongoing, this information is preliminary and subject to change upon further monitoring.

Published reports on RSE and SRSE have stated mortality rate ranges from 35% to 65%. The underlying etiologies of SE in the 547-SAGE-201 study and EINDs are heterogeneous, and each

one conveys a different risk of mortality and longer term morbidity. However, the death rate in subjects who have received SAGE-547, 6 out of 30 (20%) subjects, appears to be lower than the published rates. None of the deaths were considered related to SAGE-547: brain tumor, organophosphate toxicity, respiratory failure, respiratory arrest due to ventilator support withdrawal, and breast cancer.

In the Phase 2 study, 20 SAEs (15 non-fatal) have been reported in 13 (65%) subjects, and of these 3 events in 2 subjects (10%) were considered by the investigator to be related to SAGE-547: pulmonary emboli and tracheostomy dehiscence/infection. The Sponsor did not consider these events to be related to SAGE-547, rather to the underlying disease states. Four of the 20 subjects (20%) experienced AEs considered possibly related to SAGE-547 by the investigator, namely moderate myopathy and severe pulmonary emboli in 1 subject, moderate tracheostomy dehiscence and tracheostomy infection in 1 subject, moderate thrombocytosis in 1 subject and moderate BUN, ALT and AST elevation in 1 subject.

Review of the most current safety data from 547-SAGE-201 reveals that there were changes in serum chemistry, hematology, and urinalysis during the study, but that none of those changes were assessed as related to SAGE-547. There were also no SAGE-547-related changes to vital signs.

Despite the heterogeneity in the underlying causes of SE, the ages of the subject, comorbidities, which normally complicate the treatment of SE, and the fact that all subjects had failed current standard of care treatment, a large majority of subjects had a successful therapy outcome, with discontinuation of all third-line agents and resolution of SE.

Refer to the Investigational Brochure for further information on the pre-clinical and clinical data supporting the use of SAGE-547 in SRSE.

### **3.5. Study Rationale - SAGE-547 in SRSE**

#### **3.5.1. Justification for the Control Group**

Although SAGE-547 has demonstrated extremely promising activity in subjects with SRSE, both in the Phase 2 study and during the EINDs, these have been open-label investigations with no control data for comparison. Generally in the literature there are few data describing the success rates of wean attempts of third-line agents, and few comparative data on the effectiveness of the three main third-line agents, propofol, pentobarbital, and midazolam.

Several options for a control group in Study 547-SSE-301 were considered:

- No control group was thought to be unacceptable since there are no reliable published data on success rates in this population that could be used for broad comparisons;
- An active control was considered but found to be impractical since none of the third-line agents are approved for their use in SRSE, no standardized dosing regimens or treatment guidelines have been adopted for the management of SRSE, and clinicians were unlikely to agree which of the available third-line agents would be reserved for the active control arm;
- Historical controls were considered but abandoned because of the practical difficulties of obtaining high quality data, the lack of ability to prospectively match cases, and a suspicion that clinical practice in the standard of care of SRSE is evolving, mandating the use of prospective, concurrent control data;

- Comparison to standard of care alone was considered as a feasible design. However, in a field where no widely adopted treatment guidelines exist, there was a concern that knowledge of the treatment group (SAGE-547 plus standard of care versus standard of care alone) would alter the behavior of the investigators such that they could be more aggressive with weaning in the SAGE-547 group;
- Placebo control is not without its challenges since the preliminary efficacy data for SAGE-547 show that the compound exerts central pharmacological effects and is associated with positive outcomes in around 70% of patients. There is therefore a potential ethical concern about administering placebo to desperately ill patients who have often exhausted all treatment options for SRSE. This concern has been addressed in two ways: firstly all patients receive current standard of care; secondly, all subjects who fail to be weaned from their third-line agents at the end of the blinded infusion of study drug will be administered open-label SAGE-547 without un-blinding their initial treatment allocation, so treatment with the investigational product is not denied, but delayed about a week in the setting of ongoing receipt of full current standard of care.

It was therefore decided that a blinded, placebo-controlled design was appropriate for Study 547-SSE-301.

### **3.5.2. Justification for the Dose Regimen**

The standard dose regimen has been studied in 19 subjects in the 547-SSE-201 Phase 2 trial; the average peak plasma concentration of SAGE-547 at the end of the loading dose was approximately 144 ng/ml. The average plasma concentration during the maintenance infusion was approximately 70 ng/ml. At these concentrations, there were no clear safety signals although two-thirds of subjects experienced an SAE and there were four deaths, all related to the underlying comorbid conditions. The standard dosing regimen was associated with an approximate 70% successful treatment outcome. For these reasons, the standard dosing regimen has been adopted for the initial SAGE-547 infusion to be compared in a blinded fashion to placebo.

In the 547-SSE-201 trial, three subjects have thus far received the higher dose regimen. This dose regimen has also been well tolerated. The average peak plasma concentrations at the end of the loading dose for both dosing regimens will be in the same range, as the loading dose is the same for both regimens. The average plasma concentrations observed during the higher maintenance dose are 102 ng/ml (n=2). The rationale for adopting the higher dose regimen as the open-label infusion of SAGE-547 for subjects who are retreated in this 547-SSE-301 trial is that those who fail on the standard SAGE-547 dose regimen are afforded the opportunity to have access to a higher dose. The justification to also administer the higher dose regimen to failures on placebo is that the regimen has thus far been well tolerated, and this methodology preserves the blind for the initial infusion.

A five-day dosing regimen with SAGE-547 was investigated in the Phase 2 study, 547-SSE-201. There were some cases when weaning off all third-line agents was not possible within 48 hours, but weaning was completed after the end of the infusion of SAGE-547. For this reason, the duration of dosing with SAGE-547 has been increased from 120 hours (five days) in Phase 2 to 144 hours (six days) in this Phase 3 study.

### **3.5.3. Rationale for Genetic Testing Sub-study**

Sage Therapeutics intends to perform genetic research in the SAGE-547 development program in order to explore how genetic variations may affect the metabolism and activity of SAGE-547. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials, and, possibly, to genetically-guided treatment strategies for optimizing decision making with respect to individual benefit:risk. Participation of subjects in genetic research as part of the overall clinical study is optional.

### **3.6. Benefit-Risk Evaluation of the Present Study**

Previous reports of human administration of exogenous allopregnanolone indicate that for exposures in men and women up to 150 nM, the most commonly reported AEs were sedation (recorded as sleepiness or tiredness), feelings of intoxication (like alcohol), flushing, and mild headache (Timby, Balgord et al. 2006; van Broekhoven F, T et al. 2007). No SAEs were reported (Navarro, Kaddouz et al. 2003; Timby, Balgord et al. 2006; van Broekhoven F, T et al. 2007; Kask, Backstrom et al. 2008; Kask, Backstrom et al. 2009; Timby, Hedstrom et al. 2011a). In view of the reduced consciousness and sedation of study subjects at entry into this protocol, none of these previously-reported events are likely to impact subjects in this study.

To date, in the SAGE-547 Phase 2 study and the EIND subjects, a majority of subjects demonstrated a successful therapy outcome (>70%). The majority in the clinical trial (65%) have also experienced SAEs, but none has been considered related to SAGE-547 by the Sponsor (SAEs in 2 subjects (10%) were considered possibly related by Investigator). Five deaths have been reported in 30 subjects (20%), all related to the underlying cause of SRSE and not related to SAGE-547 – this is in the context of published mortality rates between 35% and 65%. These preliminary data suggest that SAGE-547 has the potential to provide clinically relevant improvements over current standard of care for SRSE, a serious condition with a high morbidity and mortality rate.

The underlying etiologies of SE are heterogeneous, and each one conveys a different risk of mortality. Subjects who survive SRSE still have a high risk of severe morbidity (Neligan and Shorvon 2010). The subjects treated with SAGE-547 in Study 547-SSE-201, are heterogeneous in factors such as age and etiology of SE, factors that usually complicate treatment and can increase morbidity and mortality. Even with this heterogeneity, the preliminary efficacy and safety data for SAGE-547 are very encouraging, and the mortality rate suggests that the risk to benefit assessment of this treatment rests on the side of benefit.

## **4. ETHICS**

### **4.1. Institutional Review Board or Independent Ethics Committee**

This protocol will be reviewed and approved by the Institutional Review Board (IRB) where the study is conducted. The IRB will meet all FDA requirements governing IRBs (CFR, Title 21, Part 56).

### **4.2. Ethical Conduct of the Study**

The Sponsor, the Medical Monitor, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable ICH and GCP guidelines, and must also conduct the study in accordance with local regulations.

### **4.3. Subject Information and Informed Consent**

Subjects prospectively enrolled in this study will be unable to give consent. Therefore, consent will be given by proxy by a legally authorized representative (LAR). Written informed consent is required for each subject prior to any testing under this protocol not considered standard of care, including screening tests and evaluations. Should a subject gain the ability to sufficiently comprehend the situation and consent during the course of the study, written informed consent or verbal assent will be documented as required or recommended by the institution's IRB.

The form of consent to be obtained will depend on the condition of the subject as determined by the Principal Investigator. The informed consent form (ICF), as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50.

It is the responsibility of the Investigator to obtain consent and to provide the subject's LAR with a copy of the signed and dated informed consent form. The informed consent form for subject participation must also be available as part of the subject file for review by the site's dedicated study monitor or any authorized auditor of the Sponsor or regulatory authorities.

All ICFs used in this study must be approved by the appropriate IRB and by the Sponsor. The ICF must not be altered without the prior agreement of the relevant IRB and the Sponsor.

### **4.4. Ethical and Regulatory Considerations for Pharmacogenetic Sub-study**

#### **4.4.1. Informed Consent for Pharmacogenetics**

The genetic component of this study is optional and subjects may participate in other components of the main study without having to agree to participate in the genetic component. If subject chooses to participate in the genetic component of the study, the subject or LAR must sign and date a specific consent form for the genetic component of the study in addition to the main study consent form. The principal investigator(s) is responsible for ensuring that consent is freely given and that the subject understands that they may discontinue from the genetic aspect of the study independent of their decision to remain within or withdrawal from the main study.

#### **4.4.2. Subject Data Protection Relative to Pharmacogenomics**

Sage Therapeutics will not provide individual genotype results to subjects, their family members, their general physician, their employer or any insurance company unless required to do so by law. While extra precautions will be taken to preserve confidentiality and to prevent genetic data from being linked to an individual's identity outside of a restricted access site, in certain exceptional situations (e.g. in case of a medical emergency or as a consequence of a specific regulatory need), certain individuals may see both genetic data and the personal identifiers of a subject; however in all cases a subject's medical information and genetic files will remain physically separated.

## **5. STUDY OBJECTIVES**

### **5.1. Primary Objective**

To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult and pediatric subjects with SRSE, and for the response to endure at least 24 hours after cessation of the SAGE-547 or placebo infusion (primary response).

### **5.2. Secondary Objectives**

1. To compare between SAGE-547 and placebo the time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. To compare between SAGE-547 and placebo secondary response, defined as success of weaning the subject off all third-line agents before the end of the first infusion of SAGE-547 or placebo;
3. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. To compare the change in Clinical Global Impression Scale between SAGE-547 and placebo up to Visit 12;
5. To determine the number of days after the end of the first infusion of study drug that the subject does not have status epilepticus, up to Visit 12;
6. To determine the number of days after the end of the first infusion of study drug that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. To determine the number of separate episodes of status epilepticus occurring up to Visit 12;
8. To determine the proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### **5.3. Safety Objectives**

To determine the safety and tolerability of a 144-hour infusion of SAGE-547 in four groups of subjects with SRSE (one infusion of SAGE-547, one infusion of placebo, one infusion of placebo followed by one infusion of SAGE-547, and two infusions of SAGE-547) via:

- a. Adverse events and medications;
- b. Laboratory testing (hematology, serum chemistry, and urinalysis);
- c. Vital signs (blood pressure, heart rate, respiratory rate, temperature, oxygen saturation, weight);
- d. ECG parameters;
- e. Mortality.

## 5.4. Other Objectives

1. To evaluate the impact of retreatment with a higher dose of SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;
2. To evaluate the pharmacokinetics of SAGE-547, and present Captisol<sup>®</sup> and identified SAGE-547 metabolite plasma concentrations;
3. To correlate QT/QTc interval with plasma concentrations of SAGE-547;
4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital;
5. To evaluate the Full Outline of UnResponsiveness (FOUR) Score;
6. To evaluate the Glasgow Outcome Score (GOS);
7. To evaluate the Supervision Rating Scale (SRS);
8. To evaluate the Modified Rankin Score (mRS) (age  $\geq 18$  years).

## 6. ENDPOINTS

### 6.1. Primary Endpoint

Success or failure, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo, and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the first infusion of SAGE-547 or placebo, and concurrent signs of physiologic brain activity as determined by EEG (primary response).

### 6.2. Secondary Endpoints

1. The time between meeting the primary response endpoint and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
2. Secondary response, defined as success of weaning the subject off all third-line agents before the end of the first SAGE-547 or placebo infusion;
3. The time between meeting the secondary response endpoint, defined in (2) above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
4. The assessment of clinical status as measured by change in the CGI from Visit 1 (Screening) and to Visit 12;
5. The number of days after the end of the first study drug infusion that the subject does not have status epilepticus, up to Visit 12;
6. The number of days after the end of the first study drug infusion that the subject does not have seizures (convulsive and non-convulsive) up to Visit 12;
7. The number of separate episodes of status epilepticus occurring up to Visit 12;
8. The proportion of subjects with a new diagnosis of epilepsy after Visit 11.

### 6.3. Safety Endpoints

1. Adverse events and medications;
2. Laboratory testing (hematology, serum chemistry, and urinalysis);
3. Vital signs (blood pressure, heart rate, respiratory rate, temperature, oxygen saturation, weight);
4. ECG parameters;
5. Mortality.

### 6.4. Other Endpoints

1. The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who fail to respond to their randomized double blind treatment and are retreated with a higher dose of SAGE-547;
2. Standard pharmacokinetic data derived from SAGE-547 plasma concentrations, and presentation of Captisol<sup>®</sup> and identified SAGE-547 metabolite plasma concentrations;
3. QT/QTc interval changes and plasma concentrations of SAGE-547;
4. Number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital;
5. Full Outline of UnResponsiveness (FOUR) Score;
6. Glasgow Outcome Score (GOS);
7. Supervision Rating Scale (SRS);
8. Modified Rankin Score (mRS) (age  $\geq 18$  years).

## 7. INVESTIGATIONAL PLAN

### 7.1. Overview of Study Design

This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.

[Figure 1](#) provides an overview of the study design and [Figure 2](#) gives the details of treatment and follow-up on the active treatment arm. Patients will follow one of three paths to entry to the study. The first path is for patients who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst suppression with a third-line agent. These patients will be consented for the study after admission to the intensive care unit, but before any third-line agents are administered for burst suppression. These subjects are unlikely to be able to consent themselves for the study due to coma or mental incapacity from the status epilepticus, and so consent will be obtained from their LAR. Subjects will be administered one or more third-line agents at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours. Once burst suppression has been maintained for 24 hours, the third-line agent or agents will be weaned. This wean is called the qualifying wean (QW), and subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (see [Table 3](#)). Subjects who



fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo.

The second path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who are already on a continuous intravenous infusion of third-line agent with a burst suppression pattern on the EEG. These patients may have had one or more previous unsuccessful weans and may be on more than one third-line agent. Appropriate consent will be obtained and the third-line agent will be continued after consent until at least 24 hours of continuous burst suppression has been achieved. The duration of post-consent third-line agent administration will depend on how long this episode of burst suppression was maintained prior to consent being obtained. Once at least 24 hours of continuous EEG burst suppression has been achieved, the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo.

The third path to entry to the study is for patients who have either been transferred from another hospital or from within the study site institution and who arrive at the study site intensive care unit without a burst suppression pattern on the EEG or not on a continuous infusion of at least one third-line agent. These patients may have had one or more previous unsuccessful weans. It is common practice to stop all third-line agents in these subjects to assess the underlying clinical and EEG presentation, while optimizing concomitant AEDs. If the decision is made to re-administer a third-line agent, consent will be obtained from the subject's LAR. The subject will then be administered one or more third-line agent at a dose sufficient to maintain a burst suppression pattern on the EEG for 24 hours, at which time the third-line agent or agents will be weaned. This is the QW. Subjects who are successfully weaned will be followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data. Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo.

Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within six hours of the investigator's determination that they failed the QW.

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. Randomization will be stratified by concomitant pentobarbital use (yes or no) and number of previous third line agent wean attempts prior to randomization (one vs two or more).

The randomized portion of the study will be blinded, with the two treatments (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

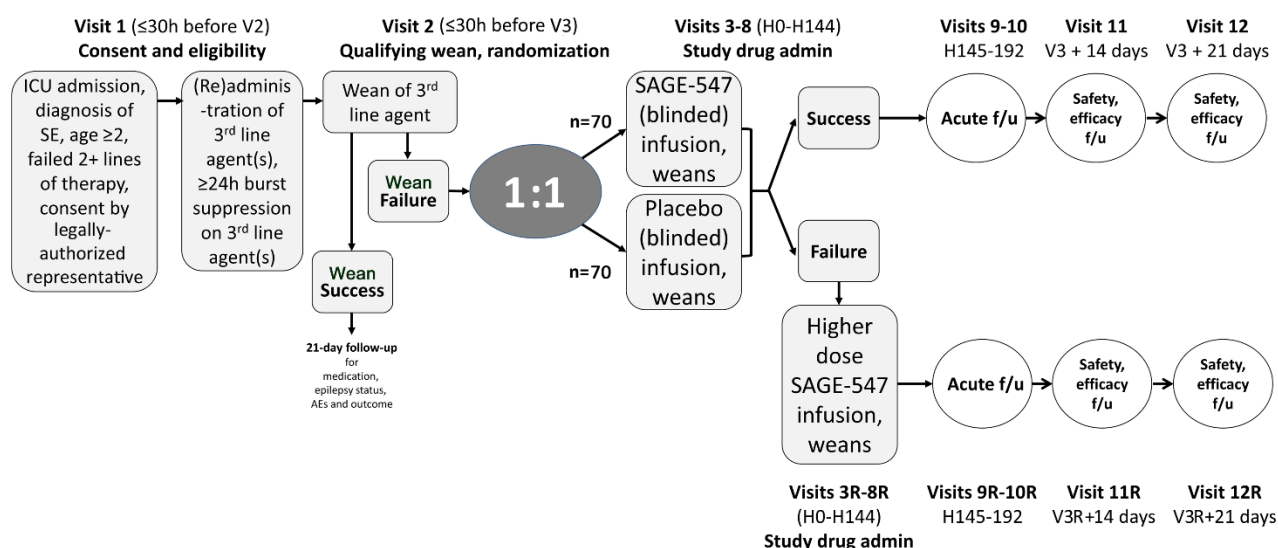
For all subjects in the study, attempts will be made to wean the subject off all third-line agents starting at hour (H) 49 of the blinded study treatment infusion, with the aim of completing all weans by hour (H) 120 of the study treatment infusion.

Efficacy will be evaluated by applying success criteria, with a success defined as the ability to wean the subject off all third-line agents before the end of the first infusion of blinded study

medication without the need to reinstitute a third-line agent for at least 24 hours following cessation of the blinded study medication. Subjects must also have evidence of physiologic brain activity at the end of the primary endpoint assessment period as determined by EEG in order to be deemed a success. Details of the assessments and time points are provided in the schedule of assessments (Table 1, Table 2 and Table 3).

Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. The blind will be maintained for all subjects in the study, so subjects who failed on SAGE-547 and subjects who failed on placebo will all subsequently be eligible to be administered SAGE-547 at the higher dose.

**Figure 1: Study Design**



## 7.2. Trial Conduct

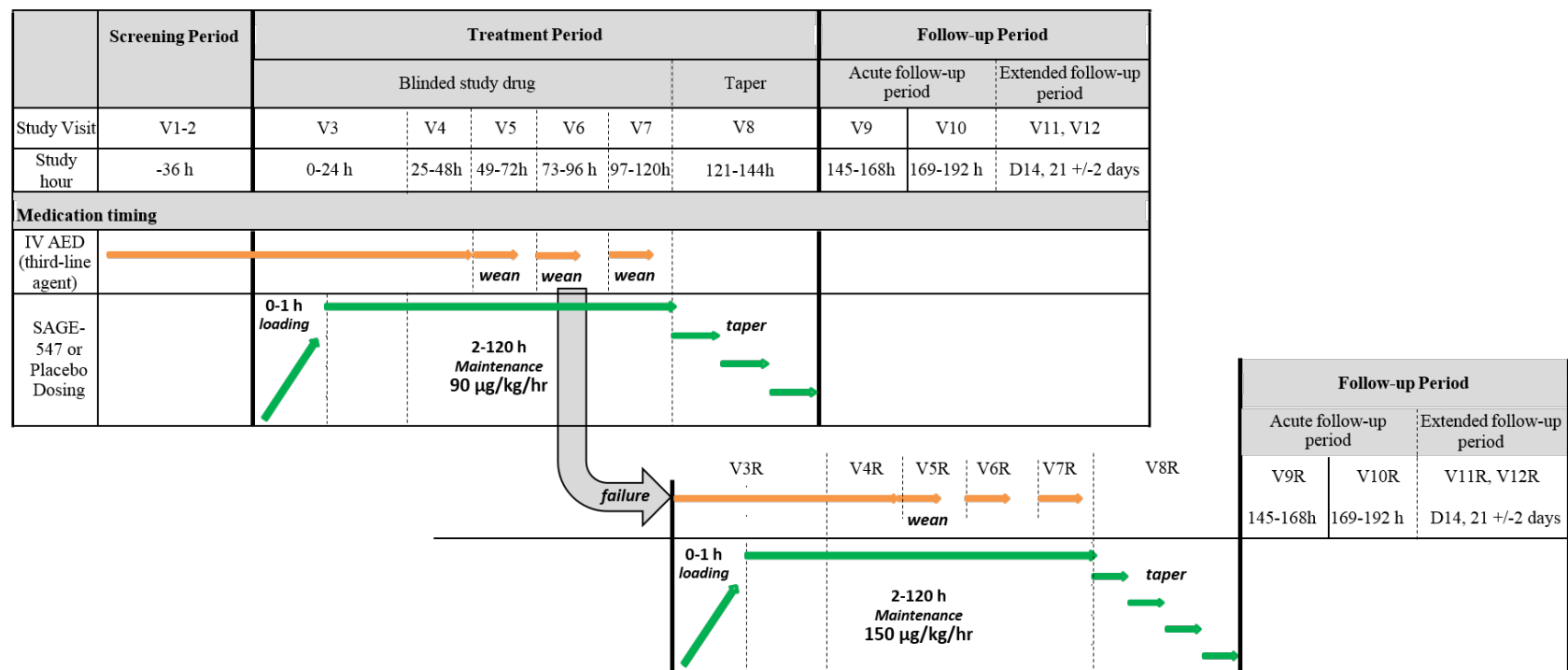
This study will be conducted according to the principles of the World Medical Association Declaration of Helsinki and most recent amendment (2008), and in compliance with the protocol approved by the IRBs/Independent Ethics Committees (IECs), and in accordance with ICH Guidelines on GCP standards.

## 7.3. Blinding and Randomization

Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo. The randomization will be stratified by concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). A dynamic randomization (minimization algorithm) will be used to achieve 1:1 balance across the stratification factors and between the treatment groups (SAGE-547 and placebo). Details of the dynamic randomization process will be included in the SAP.

The randomized portion of the study will be blinded, with the two treatment products (SAGE-547 and placebo) being indistinguishable so that patients, relatives, nursing and medical staff, pharmacists and monitors will not be able to ascertain which subject was allocated to which treatment.

The second infusion of SAGE-547 will be administered on an open label basis to subjects who failed the primary endpoint wean.

**Figure 2: Details of Treatment Administration and Follow-up**

## 8. SELECTION AND WITHDRAWAL OF SUBJECTS

The study will randomize 140 patients at up to 150 sites. All subjects deemed eligible to enroll must have written Medical Monitor approval on a case-by-case basis prior to undertaking the qualifying wean.

### 8.1. Inclusion Criteria

The following inclusion criteria must be met for individuals to be eligible for the trial.

1. Subjects two (2) years of age and older.
2. Subjects who have:
  - Failed to respond to the administration of at least one first-line agent (e.g., benzodiazepine or other emergent initial AED treatment), according to institution standard of care, and;
  - Failed to respond to at least one second-line agent (e.g., phenytoin, fosphenytoin, valproate, phenobarbital, levetiracetam or other urgent control AED), according to institution standard of care, and;
  - Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; *or* who have previously failed one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst suppression pattern; *or* who have previously failed one or more wean attempts from third-line agents and are now either not on a continuous intravenous infusion of at least one third-line agent or are on a continuous intravenous infusion of one or more third-line agent but not in an EEG burst suppression pattern.

### 8.2. Exclusion Criteria

None of the following exclusion criteria can be met for individuals to be eligible for the trial.

1. Subjects who are pregnant.
2. Subjects with a known allergy to progesterone or allopregnanolone.
3. Subjects with SRSE due to anoxic/hypoxic encephalopathy.
4. Children (subjects aged less than 18 years) with an encephalopathy due to an underlying progressive neurological disorder.
5. Subjects who have any of the following:
  - a. a GFR low enough to warrant dialysis but for whatever reason, dialysis is not planned or non-continuous dialysis planned (that would not adequately remove Captisol<sup>®</sup>);
  - b. severe cardiogenic or vasodilatory shock requiring two or more pressors that is not related to third-line agent use;
  - c. fulminant hepatic failure;
  - d. no reasonable expectation of recovery (for instance, a likely outcome is persistent vegetative state) or life-expectancy, in the experience of the investigator, is less than 30 days;
  - e. a do not resuscitate (DNR) order.

6. Subjects who are being administered more than three third-line agents concomitantly or for whom the qualifying wean cannot be completed within 24 hours or who are being administered a third-line agent for indications such as raised intra-cranial pressure that would preclude weaning according to this protocol.
7. Subjects with a living will that does not allow heroic measure.
8. Subjects who have been exposed to an investigational medication or device within 30 days; the exception to this is that participation in the Established Status Epilepticus Treatment Trial or ESETT within 30 days of screening for the 547-SSE-301 trial is allowed.
9. Subjects who have been enrolled in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not withdraw or complete and then re-enroll).

### **8.3. Selection and Consent of Subjects for Pharmacogenetic Substudy**

All subjects will be asked to participate in pharmacogenetic research; however, participation in research is voluntary and a subject can decide to decline his/her participation without penalty or loss of benefit. Participation or lack thereof will not be a cause for exclusion from any aspect of the main study. In addition to fulfilling all of the selection criteria described above, for inclusion in genetic research, subjects will also need to provide specific informed consent for genetic sampling and analyses, not have received a non-leukocyte-depleted transfusion within 120 days and not have had a previous allogenic bone marrow transplant.

### **8.4. Subject Withdrawal / Study Termination**

#### **8.4.1. Withdrawal/Discontinuation of Individual Subjects**

The reasons for study drug discontinuation and/or subject withdrawal from the study must be recorded in the subject's electronic case report form (eCRF). The Investigator must notify the Sponsor and/or the Medical Monitor immediately when a subject has been discontinued/withdrawn due to an AE.

##### **8.4.1.1. Withdrawal from the Study**

Subjects or their LAR may withdraw subjects from the study at any time for any reason without compromising the subject's medical care. The Investigator will also withdraw subjects upon the request of Sage Therapeutics or upon termination of the study.

Subjects who withdraw from the study prior to Visit 10 (or 10R) should complete the procedures scheduled for the day of study drug taper (hour 121-144; Visit8/8R) on the day of their withdrawal, including the SAGE-547 taper schedule, with the addition of the mortality assessment from Visit 12/12R. Subjects who withdraw from the study after Visit 10/10R should undergo study procedures as outlined for Visit 12/12R on the day of their withdrawal. In all cases, the reason for subject withdrawal will be recorded in the eCRF.

Withdrawal of subjects for any reason should be discussed with the Medical Monitor.

##### **8.4.1.2. Discontinuation of Study Drug**

If it is necessary to discontinue the study drug earlier than planned, subjects should continue to be followed per protocol to capture safety and efficacy assessments for the duration of the study period.

The investigator may withdraw the subject from the study drug for the following reasons:

- Upon subject's or LAR's request
- The subject or LAR is unwilling or unable to adhere to the protocol-specified visits
- The subject experiences an intolerable adverse event
- During the course of the study, the subject develops symptoms or conditions listed in the exclusion criteria.
- Other medical reason, at the discretion of the Investigator and/or the Medical Monitor

Subjects who discontinue the study due to an AE considered related to study drug should be followed until the event is resolved, considered stable, or the Investigator determines the event is no longer clinically significant. Study drug discontinuation due to AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

#### **8.4.2. Study Termination**

Sage Therapeutics may terminate this study or any portion of the study at any time for safety reasons including the occurrence of AEs or other findings suggesting unacceptable risk to subjects, administrative or operational reasons. In the event of study termination, Sage Therapeutics will provide written notification to the Investigator. Investigational sites must promptly notify their IRB and initiate withdrawal procedures for participating subjects.

## **9. INVESTIGATIONAL PRODUCT**

### **9.1. Identity of Investigational Product**

SAGE-547 Injection (allopregnanolone)

### **9.2. Clinical Supplies**

#### **9.2.1. SAGE-547**

Adequate supplies of SAGE-547 Injection and materials for intravenous administration will be provided to each site.

SAGE-547 Injection is a clear, colorless sterile solution of allopregnanolone intended for intravenous injection. SAGE-547 Injection is an aqueous solution of 5 mg/mL allopregnanolone in 250 mg/mL Captisol® (betadex sulfobutyl-ether sodium, NF). It is presented either un-buffered or buffered with 10 mM citrate at a pH of 6.0 in either 20 mL or 50 mL vials. SAGE-547 is further diluted according to the Pharmacy Manual to achieve an approximately isotonic solution and will be administered intravenously.

No preservatives are included in the drug product, which is intended to be used as a single-use vial. All inactive components (excipients) used in the formulation are compendial grade and conform to current USP/EP, and include sodium citrate, citric acid and betadex sulfobutyl-ether sodium (Captisol®).

**9.2.2. Placebo**

Placebo will be identical to SAGE-547 and presented in identical vials. Placebo will be manufactured in a similar way to SAGE-547 and comprises all excipients but no SAGE-547.

**9.2.3. Blinding**

The vials of SAGE-547 and placebo will be identical in every way so that they are indistinguishable by the pharmacist, investigator, anyone treating or managing the patient, the monitors, and the sponsor. In this way the first infusion of study drug administered to each patient will be double-blind.

For the blinded study drug infusions, subject-specific dosing kits will be provided. These dosing kits will be pre-labelled with kit number for the first blinded infusion. For the second-infusion, open-label kits will be provided, which will require subject assignment by the pharmacy for reconciliation purposes. The study kits must be stored under refrigerated conditions (2-8 °C). IV administration bags and lines may be provided for the blinded and open-label infusions. Refer to the Pharmacy Manual for additional details.

The label for the SAGE-547 Injection vials will include standard product identification information according to the Code of Federal Regulations, 21CFR 312.6. All study labels will also contain the following statement:  
Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use.

**9.3. Preparation of SAGE-547 or Placebo Injection for Dosing**

The Pharmacy will be responsible for preparing the blinded and open-label study drug for subject dosing. The prepared admixture will be assigned a room temperature (20-25 °C) storage shelf life of 30 hours from time of compounding.

SAGE-547, which is hypertonic, will require dilution with SWFI to achieve an approximately isotonic solution according to the instructions provided in the Pharmacy Manual. Exactly the same procedures will be used to prepare the placebo admixture, so that all site staff remain blinded as to treatment allocation for the first infusion of study drug. SAGE-547 Injection is not intended to be administered to patients undiluted.

Refer to the Pharmacy Manual for specific instructions regarding infusion preparation.

**9.4. Administration and Accountability**

The Pharmacy will maintain accurate records of all investigational product supplies. Accurate records will be kept regarding the volume of SAGE-547 Injection or placebo used for each IV preparation, as well as the required infusion rate or rates, and the date and time of preparation. Reasons for departure from the expected dosing regimen must also be recorded. To satisfy regulatory requirements regarding drug accountability, all study medication will be reconciled in full. Refer to the Pharmacy Manual for additional details.



## 10. TREATMENT OF SUBJECTS

### 10.1. Dosing Schedule (Blinded Infusions)

SAGE-547 Injection or placebo will be administered according to the dosing schedules in Table 5. The infusion rates to accomplish these  $\mu\text{g/kg/h}$  doses will be calculated according to the weight of the subject. The infusion rates will be applied to blinded study drug for the first infusion of study medication.

**Table 5: SAGE-547 or Placebo Dosing Schedule**

Hour	Type and Duration of Study Drug Infusion	Description
H1	One hour loading Infusion	300 $\mu\text{g/kg/h}$
H2 – H120	119 hour maintenance infusion	90 $\mu\text{g/kg/h}$
H121 – H128	8 hour taper	65 $\mu\text{g/kg/h}$
H129 – H136	8 hour taper	45 $\mu\text{g/kg/h}$
H137 – H144	8 hour taper	25 $\mu\text{g/kg/h}$

### 10.2. Dosing Schedule (Open-Label Infusions)

If a subject fails wean from third-line agent(s) or requires re-instatement of third-line therapy within 24 hours of discontinuing the initial infusion of study drug, SAGE-547 Injection will be re-administered according to the dosing schedule in Table 6. The infusion rates to accomplish these  $\mu\text{g/kg/h}$  doses will be calculated according to the weight of the subject. These infusion rates will be applied to SAGE-547 re-treatment for the open-label second infusions of study medication.

**Table 6: SAGE-547 Open Label Dosing Schedule**

Hour	Type and Duration of SAGE-547 Infusion	Description
H1	One hour loading Infusion	300 $\mu\text{g/kg/h}$
H2 – H120	119 hour maintenance infusion	150 $\mu\text{g/kg/h}$
H121 – H126	6 hour taper	125 $\mu\text{g/kg/h}$
H127 – H132	6 hour taper	95 $\mu\text{g/kg/h}$
H133 – H138	6 hour taper	65 $\mu\text{g/kg/h}$
H139 – H144	6 hour taper	35 $\mu\text{g/kg/h}$

### 10.3. Route of Administration

SAGE-547 Injection is intended for IV administration only. The compatibility of SAGE-547 with other drugs is unknown, and the product should be administered via a dedicated peripheral IV line using any Sage-supplied study-specific IV administration bags and lines. In order to preserve blinding, these instructions also apply to the blinded placebo infusions.

### 10.4. Treatment Period

The treatment period with double-blind SAGE-547 or placebo is six 24-hour periods (144 hours), which may encompass 6-7 calendar days. The retreatment period is of identical duration.

## **10.5. Concomitant Medications**

Subjects will receive the standard of care for SRSE. Any concomitant medication determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. All concomitant medications should be documented throughout the study from Screening through Visit 12/12R and recorded on the eCRF.

SAGE-547 has demonstrated inhibitory effects on cytochrome P450 isoenzyme 2C9 (CYP2C9). Therefore, AEDs such as phenytoin and phenobarbital that are primarily metabolized by CYP2C9 should be closely monitored during SAGE-547 administration to ensure target exposures are maintained.

### **10.5.1. Concomitant AEDs**

Subjects may enter the study on AEDs, and be administered AEDs during the study. All of these must be recorded on the eCRF with details including date and time of starting and stopping each AED, the route of administration, changes in doses, and frequency of administration. In addition, details of the first-line and second-line agents used to treat the subject prior to consenting for the study will be recorded on the eCRF, noting at what point the subject was deemed to have “failed first-line agents” and “failed second-line agents”.

### **10.5.2. Concomitant Third-Line Agents**

All third-line agents (as defined in [Section 8](#)) administered since the diagnosis of SE will be recorded on the eCRF, whatever path the patient took for entry into the study. Details will include the name of the drug, the start and stop dates and times, and the doses with start and stop times for each change in dose. This recording of third-line agents will continue throughout the study until Visit 12/12R.

In addition, those changes in dose that constitute a wean attempt will be marked as such on the eCRF. In this way the start and stop dates and times of all wean attempts (see [Section 11](#) for definitions) will be recorded, as will the type of wean (QW, OW, or TW) and the outcome of the wean attempt (successful, failed and dose of this third-line agent increased or failed and this third-line agent stopped and another third-line agent started). Those wean attempts that occur after the TW up to and including Visit 12/12R will be marked “AW”.

Some third-line agents (such as propofol) are also used to induce sedation to facilitate a subject’s ability to tolerate the ventilator, or as analgesics to cover potentially painful procedures. For subjects requiring such sedation, propofol is the preferred agent unless there are contraindications. The eCRF will make clear from the indication for the third-line agent when it is being used for burst or seizure suppression and when it is being used as ventilator support or for another purpose. The investigator will add a note to the eCRF to justify that the doses used are appropriate for sedation and not for seizure or burst suppression. The doses used for ventilator support and other similar uses are usually much lower than those used for seizure or burst suppression, and use of these third-line agents for these other purposes does not constitute a wean failure under this protocol.

### **10.5.3. Concomitant Pressors**

The start and stop dates and times of all pressors will be recorded as well as the start and stop dates and times of all dose changes.

#### **10.5.4. Other Concomitant Medications**

All other concomitant medications must be recorded on the eCRF with details including date and time of starting and stopping, the route of administration, dose, and frequency of administration.

### **11. STUDY ASSESSMENTS**

#### **11.1. Efficacy Assessments**

##### **11.1.1. Primary Efficacy**

Success or failure will be determined, with success defined as weaning the subject off all third-line agents before completion of the first blinded infusion of SAGE-547 or placebo infusion and not having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the blinded (first) infusion of SAGE-547 or placebo. In addition, subjects must have evidence of physiologic brain activity (determined by EEG) to be deemed to be successes.

##### **11.1.1.1. Weaning**

Third-line agents are anesthetic agents that are administered in order to reach a burst suppression EEG pattern. For the purposes of this study, third-line agents are defined as continuous intravenous infusions of pentobarbital, midazolam, propofol, and ketamine at maintenance doses alone or in combination sufficient to produce a burst suppression pattern on the EEG. The following are considered to be minimum maintenance doses of these agents that may be expected alone or in combination to achieve EEG burst suppression. If subjects are on lower doses than these and are not in EEG burst suppression for the 24 hours prior to the QW, they will be considered to be screen failures and will exit the study after the QW.

- Pentobarbital: 1 mg/kg/hour
- Midazolam: 0.1 mg/kg/hour
- Propofol: 3 mg/kg/hour
- Ketamine 1.2 mg/kg/hour

The timing and nature of the third-line agent weans will be determined by the standard of care at the site and the clinical judgment of the investigator, and will always be primarily done in the best medical interests of the subject. However, the following guidance must be followed and if questions arise regarding the weaning of third-line agents, specifics should be discussed with the medical monitor. Additionally, advice about weaning may be sought from fellow investigators in the study, particularly those with the most experience of performing clinical trials in subjects with SRSE.

The following guidance for weaning applies to all weans of third-line agents undertaken during the study. These weans include the qualifying wean (QW); the terminal wean (TW), which is the wean of the third-line agent if the subject is on only one third-line agent or the wean of the last third-line agent if the subject is on more than one third-line agent; the other weans (OW), which are the weans of the third-line agents other than the TW if the subject is on more than one third-line agent. The guidance also applies to additional weans (AW), which are the weans from third

line agents that take place after the TW for the first blinded study drug infusion or the second open-label study drug infusion.

### **QW Guidance**

- Wean to be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace that third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.

### **OW Guidance**

- First OW should begin at H49 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- If the subject is on two third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- If the subject is on three third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the wean of the second agent. The second agent should be weaned over 24 hours and that wean completed before starting the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.
- All OWs should be completed before H96 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

### **TW Guidance**

- If the subject is on one third-line agent, the TW should begin at H49 after starting administration of study drug or starting the open-label infusion of SAGE-547. If the subject has had one or more OWs, the TW should begin as soon as the last OW is complete but in any case not later than H97 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.
- The TW must be completed as soon as possible, but in any case over no more than 24 hours.
- Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens. If breakthrough seizures cannot be managed in this way, the third-line agent being weaned should be re-instituted at a dose that was controlling seizures, or a new third-line agent should be started to replace this

third-line agent or be administered in addition to the third-line agent that is the subject of the wean attempt.

- Every effort must be made to complete the TW before H120 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547, but the TW must be complete before H144 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.

## **AW Guidance**

- AWs will take place when medically indicated in the opinion of the investigator.
- Ideally the AW should take place over 24 hours. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.

### **11.1.1.2. EEG**

Electroencephalographs (EEGs) that are representative of the intermittent or continuous EEG being used to support key investigator decisions will be collected at the following time points:

- A six-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst suppression for the second path to eligibility, and a variable pattern for the third path to eligibility.
- EEG will be performed to cover the qualifying wean (QWEEG). EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for the one hour after the end of the QW. The duration of the QWEEG will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s) or the decision to re-institute a third-line agent(s) at doses intended to induce burst suppression.
- EEG will be performed from three hours prior to the start of the blinded infusion to five hours after the start of the blinded infusion. The intent of this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG.
- EEG will be performed to cover the final or terminal wean of third-line agent (TWEEG). The TW is the wean of the final third-line agent during the blinded administration of study drug or the open-label infusion of SAGE-547; if the subject was on one third-line agent, the TW is the wean of that agent. If the subject was on three third-line agents, the TW is the wean of the third and final agent. EEG recording will start 30 minutes prior to the start of the TW, continue for up to 24 hours during the TW, and then continue for the one hour after the end of the TW. The duration of the TWEEG will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the final third-line agent or the decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity could not be managed using intermittent bolus doses of AEDs.

- EEG will be performed during the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 (TAEED). The TAEED is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the start of the taper (at Hour 119.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours during the taper, and then continue for the one hour after the end of the taper (to Hour 145 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547). The duration of the TAEED will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity seen during the taper could not be managed using intermittent bolus doses of AEDs.
- EEG will be obtained to cover the end of the taper of the blinded administration of study treatment or the open-label infusion of SAGE-547 and the ensuing 24-hour period, during which the primary endpoint is assessed (PAEED). The PAEED is recorded for all subjects, whether they are deemed to be successes or failures on the primary endpoint. The EEG recording will start 30 minutes prior to the end of taper (at Hour 143.5 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547), continue for 24 hours after the end of the blinded administration of study treatment or the open-label infusion of SAGE-547, and then continue for the one hour after the end of the 24-hour assessment period (to Hour 169 after starting the blinded administration of study treatment or after starting the open-label infusion of SAGE-547). The duration of the PAEED will be 25.5 hours. The EEG will therefore include the EEG patterns that correspond to any decision to re-institute a third-line agent at doses intended to induce burst suppression because any seizure activity seen in the 24 hours following the end of the blinded administration of study treatment or the open-label infusion of SAGE-547 that could not be managed using intermittent bolus doses of AEDs.

In practice, most subjects are on continuous EEG monitoring or long periods of intermittent EEG monitoring. However, this protocol does not mandate continuous EEG monitoring and breaks from EEG monitoring to provide relief to the scalp from the irritating effects of the electrodes are advised, particularly in children, according to local practice. If a break in EEG monitoring is mandated by local practice guidelines at a time when one of the protocolled EEG segments is to be collected, the break in EEG monitoring will take precedence, with the reason for missing the EEG reading noted on the eCRF. The EEGs obtained for the study are therefore part of the existing EEG record rather than being obtained de-novo at each timepoint. For timepoints where there might be some ambiguity, such as the TWEEG, the final EEG record is that of the final attempt to wean the last third-line agent, even if earlier attempts to wean that agent took place. In some cases (the TAEED and PAEED, for instance), the EEG records will overlap, but different cuts are taken to service the different EEG record requirements.

The electronic EEG file will be de-identified, the date and time of the start and stop of the EEG and the subject number will be attached to the file, and the study time point will be indicated (CEEG, QWEEG, TWEEG, TAEED, and PAEED). The PI will indicate on the eCRF what the EEG shows, as follows:

- For the CEEG, the PI will describe the EEG pattern that determined which path to eligibility the subject was on.

- For the QWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure on the qualifying wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the qualifying wean).
- For the TWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure on the terminal wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the terminal wean).
- For the TAEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst suppression before the end of the SAGE-547 infusion).
- For the PAEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported any decision to determine that the subject was a failure on the primary endpoint (inability to wean off the third-line agent by the end of the SAGE-547 infusion or the third-line agent reinstituted for burst suppression in the 24 hours following the end of the SAGE-547 infusion).

The six EEG records for each subject will be read centrally to confirm the PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period. The EEG records may be subject to quantitative EEG analysis.

### **11.1.2. Secondary Efficacy**

#### **11.1.2.1. Clinical Global Impression Scale (CGI)**

The CGI scales are validated measures often utilized in clinical trials to allow clinicians to integrate several sources of information into a single rating of the subject's condition. Both the CGI-Severity (CGI-S) and the CGI-Improvement (CGI-I) employ a 7-point Likert scale measuring severity of the disease state in the subject and improvement, respectively. All severity assessments after initiation of SAGE-547 treatment should consider the general state of the subject over the preceding week.

- The CGI will be evaluated at Visit 1 and at the last visit, Visit 12 or 12R.

#### **11.1.2.2. Epilepsy Status**

At Visit 1, the diagnosis of epilepsy will be documented as a no/yes question. If there was a previous diagnosis of epilepsy, further details will be documented, including:

- Date of diagnosis;
- Details of anti-epileptic drugs currently being taken;
- Type of epilepsy;
- Seizure frequency in the past month.

Information about the current (index) episode of status epilepticus will be obtained at Visit 1:

- Date of onset
- Date of failure to respond to first line agent(s) and the name(s) of the agent(s)
- Date of failure to respond to second line agent(s) and the name(s) of the agent(s)
- Any previous treatment with third line agents and the response to those agents (details of the third line agent drugs and previous wean attempts will be recorded on the Third Line Agent Medication CRF)
- The cause of the index episode of status epilepticus
- If the subject was transferred from another hospital or from within the hospital, the reason for the transfer will be recorded (such as for study enrollment, due to lack of medical options at original hospital or unit, due to lack of beds at the original hospital or unit, family request, other)

Previous (non-index) diagnosis of status epilepticus will be documented as a no/yes question. If SE did occur in the past, further information will be gathered, including:

- SE, RSE, or SRSE diagnosis;
- Cause;
- Treatment, including experimental treatments and need for intubation/ventilation;
- Dates of onset and duration.

At Visit 12 or Visit 12R, the following information will be gathered:

- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of SE up to and including Visit 12 or Visit 12R;
- The number of calendar days since H144 at the end of Visit 8 or Visit 8R that the subject has been free of seizures (convulsive and non-convulsive) up to and including Visit 12 or Visit 12R;
- Number of separate episodes of SE after H144 at the end of Visit 8 or Visit 8R (no/yes); if yes,
  - SE, RSE, or SRSE diagnosis;
  - Cause;
  - Treatment, including experimental treatments and need for intubation/ventilation;
  - Dates of onset and duration.

Note that a separate episode of SE is defined as an episode of SE separated from other periods of status epilepticus by at least 24 hours.

- Diagnosis of epilepsy since Visit 11 or Visit 11R will be documented as a no/yes question. If a diagnosis of epilepsy has been made, further details will be documented, including:
  - Status as ongoing or new epilepsy since Visit 11 or Visit 11R after initiation of SAGE-547 treatment;
  - Details of anti-epileptic drugs currently being taken;



- Type of epilepsy and seizure frequency in the past week.

## 11.2. Safety Assessments

The safety and tolerability of SAGE-547 will be assessed using adverse events, clinical laboratory measures, vital signs, ECG intervals and morphology, and mortality. All safety assessments should be performed per hospital standard of care and will be collected periodically throughout the study according to [Table 1](#), [Table 2](#) and [Table 3](#) (Schedules of Assessments).

### 11.2.1. Adverse Events

AEs will be collected after informed consent has been signed and prior to study-specific screening procedures not considered standard of care, during subject preparation for SAGE-547 administration and through Visit 12 or Visit 12R. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™) coding system (current version). See [Section 14](#) for additional details.

### 11.2.2. Clinical Laboratory Tests

Blood samples will be taken for hematology, and serum chemistry and GFR will be calculated at:

- Visit 1 and then at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.
- Blood samples will be taken at Visit 11 or Visit 11R for serum chemistry (renal panel only).

Urine samples will be taken for urinalysis at:

- Visit 1 and at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.

These samples will be analyzed at a central laboratory; hour-to-hour medical decisions will be based on sampling for laboratory testing done outside the protocol as part of normal standard of care.

Any out-of-range values will be flagged by the laboratory; the investigator will add a comment about whether the abnormality is clinically significant. Clinical significant abnormalities are those that prompt an intervention and will be recorded as adverse events.

#### 11.2.2.1. Hematology and Serum Chemistry

Hematology will include complete blood count (CBC) white blood cell count with differential, platelet count and red blood cell (RBC) count, hemoglobin and hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), NAG, calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose.

#### **11.2.2.2. Pregnancy Test**

Females of child-bearing potential will be tested for pregnancy by serum pregnancy test at Visit 1. In this study, since an accurate history of menstruation in girls and menopause in older women may not be available at Visit 1, “child-bearing potential” is taken to mean any female aged 12 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy. Female subjects with a positive pregnancy test will be ineligible for study participation.

#### **11.2.2.3. Urinalysis**

Urinalysis will include assessment of protein, blood, leukocytes, glucose, ketones, urobilinogen, pH, and specific gravity.

#### **11.2.3. Vital Signs**

Blood pressure, heart rate, respiratory rate, temperature, and oxygen saturation will be recorded at the following time points relative to the first infusion of study drug, and to the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547:

- Visit 1;
- At 0, +30, +60 minutes (+/-15 minutes) and +2, +4 and +8 hours (+/- 30 minutes) after the start of the infusion;
- At +24, +48, +72, +96, +120, +144, +168, and +192 hours (+/- 2 hours) after the start of the infusion.

Respiratory rate does not need to be collected if the subject is mechanically ventilated at the due time of the vital sign assessment.

#### **11.2.4. Weight and Height**

Weight and height will be measured at Visit 1 and weight will also be measured once during each 24 hour period of the first infusion of study drug, and of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547. These daily weights will be used to modify the dose of SAGE-547 if required.

#### **11.2.5. ECG**

12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug. All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours; at other times the allowed time window for ECGs is +/- 2 hours:

- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +128, +136, +144, +152, +160, and +192 hours after the start of the blinded (first) study drug infusion
- pre-dose and at +0.5, +1, +3, +6, +12, +24, +48, +72, +96, +120, +126, +132, +138, +144, +152, +160, and +192 hours after the start of the open-label (second) study drug

The heart rate and PR, QRS, QT, and QTc intervals will be recorded, as well as any clinically significant abnormalities in the rhythm.

### 11.2.6. Mortality

Mortality will be recorded on the Visit 12 or Visit 12R case report form. If the subject has died, the following information will be collected:

- Date of death;
- Cause of death.

As accurate as possible cause of death will be collected, which will be further categorized as due to one of the following causes:

- SE;
- complications of long term intubation and third-line agent infusions;
- underlying cause of qualifying SE;
- co-morbidity existing at the time of the qualifying SE;
- new co-morbidity or trauma;
- other (specify).

### 11.2.7. Pharmacogenetic Samples

If a subject's LAR consents to pharmacogenetic sampling, a blood sample for genetic research will be collected at Visit 1 in order to avoid the possible introduction of bias through the exclusion of patients who may withdraw from study due to an AE (a subject population that may be of specific interest for subsequent genetic analysis). If for any reason a sample cannot be taken prior to treatment, a sample can be drawn at any point prior to completion with the restriction that no more than one genetic sample be taken per subject.

The objective of this research is to collect and store blood samples for possible DNA extraction and exploratory research into how genes or specific genetic variation may influence response (i.e. distribution, safety, tolerability, and efficacy) to SAGE-547. Specific genetic variations of interest include but are not limited to: classes of metabolizing enzymes (e.g. Cytochrome P450 supra-family genes), genes encoding enzymes involved in the production and metabolism of allopregnanolone (e.g. AKR1C4 (3 $\alpha$ -hydroxysteroid dehydrogenase)), genes associated with the GABA receptor (e.g. GABRA1-A6, GABRB1-B3, GABRD, GABRE, GABRG1-3) and genes associated with the production and degradation of GABA.

Future research may suggest other genes or gene categories as candidates for influencing not only response to SAGE-547 but also susceptibility to disorders for which SAGE-547 is being evaluated. Thus, the genetic research may involve study of additional unnamed genes or gene categories, but only as related to disease susceptibility and drug action.

#### 11.2.7.1. Biological Sampling and Coding Procedures (Pharmacogenetics)

To ensure patient confidentiality, utmost care will be taken in the coding and storage of pharmacogenetic samples.

*Extraction and coding:* DNA will be extracted from the blood sample and the DNA sample will be assigned a unique number replacing information from sampling tube. The assigned DNA number will be used to identify the sample and its corresponding information within Sage Therapeutics or at any designated contract laboratory for the purpose of sequencing of other DNA specific

analysis. No personal details sufficient for individual identification will be available to any person (internal or external to Sage Therapeutics) working with the DNA.

*Genotype/Phenotype Analysis:* Samples and data from genetic analysis will be coded. The link between subject enrollment / randomization code and DNA number will be maintained and stored in a secure environment with restricted access. The established link will be used to identify relevant DNA samples for analysis, facilitated correlation of genotype results with clinical data, allow regulatory audit, and to trace samples for destruction in case of withdrawal of consent.

#### **11.2.7.2. Retention of Biological Samples for Pharmacogenetic Analysis**

Extracted DNA is a finite research that is destroyed in the process of being analyzed. Primary blood samples from which DNA can be extracted will be stored and used until no further analyses are possible, a maximum storage period of 25 years from time of last subject last visit has been reached, or an individual or LAR withdrawals his/her or their consent.

#### **11.2.8. Other Outcomes**

##### **11.2.8.1. Pharmacokinetic Data**

Formal plasma and urine analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS)). In addition, all samples will be analyzed for important SAGE-547 metabolites (if and when these are identified) and Captisol® concentrations.

##### Plasma Analysis

Plasma will be collected to assay for SAGE-547 concentrations at the following time points relative to the start of each infusion of study drug:

- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +128 (immediately prior to the end of the first taper step), +136 (immediately prior to the end of the second taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the blinded SAGE-547 or placebo study drug infusion.
- pre-dose and at +0.5, +1 (immediately prior to the end of the loading dose), +3, +6, +12, +24, +48, +72, +96, +120 (immediately prior to the end of the maintenance infusion), +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 (immediately prior to the end of the third taper step), +144 (immediately after stopping the study drug infusion), +152, and +160 hours after the start of the open label SAGE-547 study drug infusion.
- All samples will also be analyzed for plasma concentrations of important metabolites of SAGE-547 if and when these are identified.
- All samples will also be analyzed for plasma concentrations of Captisol®.

The plasma samples will be drawn from an arterial-line, central line or the arm contralateral to that used for drug administration. PK collection times should be adhered to as strictly as possible. The allowed time window for all samples is +/- 5 minutes. Subject-specific PK kits for sampling including instructions on collection and processing methods, and storage and shipping conditions, will be provided separately. To maintain the blind, all subjects will have samples taken as outlined

above: subjects receiving SAGE-547 will have all samples analyzed for all analytes. Subjects on placebo may have samples analyzed to investigate endogenous allopregnanolone and metabolite concentrations, as well as Captisol<sup>®</sup> concentrations; experience with the plasma concentration data will determine if and which placebo samples are analyzed.

Each blood sample will be 3 ml in volume for adults and children weighing 30 kg or more, and 1.5 ml in volume for children weighing less than 30 kg. Separate aliquots will be obtained from each sample to service the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum blood draw for a subject having two infusions of study drug will be 99 ml (49.5 ml for children weighing less than 30 kg).

Plasma PK parameters for SAGE-547 will be calculated where appropriate (e.g.,  $C_{max}$ ,  $C_{min}$ ,  $t_{max}$ ,  $AUC_{last}$ ,  $AUC_{\infty}$ ,  $CL_s$ ). In addition, similar PK parameters will be calculated for Captisol<sup>®</sup>. PK parameters for important metabolites of SAGE-547 may be calculated. An evaluation will be made of the feasibility of adopting a population-PK approach to assess drug-drug-interactions with SAGE-547 as victim of AEDs.

In addition, the Visit 9 sample may be analyzed for plasma concentrations of third-line agents.

#### Urine Analysis

In the first 70 patients enrolled in the study, all urine voided in each 24-hour period during and after the blinded and open-label infusions of study drug will be collected and pooled. The total volume for each 24-hour period will be measured and a 20 ml sample will be taken from each pooled urine collection (0-24 hours: 25-48 hours: 49-72 hours: 73-96 hours: 97-120 hours: 121-144 hours: 145-168 hours) and analyzed for urine concentrations of SAGE-547 (and important metabolites as and when these are identified) and Captisol<sup>®</sup>.

Full details of all pharmacokinetic analyses will be described in the Pharmacokinetic Analysis Plan.

#### **11.2.8.2. Correlation of QT/QTc Changes and Plasma Concentrations of SAGE-547**

An analysis will be performed to determine whether there is any correlation between changes in QT/QTc interval and plasma concentrations of SAGE-547, in order to investigate any effect that SAGE-547 may have on QT/QTc interval.

#### **11.2.8.3. Pharmacoeconomic Data**

At Visit 12 or Visit 12R, the following information will be collected: number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital. If the subject dies before Visit 12 or Visit 12R, data will be collected up to the date of death. The definition of “hospital” is the institution that the subject was initially treated in. If the subject is transferred to another hospital, that hospital would be the “discharge destination from the hospital” and the “number of days in hospital” would be the number of days in the initial treating hospital.

#### **11.2.8.4. FOUR Score**

The Full Outline of UnResponsiveness or FOUR Score is designed to assess conscious level and unlike other scores, is suitable for subjects who are intubated. It assesses four domains of neurological function (eye responses, motor responses, brainstem reflexes, and breathing pattern).

The FOUR Score will be collected at the following time points relative to each infusion of study drug (the initial blinded infusion and the second open-label infusion if this is administered):

- baseline, +24, +48, +72, +96, +120, +144, +168, and +192 hours (all +/- 2 hours) after the start of the infusion, and at Visit 11/11R and Visit 12/12R.

#### **11.2.8.5. Glasgow Outcome Scale (GOS)**

The GOS is a relatively common assessment scale used to standardize descriptions of the objective degree of recovery from brain injury such as cerebral trauma, or in this case SRSE. It was first used in 1975 ([Jennett and Bond 1975](#)) and allows a prediction of the long-term course of rehabilitation to return to work and everyday life. The scale classifies subjects into 5 groups:

- Death: severe injury or death without recovery of consciousness
- Persistent vegetative state: severe damage with prolonged state of unresponsiveness and a lack of higher mental functions
- Severe disability: severe injury with permanent need for help with daily living
- Moderate disability: no need for assistance in everyday life, employment is possible but may require special equipment
- Low disability: light damage with minor neurological and psychological deficits.

The GOS will be assessed at Visit 12 or Visit 12R.

#### **11.2.8.6. Supervision Rating Scale (SRS)**

The Supervision Rating (SRS) measures the level of supervision that a patient/subject receives from caregivers. The SRS rates level of supervision on a 13-point ordinal scale that can optionally be grouped into five ranked categories (Independent, Overnight Supervision, Part-Time Supervision, Full-Time Indirect Supervision, and Full-Time Direct Supervision). The SRS was designed to be rated by a clinician based on interviews with the subject and an informant who has observed at first hand the level of supervision received by the subject ([Boake 2000](#)). Scoring is a one-step procedure in which the clinician assigns the rating that is closest to the subject's level. Ratings are based on the level of supervision received, not on how much supervision a subject is judged or predicted to need.

The SRS will be assessed at Visit 1 and Visit 12 or Visit 12R. The Visit 1 assessment will be a retrospective assessment of the supervision required by the subject immediately prior to the admission that included the index episode of status epilepticus.

#### **11.2.8.7. Modified Rankin Scale – 9Q (mRS-9Q)**

The Modified Rankin Scale (mRS) is a commonly used scale to determine disability and functional dependence due to neurological insult such as stroke in adults. The 7 point scale (0 – 6) denotes functional capacity from no symptoms (0) to severe disability (5) and death (6). The Modified Rankin Scale – 9Q is a shortened version consisting of 9 questions that reliably determines the mRS score and was developed to both simplify the assessment and expand the rater base to non- medically trained personnel ([Patel, Rao et al. 2012](#)). The assessment is a web-based tool in the public domain with automatic score calculation and error checking found at [www.modifiedrankin.com](http://www.modifiedrankin.com).

The mRS will be assessed at Visit 1 and at Visit 12 or Visit 12R in subjects  $\geq 18$  years of age. The baseline assessment will be a retrospective assessment of the disability and dependence of the subject immediately prior to the admission that included the index episode of status epilepticus.

## 12. STUDY PROCEDURES

The study procedures listed below by study day reflect the required data collection times for this protocol. When a time window is necessary, this is specified below. If no time window is specified, the test may be performed at any time within the specified 24-hour period.

### 12.1. Visit 1 (V2-≤30h)

The baseline period will be approximately 36 hours prior to starting blinded study treatment and should include the assessments/procedures listed below and summarized in [Table 1](#) and [Table 2](#) (for retreatment), the Schedules of Events.

- Informed consent
- Eligibility checklist
- Verification of inclusion/exclusion criteria.
- Demographic information and medical history obtained by proxy and confirmed by the subject when possible.
- SE and wean history
- Blood will be collected from female subjects 12 years to 55 years for a serum pregnancy test unless they are known to be pre-menstrual or post-menopausal or to have had a hysterectomy.
- Blood and urine samples collected for clinical laboratory testing.
- Pharmacogenetic sample will be collected from consenting/eligible subjects.
- Vital signs
- Height
- Weight
- An ECG reading taken.
- Administration of the STESS.
- Administration of the FOUR Score.
- Administration of SRS.
- Administration of the mRS-9Q assessment.
- Assessment of the CGI scale.
- Evaluation of epilepsy status.
- Administration of continuous IV third-line agents.
- Perform EEG.
- Recording of adverse events.
- Recording of previous and concomitant anti-epileptic drugs.



- Recording of previous and concomitant third-line agents.
- Recording of concomitant pressors.
- Recording of other concomitant medications.

## **12.2. Visit 2 (V3-≤30h)**

- Recording of adverse events.
- Recording of concomitant anti-epileptic drugs.
- Recording of concomitant third-line agents.
- Recording of concomitant pressors.
- Recording of other concomitant medications.
- Wean of continuous third-line agent:
  - If wean is successful, subject is followed for approximately three weeks to collect medication, epilepsy status, adverse event, and outcome data (these subjects are Qualifying Wean Success subjects or QWS subjects);
  - If wean is not successful, there is ongoing intravenous administration of at least one continuous IV third-line agent and EEG is performed and the subject is randomized.

## **12.3. SAGE-547 Treatment Period (Hours 0-144)**

### **12.3.1. Visit 3/3R (0-24 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs will be recorded at:
  - 0, +30, +60 minutes (+/-15 minutes) and +2, +4, +8 (+/- 30 minutes) and +24 hours (+/- 2 hours) after the start of the infusion
- ECG readings will be recorded immediately after PK sampling at:
  - 0 (pre-dose) and at +0.5, +1, +3, +6, +12, and +24 hours after the start of the blinded study drug infusion.
- A blood sample for PK analysis should be collected at the following time points (all +/- 5 minutes):
  - 0 (pre-dose) and at +0.5, +1, +3, +6, +12, and +24 hours after the start of the blinded study drug infusion.
- A urine sample for PK analysis should be collected in the first 70 subjects enrolled:
  - all urine voided from 0-24 hours on study drug during the blinded and open-label infusions will be collected and pooled, and a 20 mL sample taken for analysis.
- Completion of the FOUR Score

- +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the end of the QW)
- Ongoing intravenous administration of a continuous IV third-line agent.
- Study drug administration in loading (Hour 0-1) and maintenance infusions (at completion of Hour 1).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.3.2. Visit 4/4R (25-48 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +48 hours (+/- 2 hours) after the start of the infusion
- An ECG reading taken immediately after PK sampling:
  - +48 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +48 hours (+/- 5 minutes) after the start of study drug infusion.
- A urine sample for PK analysis should be collected in the first 70 subjects enrolled:
  - all urine voided from 25-48 hours on study drug during the blinded and open-label infusions will be collected and pooled, and a 20 mL sample taken for analysis.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +48 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent.
- Ongoing study drug maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.3.3. Visit 5/5R (49-72 hours)**

- Weight
- Vital signs should be recorded at:
  - +72 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:

- +72 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +72 hours (+/- 5 minutes) after the start of study drug infusion.
- A urine sample for PK analysis should be collected in the first 70 subjects enrolled:
  - all urine voided from 49-72 hours on study drug during the blinded and open-label infusions will be collected and pooled, and a 20 mL sample taken for analysis.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR Score assessment):
  - +72 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate weaning if in the opinion of the Investigator subject seizure activity is controlled.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.3.4. Visit 6/6R (73-96 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +96 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +96 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +96 hours (+/- 5 minutes) after the start of study drug infusion.
- A urine sample for PK analysis should be collected in the first 70 subjects enrolled:
  - all urine voided from 73-96 hours on study drug during the blinded and open-label infusions will be collected and pooled, and a 20 mL sample taken for analysis.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +96 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is controlled.

- Perform EEG.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

### **12.3.5. Visit 7/7R (97-120 hours)**

- Weight
- Vital signs should be recorded at:
  - +120 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +120 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +120 hours (+/- 5 minutes) after the start of study drug infusion, immediately prior to the end of the maintenance infusion.
- A urine sample for PK analysis should be collected in the first 70 subjects enrolled:
  - all urine voided from 97-120 hours on study drug during the blinded and open-label infusions will be collected and pooled, and a 20 mL sample taken for analysis.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +120 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is controlled. Complete wean by 120 hours.
- Ongoing SAGE-547 maintenance infusion administration.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## **12.4. SAGE-547 Taper Period**

### **12.4.1. Visit 8/8R (121-144 hours)**

- Weight
- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +144 hours (+/- 2 hours) after the start of the study drug infusion

- An ECG reading taken immediately after each PK sampling:
  - +128, +136 hours and +144 hours after the start of the study drug infusion
  - During the open-label retreatment phase of the study ECG readings at: +126, +132, +138 hours and +144 hours after the start of the study drug infusion
- A blood sample for PK analysis should be collected:
  - +128 (immediately prior to the end of the first taper step), +136 hours (+/- 5 minutes, immediately prior to the end of the second taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of study drug infusion.
  - During the open-label retreatment phase of the study PK blood draws at: +126 (immediately prior to the end of the first taper step), +132 (immediately prior to the end of the second taper step), +138 hours (+/- 5 minutes, immediately prior to the end of the third taper step) and +144 hours (immediately after stopping the study drug infusion) after the start of the study drug infusion.
- A urine sample for PK analysis should be collected in the first 70 subjects enrolled:
  - all urine voided from 121-144 hours on study drug during the blinded and open-label infusions will be collected and pooled, and a 20 mL sample taken for analysis.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +144 hours (+/- 2 hours) after the start of the infusion
- Ongoing intravenous administration of a continuous IV third-line agent:
  - initiate or continue weaning if in the opinion of the Investigator subject seizure activity is controlled.
- Perform EEG.
- Taper of SAGE-547 infusion begins at hour 121.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

## **12.5. Follow-up Period (through Day 29)**

### **12.5.1. Visit 9/9R (145-168 hours)**

- Vital signs should be recorded at:
  - +168 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken immediately after PK sampling:
  - +152, +160 hours (+/- 2 hours) after the start of the study drug infusion
- A blood sample for PK analysis should be collected:

- +152 and +160 hours (+/- 5 minutes) after the start of study drug infusion.
- A urine sample for PK analysis should be collected in the first 70 subjects enrolled:
  - all urine voided from 145-168 on study drug during the blinded and open-label infusions will be collected and pooled, and a 20 mL sample taken for analysis.
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +168 hours (+/- 2 hours) after the start of the infusion
- Perform EEG.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.2. Visit 10/10R (169-192 hours)**

- Blood and urine samples collected for clinical laboratory testing.
- Vital signs should be recorded at:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- An ECG reading taken:
  - +192 hours (+/- 2 hours) after the start of the study drug infusion
- Completion of the FOUR Score (QWS subjects at approximately 24 hours after the last FOUR score assessment):
  - +192 hours (+/- 2 hours) after the start of the infusion
- At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine retreatment with higher dose of study drug.
- Assessment of the presence of physiologic brain activity using EEG.
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.3. Visit 11/11R (Visit 3/3R + 14d (±2))**

- Blood samples collected for clinical laboratory testing (renal panel only).
- Completion of the FOUR Score (QWS subjects also).
- Recording of adverse events (QWS subjects also).
- Recording of concomitant medications, including anti-epileptic drugs, third-line agents, pressors and other medications (QWS subjects also).

#### **12.5.4. Visit 12/12R (Visit 3/3R + 21d (±2))**

All assessments also performed for QWS subjects.

- Completion of the FOUR Score.
- Administration of the GOS.
- Administration of the SRS.
- Administration of the mRS-9Q assessment.
- Evaluation of epilepsy status (see [Section 11.1.2.2](#) for details).
- Assessment of the CGI Scale.
- Recording of adverse events.
- Recording of concomitant medications, including anti-epileptic drugs, third-line agents, pressors and other medications.
- Collection of pharmacoeconomic data
- Mortality will be assessed throughout the study period.

## 13. STATISTICS

### 13.1. Statistical Plan

Complete details for the analysis and reporting of data from this study will be contained in the Statistical Analysis Plan (SAP).

#### 13.1.1. Interim Analysis

When approximately 50% of subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes. Since the sponsor will be kept uninformed of the response rates at the time of the interim analysis, no statistical adjustment will be made to the level of significance for hypothesis testing at the end of the study. A detailed description of the interim analysis plan will be included in the DSMB charter.

#### 13.1.2. Study Populations

The **Safety Population** is defined as all subjects who at least had an infusion of blinded study medication initiated.

The **Modified Intent to Treat Population** is defined as all subjects who:

1. complete their initial course of blinded SAGE-547 or placebo treatment unless the non-completion was due a drug-related adverse event; and
2. have at least one attempt to wean from third-line agents prior to the end of blinded study treatment infusion unless the failure to wean was because seizures were not controlled.

Narratives will be prepared for all subjects who do not complete the infusion of blinded study medication or were not subjected to any wean attempts. Narratives will include details of the cause of SE, the comorbid conditions, the adverse event(s), and reasons for non-completion of the infusion or failure to attempt weaning. This blinded narrative will be reviewed by the DSMB and the patient adjudicated as included or excluded from the MITT. Acceptable reasons for excluding

the subject from the MITT include death or withdrawal of consent due to progression of the underlying cause of SE or comorbid conditions.

The **Intent to Treat Population** is defined as all subjects who at least had an infusion of blinded study medication initiated.

The **Pharmacokinetics Population** is defined as all subjects who at least had an infusion of blinded SAGE-547 initiated and have at least one pharmacokinetic sample collected.

The **Pharmacogenetic Population** is defined all subjects who consent to being included in the pharmacogenetic assessment and provide a pharmacogenetic sample.

Summary statistics of all data collected will be presented for subjects who were QW successes.

### 13.1.3. General Aspects

Tabular displays of descriptive statistics will be provided for all variables. Summary tables will include n, mean, mean, standard deviation, minimum and maximum for continuous variable and frequency and percentage for categorical variables.

### 13.1.4. Analysis of Primary Endpoint

The analysis of response to treatment between SAGE-547 treated subjects and placebo treated subjects will be performed on the MITT population using a Cochran-Mantel-Haenszel test with variables for treatment, concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). In this analysis, a treatment responder is a subject who is successfully weaned off all third-line agents and blinded study medication prior to the end of study treatment infusion and remains off third-line agents for at least 24 hours following cessation of the blinded study medication. In addition, subjects deemed to be successes must have evidence of physiologic brain activity as determined by EEG. The comparison of treatment response rates will be conducted at the 5% level of significance.

A sensitivity analysis of the primary endpoint will be performed on the ITT population, in which subjects who were not included in the MITT population are assumed to be treatment failures. In addition sensitivity analyses of the primary endpoint will be performed using the MITT population based on:

- the number of third-line agents (one, two, or three) subjects were administered post-randomization; and
- which third line agent was the subject of the first TW.

### 13.1.5. Analysis of Secondary Efficacy Endpoints

Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the MITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section (Section 6). Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. Summary statistics will be provided for all endpoints. Categorical endpoints (change from baseline in CGI, secondary response rates, number of episodes of status epilepticus and proportion of new diagnoses of epilepsy) will be evaluated via Cochran-Mantel-Haenszel analysis with



variables for treatment, concomitant pentobarbital use and number of previous wean attempts. Analysis of continuous endpoints (time to re-institution of third line agents for primary and secondary response, number of days without status epilepticus or days without seizures) will be performed using Analysis of Variance with variables for treatment, concomitant pentobarbital use and number of previous wean attempts. If it is found there are too many tied observations in the continuous data, a non-parametric analysis may also be performed.

#### **13.1.6. Analysis of Other Endpoints**

Safety and “Other” endpoints will only be summarized by treatment group.

Summaries of safety endpoints will be based on the overall Safety Population.

#### **13.1.7. Epilepsy and SRSE Status**

Diagnosis of epilepsy and recurrence of RSE or SRSE will be documented as the percentage of subjects by time point and overall. Kaplan-Meier curves may be plotted if sufficient data are available.

Utilization of AEDs during follow-up and during recurrence will be summarized.

#### **13.1.8. Questionnaires**

The data collected from each questionnaire will be interpreted according to the standard methodology for that questionnaire. There will be no adjustment for missing values.

#### **13.1.9. Pharmacokinetic Data Analysis**

Details of the pharmacokinetic data analysis will be described in detail in a separate Pharmacokinetic Analysis Plan.

#### **13.1.10. Pharmacogenetic Data Analysis**

Any genotype data generated in this study will be stored within a secured database within Sage Therapeutics and / or a third party contracted to work with Sage Therapeutics to analyze the samples. Because the number of subjects agreeing to participate in the genetic research component of the study is unknown, it is not possible to establish, a priori, whether sufficient samples will be obtained to support formal statistical evaluation of data. As a consequence a Pharmacogenetic Analysis Plan will only be prepared where appropriate and the results obtained from any genetic research will be reported in a report separate from the main study CSR.

#### **13.1.11. Retreated Subjects**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are retreated with SAGE-547. Separate summaries will be derived for subjects initially receiving SAGE-547 and those initially receiving placebo.

#### **13.1.12. EEG-Responders**

Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who are classified as EEG-responders/non-responders based on the independent assessment of the PAEEG. Summaries will be derived for the two randomized treatment groups.

**13.1.13. QT/QTc Assessment**

An analysis of the correlation between changes in QT/QTc intervals and SAGE-547 plasma levels will be performed to investigate if there is a potential effect that SAGE-547 may have on QT/QTc interval. A detailed description of the QT/QTc assessment will be included in the SAP.

**13.1.14. Quantitative EEG**

The six EEG records for each subject may be subjected to exploratory quantitative EEG analysis, the details of which will be included in the EEG Analysis Plan. In summary the following comparisons may be made, SAGE-547 versus placebo: the QWEEG versus the TWEEG (main analysis); the CEEG versus PAEEG (subsidiary analysis); and TAEEG versus PAEEG (exploratory analysis).

**13.2. Determination of Sample Size**

The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 63 subjects randomized to SAGE-547 and 63 subjects randomized to placebo, there would be 90% power for detecting a significant difference between groups at a 5% level of significance. To account for approximately 10% of subjects being excluded from the MITT, a total of 140 subjects will be randomized, 70 to SAGE-547 and 70 to placebo. Randomization will be stratified by concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).

**13.3. Statistical Analysis Plan**

A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. All deviations from or changes to the SAP following database lock will be described in detail in the SAP and will be summarized in the final clinical study report.

## **14. ADVERSE EVENTS**

The safety procedures in this study will be detailed in a Safety Management Plan, which will be agreed and signed before the first subject is randomized in the study. Section 14.1 summarizes Investigator responsibilities regarding the identification and documentation of AEs, the classification of AEs for relationship to study drug and severity, and the reporting of AE information to the Sponsor and the IRB.

[Section 14.2](#) summarizes Sponsor/Medical Monitor Responsibilities regarding monitoring of AE data and reporting relevant safety information to FDA.

[Section 14.3](#) lists important AE definitions.

### **14.1. Investigator Responsibilities**

#### **14.1.1. Identification and Documentation of Adverse Events by Investigator**

Subjects will be evaluated and questioned generally (if possible) to identify AEs during the course of the study. AEs will be collected from the signature of the consent form through Visit 12/12R. Adverse events that occur prior to completion of screening will be captured on the Medical History eCRF. Adverse events that occur after completion of screening will be recorded on the Adverse Event eCRF.

All AEs revealed by observation, other diagnostic procedures, or spontaneously reported by the subject and/or in response to an open question from study personnel will be recorded on the Adverse Event Form. Any clinically significant deterioration in laboratory assessments or other clinical findings are considered an AE and must be recorded on the Adverse Event Form, unless otherwise stated. AE information recorded will be entered into the database on an ongoing basis.

AEs with a relationship considered related to study drug (probable, possible) should be followed until the event is resolved or the Investigator determines the event is stable or no longer clinically significant. AEs considered not related to study drug will be followed until resolution or until Visit 12/12R, whichever is shorter.

For SAEs, an electronic Serious Adverse Event eCRF must be completed with as much information as possible and submitted in the time frame described below in [Section 14.1.3](#). When new significant information is obtained as well as when the outcome of an event is known, the electronic SAE eCRF should be updated within one working day. If the subject was an outpatient at the time of the SAE and was re-hospitalized due to the SAE, a copy of relevant hospital records (e.g., admission report, laboratory test results, discharge summary, etc.) may be requested to be included as part of the subject medical file.

All SAEs will be followed until resolved or until a stable status has been achieved.

**14.1.2. Adverse Event Classification****14.1.2.1. Relationship to Investigational Drug**

None:	No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state.
Possible:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject, but this is not known for sure.
Probable:	A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug.  The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

**14.1.2.2. Intensity**

Mild	For subjects that are unconscious, this may be a slight or minor change in a lab result or clinical sign or symptom that does not require immediate corrective action.
Moderate	For subjects that are unconscious, this may be a clinically meaningful change that may require immediate corrective action.
Severe	For unconscious subjects, this may be a significant clinical change that requires immediate corrective action.

**14.1.2.3. Action Taken with Investigational Drug**

None	Study medication was continued without change.
Discontinued	Study medication was terminated.
Dose adjusted	Study medication dose/infusion rate was changed and then continued per protocol.
Interrupted	Study medication was interrupted and then continued per protocol.
Unknown	The action taken with regard to study medication is unknown.
Not applicable	Administration of study medication was not ongoing.

**14.1.2.4. Assessment of Outcome**

Ongoing	At the end of the study, the event has not resolved or stabilized.
Ongoing and stable	The event is ongoing but has stabilized and is unlikely to change
Resolved	The event has resolved or the subject recovered without sequelae.
Resolved with sequelae	The event has at least one secondary outcome that may result in permanent disability and/or functional limitation.
Unknown	The status of the event is unknown.
Death	The subject has expired.

**14.1.3. Investigator Reporting to Sponsor and Sponsor Emergency Contact**

All new SAEs that come to the Investigator and/or Sponsor's notice during the course of the study must be reported by the Investigator on the designated electronic report form within one working day from the point in time when the Investigator becomes aware of the SAE. As additional information becomes available, the designated electronic report form must be updated within one working day. In addition, all SAEs that occur up to and including 30 days after administration of study drug must be reported within one working day from when the Investigator becomes aware of the SAE.

Investigators must report any SAE, whether or not considered drug related. The report must include an assessment of whether there is a reasonable possibility that the drug caused the event.

In a medical emergency (ie, an event that requires immediate attention regarding the treatment of a subject, operation of the clinical study, and/or the use of investigational drug), study site staff will apply appropriate medical intervention according to current standards of care, and contact the Medical Monitor.

**14.1.4. Medical Monitor and Emergency Contact Information**

[REDACTED], MD  
[REDACTED]

**14.1.5. SAE Reporting Contact Information**

Contact information and reporting instructions are provided in the Safety Management Plan.

**14.1.6. Reporting to Institutional Review Boards (IRBs)**

It is the responsibility of the Investigator to promptly notify the institution's IRB of all serious and unexpected suspected adverse reactions (see [Section 14.3](#) for definitions).

## **14.2. Sponsor/Medical Monitor Responsibilities**

### **14.2.1. Monitoring of Adverse Event Data**

The Medical Monitor will review any newly reported adverse events in an ongoing basis. If the aggregate assessment indicates that an event is occurring more frequently than would normally be expected in this population, or as previously observed, and the sponsor believes that the events are causally related to the administration of SAGE-547, the Sponsor will then report that information in an IND safety report.

### **14.2.2. Data Safety Monitoring Board**

An independent DSMB will monitor the clinical, PK and PD data for safety signals throughout the study and will be asked to assess efficacy at the time of the interim analysis to determine study continuation. In order to perform their monitoring function the DSMB will have access to unblinded data as necessary.

The composition and procedures for the board will be described in a separate DSMB Charter.

### **14.2.3. Reporting to FDA**

The Sponsor must report in an IND safety report any suspected adverse reaction to study treatment that is both serious and unexpected (21 CFR 312.32(c)(1)(i)). Before submitting an IND safety report, the Sponsor will ensure the event meets all three of the definitions: (1) suspected adverse reaction, (2) serious, (3) unexpected. If the AE does not meet all three of the definitions, it should not be submitted as an IND safety report. The Sponsor should evaluate the available information and decide whether there is a reasonable possibility that the drug caused the adverse event and, therefore, that the event meets the definition of a suspected adverse reaction.

If there is a serious and unexpected suspected adverse reaction, the Sponsor will notify the appropriate regulatory agency(ies) and all appropriate parties on an expedited basis. In addition, Sponsors must submit expedited reports of an increased rate of occurrence or severity of serious suspected adverse reactions over that listed in the protocol or Investigational Brochure.

SUSARs will be unblinded prior to reporting to FDA. Unless it is necessary to unblind for the safety of the patient, the investigator will not be informed of the unblinding of the subject.

Under 21 CFR 312.32, Sponsors should identify in the protocol SAEs that it does not plan to report individually in an expedited manner, because they are known consequences of the disease or otherwise common in the study population. Given the grave condition and prognosis of SRSE being studied, individual occurrences of seizures or seizure activity will not be reported expeditiously in this study. Regardless of which events are reported in an expedited manner, all adverse events will be closely monitored throughout the study.

## **14.3. Adverse Event Definitions**

### **14.3.1. Adverse Event**

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

### **14.3.2. Suspected Adverse Reaction**

Any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

### **14.3.3. Life-Threatening**

An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

### **14.3.4. Serious**

An AE or suspected adverse reaction is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE – see definition above
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disability
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

### **14.3.5. Unexpected**

An AE or suspected adverse reaction is considered “unexpected”:

- If it is not listed in the Investigational Brochure or is not listed at the specificity or severity that has been observed, or
- If an Investigational Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigational Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigational Brochure listed only cerebral vascular accidents.

“Unexpected,” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigational Brochure as occurring with a class of drugs or as anticipated from

the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

#### **14.4. Emergency Identification of Study Medication**

In exceptional circumstances and for the safety of the study subject, the Investigator may request unblinding of an individual subject's treatment in the study via the IVRS; this normally requires prior approval by the medical monitor. However, if the subject is at immediate risk and the Investigator believes that immediate knowledge of the study treatment will alter medical management, discussion with the medical monitor may take place after unblinding. The Investigator will not unblind the medical monitor during that discussion. The process of unblinding will ensure that only the investigator is unblinded; the medical monitor, study management team, and data management team will not be made aware of the treatment allocation of an individual subject. All cases of emergency unblinding will be fully documented in a way that does not unblind the medical monitor, study management team, and data management team.

### **15. STUDY ADMINISTRATIVE CONSIDERATIONS**

#### **15.1. Quality Control and Quality Assurance**

The Investigators and institutions will permit trial related monitoring, audits, IRB review, and regulatory inspections as requested by FDA, the Sponsor, or the Sponsor's designee, including direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed informed consent forms, etc.) in addition to case report forms.

Quality assurance and quality control systems with written standard operating procedures (SOPs) will be followed to ensure this trial will be conducted and data will be generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The site's dedicated study monitor will arrange to visit the Investigator at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

During these visits, eCRFs and other data related to the study will be reviewed and any discrepancies or omissions will be identified and resolved. The study monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality assurance officers named by Sage Therapeutics or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Agreements, made by the Sponsor with the Investigator/institution and any other parties involved with the clinical trial, will be in writing in a separate agreement.



## **15.2. Data Handling and Recordkeeping**

### **15.2.1. Data Handling**

Procedures for data handling (including electronic data) used in this protocol will be documented in a Data Management Plan.

### **15.2.2. Case Report Form Completion**

eCRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of demographics, study drug administration, study procedures, AEs, questionnaire completion, efficacy assessments and subject status, including survival.

The Investigator will maintain copies of the eCRFs at the study site. For subjects who discontinue or terminate from the study, the eCRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate eCRF.

### **15.2.3. Retention of Study Records**

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval and until there are no pending or contemplated marketing applications or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to an appropriate person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

## **15.3. Confidentiality**

To maintain subject privacy, all eCRFs, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Subjects will be notified that registration information, results, and other information about this study will be submitted to ClinicalTrials.gov, a publicly available trial registry database; however, protected health information of individual subjects will not be used.

All information regarding the investigational product supplied by Sage Therapeutics to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants, as required.

#### **15.4. Publication Policy**

All information concerning SAGE-547 is considered confidential and shall remain the sole property of Sage Therapeutics. The Investigator agrees to use this information only in conducting the study and shall not use it for any other purposes without written approval from Sage Therapeutics. No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between Sage Therapeutics and the Investigator.

#### **15.5. Protocol Amendments**

Changes to the conduct of the study should be prepared as a protocol amendment by the Sponsor. Protocol amendments should receive written IRB/IEC approval prior to implementation at the investigative site, except when necessary to eliminate immediate hazards to the subjects or when the changes involve only logistical or administrative aspects of the trial (eg, change of monitor, telephone numbers). In this case, Sage Therapeutics will amend and implement the protocol change and subsequently notify the regulatory authorities and the Investigative sites who will notify the respective IRB, as appropriate.

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## APPENDIX 1. FOUR SCORE

### FOUR score

#### Full Outline of UnResponsiveness

##### Eye response

- E4: eyelids open or opened, tracking, or blinking to command
- E3: eyelids open but not tracking
- E2: eyelids closed but open to loud voice
- E1: eyelids closed but open to pain
- E0: eyelids remain closed with pain

##### Motor response

- M4: thumbs-up, fist or peace sign
- M3: localizing to pain
- M2: flexion response to pain
- M1: extension response to pain
- M0: no response to pain or generalized myoclonus status

##### Brainstem reflexes

- B4: pupil and corneal reflexes present
- B3: one pupil wide and fixed
- B2: pupil or corneal reflexes absent
- B1: pupil and corneal reflexes absent
- B0: absent pupil, corneal and cough reflex

##### Respiration pattern

- R4: not intubated, regular breathing pattern
- R3: not intubated, Cheyne-Stokes breathing pattern
- R2: not intubated, irregular breathing
- R1: breathes above ventilatory rate
- R0: breathes at ventilator rate or apnea

Reference ([Iyer, Hoel et al. 2009](#)).

**APPENDIX 2. GLASGOW OUTCOME SCALE (GOS)****GLASGOW  
OUTCOME  
SCALE**

Patient Name: \_\_\_\_\_

Rater Name: \_\_\_\_\_

Date: \_\_\_\_\_

*Note:* The scale presented here is based on the original article by Jennett and Bond. It has become common practice in clinical trial administration, however, to use a modified version that places the scores in reverse order (i.e., "good recovery" = 1, "moderate disability" =2, etc.).

Score	Description
1	DEATH
2	PERSISTENT VEGETATIVE STATE Patient exhibits no <i>obvious cortical</i> function.
3	SEVERE DISABILITY (Conscious but disabled). Patient depends upon others for daily support due to mental or physical disability or both.
4	MODERATE DISABILITY (Disabled but independent). Patient is independent as far as daily life is concerned. The disabilities found include varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes.
5	GOOD RECOVERY Resumption of normal activities even though there may be minor neurological or psychological deficits.

TOTAL (1-5): \_\_\_\_\_

Reference ([Jennett and Bond 1975](#)).

## APPENDIX 3. SUPERVISION RATING SCALE (SRS)

### SUPERVISION RATING SCALE (SRS)

**Instructions:** Circle the rating that is closest to the amount of supervision that the patient *actually receives*. "Supervision" means that someone is responsible for being with the patient.

<u>Rating</u>	<u>Description</u>
<u>Level 1: INDEPENDENT</u>	
1	The patient lives alone or independently. Other persons can live with the patient, but they cannot take responsibility for supervision (for example, a child or elderly person).
2	The patient is unsupervised overnight. The patient lives with one or more persons who <i>could</i> be responsible for supervision (for example, a spouse or roommate), but they are <i>all</i> sometimes absent overnight.
<u>Level 2: OVERNIGHT SUPERVISION</u>	
3	The patient is only supervised overnight. One or more supervising persons are always present overnight but they are <i>all</i> sometimes absent for the rest of the day.
<u>Level 3: PART-TIME SUPERVISION</u>	
4	The patient is supervised overnight and part-time during waking hours, but is allowed on independent outings. One or more supervising persons are always present overnight and are also present during part of waking hours every day. However, the patient is sometimes allowed to leave the residence without being accompanied by someone who is responsible for supervision.
5	The patient is supervised overnight and part-time during waking hours, but is unsupervised during working hours. Supervising persons are <i>all</i> sometimes absent for enough time for them to work full-time outside the home.
6	The patient is supervised overnight and during most waking hours. Supervising persons are <i>all</i> sometimes absent for periods longer than one hour, but less than the time needed to hold a full-time job away from home.
7	The patient is supervised overnight and during almost all waking hours. Supervising persons are <i>all</i> sometimes absent for periods shorter than one hour.
<u>Level 4: FULL-TIME INDIRECT SUPERVISION</u>	
8	The patient is under full-time indirect supervision. At least one supervising person is <i>always</i> present, but the supervising person does not check on the patient more than once every 30 minutes.
9	Same as #8 plus requires overnight safety precautions (for example, a deadbolt on outside door).
<u>Level 5: FULL-TIME DIRECT SUPERVISION</u>	
10	The patient is under full-time direct supervision. At least one supervising person is always present and the supervising person checks on the patient more than once every thirty minutes.
11	The patient lives in a setting in which the exits are physically controlled by others (for example, a locked ward).
12	Same as #11 plus a supervising person is designated to provide full-time line-of-sight supervision (for example, an escape watch or suicide watch).
13	The patient is in physical restraints.

3/12/93

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#### APPENDIX 4. MODIFIED RANKIN SCALE – LEVEL OF FUNCTION SURVEY (mRS-9Q)

1. Do you have any symptoms that are bothering you? (For example, trouble with reading or writing, trouble speaking, problems with vision, numbness, weakness, balance trouble, or problems with swallowing?)	YES	<input type="radio"/>	NO	<input type="radio"/>
2. Are you able to do the same work as before?	YES	<input type="radio"/>	NO	<input type="radio"/>
3. Are you able to keep up with your hobbies?	YES	<input type="radio"/>	NO	<input type="radio"/>
4. Have you maintained your ties to friends and family?	YES	<input type="radio"/>	NO	<input type="radio"/>
5. Do you need help making a simple meal, doing household chores, or balancing a checkbook?	YES	<input type="radio"/>	NO	<input type="radio"/>
6. Do you need help with shopping or traveling close to home?	YES	<input type="radio"/>	NO	<input type="radio"/>
7. Do you need another person to help you walk?	YES	<input type="radio"/>	NO	<input type="radio"/>
8. Do you need help with eating, going to the toilet, or bathing?	YES	<input type="radio"/>	NO	<input type="radio"/>
9. Do you stay in bed most of the day and need constant nursing care?	YES	<input type="radio"/>	NO	<input type="radio"/>



## APPENDIX 5. CLINICAL GLOBAL IMPRESSION (CGI)

### Clinical Global Impression (CGI)

#### 1. Severity of illness

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

- |                             |   |
|-----------------------------|---|
| 0 = Not assessed            | 4 = Moderately ill                        |
| 1 = Normal, not at all ill  | 5 = Markedly ill                          |
| 2 = Borderline mentally ill | 6 = Severely ill                          |
| 3 = Mildly ill              | 7 = Among the most extremely ill patients |

#### 2. Global improvement: Rate total improvement whether or not, in your judgement, it is due entirely to drug treatment.

Compared to his condition at admission to the project, how much has he changed?

- |                        |                     |
|------------------------|---------------------|
| 0 = Not assessed       | 4 = No change       |
| 1 = Very much improved | 5 = Minimally worse |
| 2 = Much improved      | 6 = Much worse      |
| 3 = Minimally improved | 7 = Very much worse |

#### 3. Efficacy index: Rate this item on the basis of **drug effect only**.

Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect.

EXAMPLE: Therapeutic effect is rated as 'Moderate' and side effects are judged 'Do not significantly interfere with patient's functioning'.

#### Therapeutic effect

#### Side effects

		None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
<b>Marked</b>	Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
<b>Moderate</b>	Decided improvement. Partial remission of symptoms	05	06	07	08
<b>Minimal</b>	Slight improvement which doesn't alter status of care of patient	09	10	11	12
<b>Unchanged or worse</b>		13	14	15	16
Not assessed = 00					

Reproduced from Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare

**Summary of Changes**  
**Protocol-547-SSE-301**  
**Dated 27 May 2015**

The following changes were made to the attached protocol in this amendment. Minor typographical/editorial errors throughout the document were also corrected.

Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
2. Study Synopsis/Study Sites	2. Study Synopsis/Study Sites	Up to 150 sites in the USA and Canada.	Up to 150 sites in the USA, <b>Europe</b> , and Canada.	<i>Trial expanded to include Europe</i>
2. Study Synopsis/Study Design	2. Study Synopsis/Study Design	Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 or placebo.	Subjects who fail the QW will have the same or a different third-line agent regimen re-instituted at doses intended to result in EEG burst suppression and will be randomized to concomitant SAGE-547 treatment or placebo. <b>Burst suppression must be maintained for the first 12 hours of the infusion of study drug.</b>  <i>Changes also featured on page 39</i>	<i>To ensure a consistent period of burst suppression is maintained following the start of the infusion.</i>
2. Study Synopsis/Safety Objectives	2. Study Synopsis/Safety Objectives	c. Vital signs (blood pressure, heart rate, respiratory rate, temperature, oxygen saturation, weight);	c. Vital signs (blood pressure, heart rate, temperature, and weight);  <i>Changes also featured on pages 8, 37-38</i>	<i>Expectation is for all patients to be mechanically ventilated; respiratory rate</i>

Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
				<i>and oxygen saturation are expected to be constant for all patients.</i>
2. Study Synopsis/Other Objectives	2. Study Synopsis/Other Objectives	4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital;	4. To determine the number of days in the ICU, number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, <b>dischargeability criteria, resource use for subjects discharged from hospital before Visit 12/12R;</b>  <i>Changes also featured on pages 8,37</i>	<i>To obtain health economics and outcome data for patients who discharge from ICU prior to conclusion of study at Visit 12/12R.</i>
2. Study Synopsis/Other Objectives	2. Study Synopsis/Other Objectives	8. To evaluate the Modified Rankin Score (mRS) (age $\geq 18$ years).	8. To evaluate the Modified Rankin Score (mRS) (age $\geq 17$ years).  <i>Changes also featured on pages 8, 37, 38, and in SOA footnotes on page 16.</i>	<i>Response to FDA SPA letter re: age limit for pediatrics.</i>

Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
2. Study Synopsis/Exclusion Criteria	2. Study Synopsis/Exclusion Criteria	4. Children (subjects aged less than 18 years) with an underlying neurological disorder.	4. Children (subjects aged less than <b>17</b> years) with an <b>encephalopathy due to a rapidly progressing</b> underlying neurological disorder.  <i>Changes also featured on page 43</i>	<i>Response to FDA SPA letter re: age limit for pediatrics; additionally, to clarify the degree of neurological disorder that would be exclusionary, i.e. rapidly progressing.</i>
2. Study Synopsis/Statistical Analysis	2. Study Synopsis/Statistical Analysis	A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. All deviations from or changes to the SAP following database lock will be described in detail in the SAP and will be summarized in the final clinical study report	A separate SAP will provide a detailed description of the analyses to be performed in the study. The SAP will be finalized and approved prior to database lock. <b>Any deviations from or changes to the SAP following database lock will be described in detail in the final clinical study report.</b>  <i>Changes also featured on page 73</i>	<i>Clarification on the documentation of deviations or changes to the SAP.</i>
2. Study Synopsis/Analysis of Secondary Efficacy	2. Study Synopsis/Analysis of Secondary Efficacy	Secondary endpoints will be compared between SAGE-547	<b>The primary analysis will be repeated for the MITT</b>	<i>Response to FDA SPA letter, re: change to ITT</i>

Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
Endpoints	Endpoints	and placebo treated subjects in the MITT population with a hierarchical testing process at the 5% level of significance.	<b>population.</b> Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the <b>ITT</b> population with a hierarchical testing process at the 5% level of significance.	<i>population for primary and secondary analyses. Analyses of MITT population to be used as supportive.</i>
2. Study Synopsis/ Analysis of Secondary Efficacy Endpoints	2. Study Synopsis/ Analysis of Secondary Efficacy Endpoints	The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. Summary statistics will be provided for all endpoints.	The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. <b>Secondary analyses will be repeated for the MITT population.</b> Summary statistics will be provided for all endpoints.	<i>Response to FDA SPA letter re: change to ITT population for primary and secondary analyses. Analyses of MITT population to be used as supportive.</i>
2. Study Synopsis/ Sample Size	2. Study Synopsis/ Sample Size	Under these assumptions, with 63 subjects randomized to SAGE-547 and 63 subjects randomized to placebo, there would be 90% power for detecting a significant difference between groups at a 5% level of significance.	Under these assumptions, with <b>70</b> subjects randomized to SAGE-547 and <b>70</b> subjects randomized to placebo, there would be <b>&gt;90%</b> power for detecting a significant difference between groups at a 5% level of significance.	<i>Response to FDA SPA letter re: change to ITT population for primary analysis.</i>

Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
			<i>Changes also featured on page 73</i>	
2. Table 1-3/Schedule of Assessments	2. Table 1-3/Schedule of Assessments	V2 (V3 $\leq$ 30)	V2 (V3 $\leq$ <b>54</b> )	<i>Extended screening period to account for 24 hour confirmation period following initial Qualifying Wean Success determination.</i>
List of Abbreviations	List of Abbreviations	<i>N/A</i>	<i>Table updated to include: <b>BIEEG (Blinded Infusion EEG), ITT (Intent to Treat), and to correct TAEED from Treatment EEG to Taper EEG</b></i>	<i>Consistency and clarification re: BIEEG, ITT, and TAEED and how these terms are presented throughout the protocol.</i>
7.1 Overview of Study Design	7.1 Overview of Study Design	Subjects must also have evidence of physiologic brain activity at the end of the primary endpoint assessment period as determined by EEG in order to be deemed a success.	Subjects must also have evidence of physiologic brain activity ( <b>average EEG power at the end of Visit 9 of more than two microvolts</b> ) at the end of the primary endpoint assessment period as determined by EEG in order to be deemed a success.	<i>To clarify and quantify the physiological brain activity observed via EEG.</i>

Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
			<i>Changes also featured on page 40</i>	
7.1 Overview of Study Design	7.1 Overview of Study Design	Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study.	Those subjects who fail the primary endpoint, and require re-institution of a third-line agent regimen before the end of the blinded study drug infusion or within 24 hours of completing the blinded study drug infusion will be eligible to receive an open-label infusion of SAGE-547 at a dose higher than that administered in the blinded part of the study. <b>Eligibility for retreatment must be confirmed in writing by the medical monitor prior to the open-label infusion starting.</b>  <i>Update on Re-treatment approval also featured on page 40</i>	<i>Sponsor/Medical Monitor oversight and approval for open-label retreatment.</i>

Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
10.5 Concomitant Medications	10.5 Concomitant Medications, Procedures and Treatments	10.5 Concomitant Medications	10.5 Concomitant Medications, <b>Procedures and Treatments</b>  <i>Changes also featured on pages 12 &amp; 15 (SOA &amp; SOA footnotes), 48, 64-70</i>	<i>Clarify that Con Procedures and Treatments will also need to be recorded in source/EDC</i>
10.5.2 Concomitant Third-Line Agents	10.5.2 Concomitant Third-Line Agents	Some third-line agents (such as propofol) are also used to induce sedation to facilitate a subject's ability to tolerate the ventilator, or analgesics to cover potentially painful procedures.	Some third-line agents (such as propofol) are also used to induce sedation to facilitate a subject's ability to tolerate the ventilator.	<i>Clarification on use of third-lines for ventilator support.</i>
11.1.1 Primary Efficacy	11.1.1 Primary Efficacy	In addition, subjects must have evidence of physiologic brain activity (determined by EEG) to be deemed to be successes.	In addition, subjects must have evidence of physiologic brain activity ( <b>average EEG power at the end of Visit 9 of more than two microvolts</b> ) to be deemed to be successes. <b>All subjects who fail to complete their infusion of randomized treatment or do not have at least one attempt during study treatment to wean off all</b>	<i>Changes in response to FDA SPA letter re: change to ITT population for primary analysis and clarification of criteria for being deemed a success or failure</i>



Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
			<b>third-line agents will be considered as “failures” for the primary endpoint.</b>	<i>following the initial blinded infusion.</i>
11.1.1.1 Weaning	11.1.1.1 Weaning	Third-line agents are anesthetic agents that are administered in order to reach a burst suppression EEG pattern. For the purposes of this study, third-line agents are defined as continuous intravenous infusions of pentobarbital, midazolam, propofol, and ketamine at maintenance doses alone or in combination sufficient to produce a burst suppression pattern on the EEG. The following are considered to be minimum maintenance doses of these agents that may be expected alone or in combination to achieve EEG burst suppression. If subjects are on lower doses than these and are not in EEG burst suppression for the 24 hours prior to the QW, they will be considered to be screen failures	Third-line agents are anesthetic agents that are administered in order to reach <b>a seizure</b> or burst suppression EEG pattern. For the purposes of this study, third-line agents are defined as continuous intravenous infusions of pentobarbital, midazolam, propofol, and ketamine at maintenance doses alone or in combination sufficient to produce a burst suppression pattern on the EEG. The following are considered to be minimum maintenance doses of these agents that may be expected alone or in combination to achieve EEG burst suppression. If subjects are on lower doses than these and are not in EEG burst suppression for the 24 hours prior to the QW <b>or the first 12 hours of the blinded study drug infusion</b> , they will be	<i>Clarifying burst suppression requirements following start of the blinded study drug infusion to ensure consistency across all study sites.</i>

Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
		and will exit the study after the QW.	considered to be screen failures/ <b>protocol violators</b> and will exit the study.	
11.1.1.1 Weaning	11.1.1.1 Weaning	<p>The timing and nature of the third-line agent weans will be determined by the standard of care at the site and the clinical judgment of the investigator, and will always be primarily done in the best medical interests of the subject. However, the following guidance must be followed and if questions arise regarding the weaning of third-line agents, specifics should be discussed with the medical monitor.</p> <p>Additionally, advice about weaning may be sought from fellow investigators in the study, particularly those with the most experience of performing clinical trials in subjects with SRSE.</p>	<p>The timing and nature of the third-line agent weans will be <b>guided by the Clinical Standardization Guidelines for the study</b>, and the clinical judgment of the investigator, and will always be primarily done in the best medical interests of the subject. Advice about weaning may be sought from <b>the Clinical Standardization Team, a group of fellow investigators with</b> experience of performing clinical trials in subjects with SRSE. <b>The Clinical Standardization Team will be able to review EEGs in real time related to key study timepoints (qualifying wean, terminal wean, and the period after the end of the blinded study drug infusion) in order to provide advice about</b></p>	<p><i>Clinical Standardization Guidelines/Team established to assist sites and create consistency with weaning practices across study sites.</i></p>

Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
			<b>compliance with the Clinical Standardization Guidelines.</b>	
11.1.1.1 Weaning/QW Guidance	11.1.1.1 Weaning/QW Guidance	<i>N/A</i>	<p><i>The following was added as a new bullet under the QW Guidance section:</i></p> <ul style="list-style-type: none"> <li><b>Investigators should allow 24 hours to lapse after the end of a “successful” qualifying wean before finally declaring the QW a success. If a third-line agent needs to be re-instituted within that 24 hours, the QW is a failure, and the subject may then be randomized in the study.</b></li> </ul>	<i>Quantifies a minimum period of time from the conclusion of the QW to when the determination of being a QW success is made.</i>
11.1.1.1 Weaning/OW Guidance	11.1.1.1 Weaning/OW Guidance	<p>OW Guidance</p> <ul style="list-style-type: none"> <li>First OW should begin at H49 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.</li> <li>If the subject is on two third-line agents, ideally the first should be weaned over 24 hours</li> </ul>	<p>OW Guidance</p> <ul style="list-style-type: none"> <li>First OW <b>should not begin before</b> H49 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.</li> <li>If the subject is on two third-line agents, ideally the first should be weaned over 24 hours</li> </ul>	<i>Clarifying time frames for third-line weaning procedures.</i>

Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
		<p>and that wean completed before starting the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.</p> <ul style="list-style-type: none"> <li>If the subject is on three third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the wean of the second agent. The second agent should be weaned over 24 hours and that wean completed before starting the TW. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of</li> </ul>	<p>and that wean completed before starting the TW. <b>However the OW may be completed over a shorter or longer time period and may overlap if clinically indicated with the start of the TW.</b> Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.</p> <ul style="list-style-type: none"> <li>If the subject is on three third-line agents, ideally the first should be weaned over 24 hours and that wean completed before starting the wean of the second agent. The second agent should be weaned over 24 hours and that wean completed before starting the TW. <b>However the OWs may be</b></li> </ul>	

Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
		AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.	<b>completed over a shorter or longer time period and may overlap if clinically indicated with each other and with the start of the TW.</b> Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.	
11.1.1.1 Weaning/TW Guidance	11.1.1.1 Weaning/TW Guidance	<p>TW Guidance</p> <ul style="list-style-type: none"> <li>If the subject is on one third-line agent, the TW should begin at H49 after starting administration of study drug or starting the open-label infusion of SAGE-547. If the subject has had one or more OWs, the TW should begin as soon as the last OW is</li> </ul>	<p>TW Guidance</p> <ul style="list-style-type: none"> <li><b>The TW is defined as the wean of the last third-line agent.</b></li> <li>If the subject is on one third-line agent, the TW <b>should not begin before H49 and should begin no later than H97</b> after starting administration of study drug or starting the open-label</li> </ul>	<i>Clarifying time frames for third-line weaning procedures.</i>

Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
		complete but in any case not later than H97 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.	infusion of SAGE-547. If the subject has had one or more OWs, the TW should <b>ideally</b> begin as soon as the last OW is complete but in any case not later than H97 after starting the blinded administration of study drug or after starting the open-label infusion of SAGE-547.	
11.1.1.1 Weaning/AW Guidance	11.1.1.1 Weaning/AW Guidance	<ul style="list-style-type: none"> <li>Ideally the AW should take place over 24 hours. Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.</li> </ul>	<ul style="list-style-type: none"> <li>Ideally the AW should take place over 24 hours, <b>but completion may be over a shorter or longer time period than this.</b> Breakthrough seizures must be managed as far as possible with intermittent bolus doses of AEDs and optimization of the repeat dose regimens of AEDs. If breakthrough seizures cannot be managed in this way, the dose of the third-line agent being weaned should be adjusted to control seizures, with the weaning attempt continued once the seizure activity abates.</li> </ul>	<i>Clarifying time frames for third-line weaning procedures.</i>

Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
11.1.1.2 EEG	11.1.1.2 EEG	<ul style="list-style-type: none"> <li>EEG will be performed from three hours prior to the start of the blinded infusion to five hours after the start of the blinded infusion.</li> </ul>	<ul style="list-style-type: none"> <li>EEG will be performed from three hours prior to the start of the blinded infusion to five hours after the start of the blinded infusion. <b>This will be called the BIEEG.</b></li> </ul> <p><i>Changes also featured on pages 24 (List of Abbreviations), and 51</i></p>	<i>Defining the Blinded Infusion EEG for clarification and reporting purposes.</i>
11.1.1.2 EEG	11.1.1.2 EEG	The six EEG records for each subject will be read centrally to confirm the PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period. The EEG records may be subject to quantitative EEG analysis.	<p><b>A maximum of nine</b> EEG records for each subject will be <b>collected and stored</b> centrally; <b>of these, the following will be read centrally</b> to confirm the PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period <b>(average EEG power at the end of Visit 9 of more than two microvolts).</b></p> <ul style="list-style-type: none"> <li><b>All subjects will have the CEEG and QWEEG collected and stored, and the QWEEG</b></li> </ul>	<i>Clarification on the EEG collection/storage and reading requirements for the central EEG reader.</i>

Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
			<p>read;</p> <ul style="list-style-type: none"><li>• Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;</li><li>• Those subjects randomized who are not retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read;</li><li>• Those subjects randomized who are retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion and the TWEEG, TAEED, and PAEEG related to the open-label study drug infusion collected and stored, and the QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion</li></ul>	



Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
			<b>read.</b> All EEG records may be subject to quantitative EEG analysis.	
11.1.2.1 Clinical Global Impression Scale (CGI)	11.1.2.1 Clinical Global Impression Scale (CGI)	<p>The CGI scales are validated measures often utilized in clinical trials to allow clinicians to integrate several sources of information into a single rating of the subject's condition. Both the CGI-Severity (CGI-S) and the CGI-Improvement (CGI-I) employ a 7-point Likert scale measuring severity of the disease state in the subject and improvement, respectively. All severity assessments after initiation of SAGE-547 treatment should consider the general state of the subject over the preceding week.</p> <p>The CGI will be evaluated at Visit 1 and at the last visit, Visit 12 or 12R.</p>	<p>The <b>clinical global impression</b> scales are often utilized in clinical trials to allow clinicians to integrate several sources of information into a single rating of the subject's condition. Both the CGI-Severity (<b>Question 1</b>, CGI-S) and the CGI-Improvement (<b>Question 2</b>, CGI-I) employ a 7-point Likert scale measuring severity of the disease state in the subject and improvement, respectively. All severity assessments after initiation of SAGE-547 treatment should consider the general state of the subject over the preceding week.</p> <p><b>The third question on the scale will not be employed in this trial, and where the scale states "mental illness", this means "physical illness" in this trial.</b></p> <p>The CGI-S will be evaluated at</p>	<i>Clarification re: the questions on the CGI scale.</i>

Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
			Visit 1 and at the last visit, Visit 12 or 12R. <b>The CGI-I will be evaluated at Visit 12 or 12R.</b>	
11.1.2.2 Epilepsy Status	11.1.2.2 Epilepsy Status	<p>Previous (non-index) diagnosis of status epilepticus will be documented as a no/yes question. If SE did occur in the past, further information will be gathered, including:</p> <ul style="list-style-type: none"> <li>• SE, RSE, or SRSE diagnosis;</li> <li>• Cause;</li> <li>• Treatment, including experimental treatments and need for intubation/ventilation;</li> <li>• Dates of onset and duration.</li> </ul>	<p>Previous (non-index) diagnosis of status epilepticus will be documented as a no/yes question. If SE did occur in the past, further information will be gathered, including:</p> <ul style="list-style-type: none"> <li>• SE, RSE, or SRSE diagnosis, <b>whichever was the most severe diagnosis for each episode;</b></li> <li>• Cause;</li> <li>• Treatment, including experimental treatments and need for intubation/ventilation;</li> <li>• Dates of onset and duration <b>if the episode of status epilepticus occurred in the past 12 months.</b></li> </ul>	<i>Clarification on the severity and onset/duration of past diagnosis of SE that need to be recorded in source/EDC.</i>
11.2.2 Clinical Laboratory Tests	11.2.2 Clinical Laboratory Tests	<p>Urine samples will be taken for urinalysis at:</p> <ul style="list-style-type: none"> <li>• Visit 1 and at Hour 24, 48,</li> </ul>	<p>Urine samples <b>(20 ml)</b> will be taken for urinalysis and urine <b>NAG analysis</b> at:</p>	<i>Correction that NAG will be part of the Urinalysis panel, previously</i>

Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
		<p>96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.</p> <p>These samples will be analyzed at a central laboratory; hour-to-hour medical decisions will be based on sampling for laboratory testing done outside the protocol as part of normal standard of care.</p>	<ul style="list-style-type: none"> <li>Visit 1 and at Hour 24, 48, 96, 144 and 192 (all +/- 2 hours) relative to the start of the first infusion of study drug, and to the start of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547.</li> </ul> <p>These samples will be analyzed at a central laboratory; hour-to-hour medical decisions will be based on sampling for laboratory testing done outside the protocol as part of normal standard of care. <b>GFR will be calculated using values from local laboratory tests.</b></p> <p><i>NAG updated also featured on page 16 (SOA footnotes)</i></p>	<p><i>was listed as part of the Serum Chemistry panel (removed from pg. 56 list of Serum Chem. panel tests). Additionally, clarified that GFR is calculated at the local lab opposed to the central lab.</i></p>
11.2.2.2 Pregnancy Test	11.2.2.2 Pregnancy Test	<p>In this study, since an accurate history of menstruation in girls and menopause in older women may not be available at Visit 1, “child-bearing potential” is taken</p>	<p>In this study, since an accurate history of menstruation in girls and menopause in older women may not be available at Visit 1, “child-bearing potential” is taken to mean</p>	<p><i>Revised child bearing potential age range from 10 – 55 y.o. per the request of central IRB.</i></p>

Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
		to mean any female aged 12 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy	any female aged <b>10</b> years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy  <i>Changes also featured on pages 16 (SOA footnotes), and 56</i>	
11.2.3 Vital Signs	11.2.3 Vital Signs	Respiratory rate does not need to be collected if the subject is mechanically ventilated at the due time of the vital sign assessment.	<i>Deleted in Sec. 11.2.3 as well as from SOA footnotes on page 16</i>	<i>Respiratory Rate will no longer be collected.</i>
11.2.6 Mortality	11.2.6 Mortality	<ul style="list-style-type: none"> <li>SE;</li> <li>complications of long term intubation and third-line agent infusions;</li> <li>underlying cause of qualifying SE;</li> <li>co-morbidity existing at the time of the qualifying SE;</li> <li>new co-morbidity or</li> </ul>	<ul style="list-style-type: none"> <li>SE;</li> <li>complications of long term intubation and third-line agent infusions;</li> <li>underlying cause of qualifying SE;</li> <li>co-morbidity existing at the time of the qualifying SE;</li> <li>new co-morbidity or trauma;</li> </ul>	<i>Study drug added to list of possible causes of death.</i>

Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
		trauma; • other (specify).	<ul style="list-style-type: none"> <li>• <b>study drug;</b></li> <li>• other (specify).</li> </ul>	
11.2.8.1 Pharmacokinetic Data	11.2.8.1 Pharmacokinetic Data	The plasma samples will be drawn from an arterial-line, central line or the arm contralateral to that used for drug administration. PK collection times should be adhered to as strictly as possible. The allowed time window for all samples is +/- 5 minutes.	<p>The plasma samples will be drawn from the arm contralateral to that used for drug administration.</p> <p><b>Drawing samples from peripheral arterial or venous lines or from a central line is permissible.</b> PK collection times should be adhered to as strictly as possible. The allowed time window for all samples is: <b>pre-dose in the two hours prior to starting the infusion of study drug; samples up to and including 1h, +/- 5 minutes; subsequent samples, +/- 15 minutes.</b></p> <p><i>Language on PK sample collection windows also featured on pages 16 (SOA footnotes), and 65 - 69</i></p>	<i>Clarifying PK sample collection procedure and windows.</i>
11.2.8.1 Pharmacokinetic Data	11.2.8.1 Pharmacokinetic Data	Each blood sample will be 3 ml in volume for adults and children weighing 30 kg or more, and 1.5 ml in volume for children	Each blood sample will be 3 ml in volume for adults and children weighing 30 kg or more, and <b>2 ml</b> in volume for children weighing	<i>Revised based on PK vendor feedback.</i>

Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
		weighing less than 30 kg. Separate aliquots will be obtained from each sample to service the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum blood draw for a subject having two infusions of study drug will be 99 ml (49.5 ml for children weighing less than 30 kg).	less than 30 kg. Separate aliquots will be obtained from each sample to service the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum blood draw <b>for PK analysis</b> for a subject having two infusions of study drug will be 99 ml ( <b>66 ml</b> for children weighing less than 30 kg).	
11.2.8.1 Pharmacokinetic Data	11.2.8.1 Pharmacokinetic Data	<p>Urine Analysis</p> <p>In the first 70 patients enrolled in the study, all urine voided in each 24-hour period during and after the blinded and open-label infusions of study drug will be collected and pooled. The total volume for each 24-hour period will be measured and a 20 ml sample will be taken from each pooled urine collection (0-24 hours: 25-48 hours: 49-72 hours: 73-96 hours: 97-120 hours: 121-144 hours: 145-168 hours) and</p>	<p><b>Other Analysis</b></p> <p><b>If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations.</b></p> <p><i>Urine Analysis information deleted from Sec. 11.2.8.1 also removed</i></p>	<p><i>Urine PK was removed as a study assessment. For patients that may undergo a spinal or ventricular tap, LAR/subject may elect to permit a sample be used for PK analysis.</i></p>

Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
		analyzed for urine concentrations of SAGE-547 (and important metabolites as and when these are identified) and Captisol®.	<i>from SOA footnotes on page 16</i>	
11.2.8.3 Pharmacoeconomic Data	11.2.8.3 Pharmacoeconomic Data	<i>N/A</i>	<p><i>Added the following text to this section:</i></p> <p><b>For those subjects discharged from hospital before Visit 12/12R, the following questions will be asked:</b></p> <ul style="list-style-type: none"> <li><b>On what study day was the subject discharged from hospital?</b></li> <li><b>What type of facility was the subject discharged to (another hospital, a rehabilitation center, a supported care facility, home, other)?</b></li> <li><b>How many days did the subject stay in this facility?</b></li> </ul> <p><b>The following questions will be answered regarding the stay in</b></p>	<p><i>Sponsor interest in obtaining Health Economics and Outcome data for patients who discharge from ICU prior to completion of V12/12R.</i></p>

Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
			<p><b>the ICU and hospital:</b></p> <ul style="list-style-type: none"> <li>• Was the subject still in the ICU at the end of Visit 10/10R?</li> <li>• If the FOUR Score was &gt;12 at Visit 10/10R and the subject was in the ICU at Visit 10/10R, what was the reason for the subject not being discharged from the ICU (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, other)?</li> <li>• Was the subject still an in-patient in the hospital at the end of Visit 12/12R?</li> <li>• If the FOUR Score was &gt;15 at Visit 12/12R and the subject was in the hospital at Visit 12/12R, what was the reason for the subject not being discharged from the hospital (underlying disease, ICU comorbidity, no available bed elsewhere, hospital policy, unsuitable home circumstances,</li> </ul>	



Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
			other)?	
N/A	11.2.8.4 STESS	N/A	<b>The STESS will be assessed during Visit 1 in order to assess the severity of the status epilepticus.</b>	<i>Previous omission.</i>
12.1 Visit 1 (V2-≤30h)	12.1 Visit 1 (V2-≤30h)	The baseline period will be approximately 36 hours prior to starting blinded study treatment and should include the assessments/procedures listed below and summarized in Table 1 and Table 2 (for retreatment), the Schedules of Events.	The baseline period will be <b>up to</b> approximately <b>84</b> hours prior to starting blinded study treatment and should include the assessments/procedures listed below and summarized in Table 1 and Table 2 (for retreatment), the Schedules of Events.	<i>As amended in the 'QW Guidance', previously listed in this SOC, the screening window was expanded to account for the new requirement for Investigators to wait 24 hours after a subject is first believed to have successfully been weaned off of third-line agents during the QW.</i>
12.4.1 Visit8/8R (121-144 hours)	12.4.1 Visit8/8R (121-144 hours)	<ul style="list-style-type: none"> <li>Ongoing intravenous</li> </ul>	<ul style="list-style-type: none"> <li><b>Complete wean of third</b></li> </ul>	<i>Reconciles with the guidance in</i>

Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
		administration of continuous IV third-line agent:  - Initiate of continue weaning if in the opinion of the Investigator subject seizure activity is controlled.	<b>line agents by H144 if not completed by H120</b>	<i>the '11.1.1.1 Weaning' section of the protocol (pages 49 – 51) and clarifies the goal of having third-line agents off before the end of the study drug infusion period.</i>
12.5.2 Visit 10/10R (169-192 hours)	12.5.1 Visit 9/9R (169-192 hours)	Assessment of the presence of physiologic brain activity using EEG.	Assessment of the presence of physiologic brain activity using EEG.	<i>Moved from the bulleted list of assessments under Visit 10/10R to Visit 9/9R to match SOA.</i>
13.1.2 Study Population	13.1.2 Study Population	The Safety Population is defined as all subjects who at least had an infusion of blinded study medication initiated.  The Modified Intent to Treat Population is defined as all subjects who:  1. complete their initial	<b>The Safety Population is defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to actual treatment. This analysis population will be used for all safety analyses.</b>  <b>The Intent to Treat Population is</b>	<i>Changes in response to FDA SPA letter re: change to ITT population for primary analysis and clarification of treatment assignment for analyses.</i>

Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
		<p>course of blinded SAGE-547 or placebo treatment unless the non-completion was due a drug-related adverse event; and</p> <p>have at least one attempt to wean from third-line agents prior to the end of blinded study treatment infusion unless the failure to wean was because seizures were not controlled.</p> <p>Narratives will be prepared for all subjects who do not complete the infusion of blinded study medication or were not subjected to any wean attempts. Narratives will include details of the cause of SE, the comorbid conditions, the adverse event(s), and reasons for non-completion of the infusion or failure to attempt weaning. This blinded narrative will be reviewed by the DSMB and the patient adjudicated as included or excluded from the MITT. Acceptable reasons for excluding</p>	<p><b>defined as all subjects who at least had an infusion of blinded study medication initiated. Subjects will be classified according to randomized treatment. This analysis population will be used for all efficacy analyses.</b></p> <p>The Modified Intent to Treat Population is defined as all subjects who:</p> <ol style="list-style-type: none"> <li>complete their initial course of blinded SAGE-547 or placebo treatment unless the non-completion was due a drug-related adverse event; and</li> <li>have at least one attempt to wean from third-line agents prior to the end of blinded study treatment infusion unless the failure to wean was because seizures were not controlled.</li> </ol> <p><b>Subjects will be classified according to randomized treatment. This analysis</b></p>	

Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
		<p>the subject from the MITT include death or withdrawal of consent due to progression of the underlying cause of SE or comorbid conditions.</p> <p>The Intent to Treat Population is defined as all subjects who at least had an infusion of blinded study medication initiated.</p>	<p><b>population will be used for sensitivity analyses of the primary endpoint and select secondary efficacy endpoints.</b></p> <p>Narratives will be prepared for all subjects who do not complete the infusion of blinded study medication or were not subjected to any wean attempts. Narratives will include details of the cause of SE, the comorbid conditions, the adverse event(s), and reasons for non-completion of the infusion or failure to attempt weaning. This blinded narrative will be reviewed by the <b>medical monitors and</b> the patient adjudicated as <b>MITT eligible or ineligible</b>. Acceptable reasons for <b>defining a</b> subject as MITT ineligible include death or withdrawal of consent due to progression of the underlying cause of SE or comorbid conditions, <b>unless the cause of death or progression of disease were thought by the investigator,</b></p>	

Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
			<p>sponsor, or DSMB to be related to study drug.</p> <p><b>The Per-Protocol (PP) Population is defined as a subset of the MITT population but will exclude data from all subjects with significant protocol violations or deviations. Subjects will be classified according to actual treatment received. This data set will be used for sensitivity analyses to examine the robustness of results for the primary and key secondary efficacy endpoints.</b></p>	
13.1.4 Analysis of Primary Endpoint	13.1.4 Analysis of Primary Endpoint	The analysis of response to treatment between SAGE-547 treated subjects and placebo treated subjects will be performed on the MITT population using a Cochran-Mantel-Haenszel test with variables for treatment, concomitant pentobarbital use	The analysis of response to treatment ( <b>see Section 11.1.1 for definition of primary endpoint</b> ) between SAGE-547 treated subjects and placebo treated subjects will be performed on the <b>ITT</b> population using a Cochran-Mantel-Haenszel ( <b>CMH</b> ) test with variables for	<i>Changes in response to FDA SPA letter re: change to use of ITT population for primary analysis and additional detail provided for</i>

Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
		<p>(yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). In this analysis, a treatment responder is a subject who is successfully weaned off all third-line agents and blinded study medication prior to the end of study treatment infusion and remains off third-line agents for at least 24 hours following cessation of the blinded study medication. In addition, subjects deemed to be successes must have evidence of physiologic brain activity as determined by EEG. The comparison of treatment response rates will be conducted at the 5% level of significance.</p> <p>A sensitivity analysis of the primary endpoint will be performed on the ITT population, in which subjects who were not included in the MITT population are assumed to be treatment</p>	<p>treatment, concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more). <b>The CMH general association statistic and its associated p-value will be presented. The comparison of treatment response rates will be conducted at the 5% level of significance. To confirm the CMH results, a permutation test will also be conducted.</b></p> <p><b>An additional</b> analysis of the primary endpoint will <b>also</b> be performed on the <b>MITT</b> population. In addition sensitivity analyses of the primary endpoint will be performed using the <b>ITT</b> population based on:</p>	<i>primary statistical analysis</i>

Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
		failures. In addition sensitivity analyses of the primary endpoint will be performed using the MITT population based on:		
13.1.5 Analysis of Secondary Efficacy Endpoints	13.1.5 Analysis of Secondary Efficacy Endpoints	Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the MITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section (Section 6). Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. Summary statistics will be provided for all endpoints.	Secondary endpoints will be compared between SAGE-547 and placebo treated subjects in the <b>ITT</b> population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints as listed in the Endpoints Section (Section 6). Assuming there is a significant difference between groups in the primary endpoint, the first secondary endpoint will be compared between groups. The testing process will continue until all endpoints have been evaluated or one of the analyses yields a non-significant result. <b>The analysis of the secondary endpoints will also be performed on the MITT population.</b> Summary statistics	<i>Changes in response to FDA SPA letter re: change to use of ITT population for primary analysis</i>

Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
			will be provided for all endpoints.	
14.1.2.2 Intensity	14.1.2.2 <b>Severity</b>	<p>Mild: For subjects that are unconscious, this may be a slight or minor change in a lab result or clinical sign or symptom that does not require immediate corrective action.</p> <p>Moderate: For subjects that are unconscious, this may be a clinically meaningful change that may require immediate corrective action.</p> <p>Severe: For unconscious subjects, this may be a significant clinical change that requires immediate corrective action.</p>	<p>Mild: <b>Discomfort noticed, but no disruption to daily activity.</b></p> <p>For subjects that are unconscious, this may be a slight or minor change in a lab result or clinical sign or symptom that does not require immediate corrective action.</p> <p>Moderate: <b>Discomfort sufficient to reduce or affect normal daily activity, but is not hazardous to health; prescription drug therapy may be employed to treat the AE.</b></p> <p>For subjects that are unconscious, this may be a clinically meaningful change that may require immediate corrective action.</p> <p>Severe: <b>Inability to work or perform normal daily activity and represented a definite hazard to health; prescription drug therapy and/or hospitalization</b></p>	<p><i>Revised section from 'Intensity' to 'Severity' and provided clarifying language to assist Investigator assessments.</i></p>



Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
			<p><b>may be employed to treat the AE.</b></p> <p>For unconscious subjects, this may be a significant clinical change that requires immediate corrective action.</p>	
14.1.3 Investigator Reporting to Sponsor and Sponsor Emergency Contact	14.1.3 Investigator Reporting to Sponsor and Sponsor Emergency Contact	<p>All new SAEs that come to the Investigator and/or Sponsor's notice during the course of the study must be reported by the Investigator on the designated electronic report form within one working day from the point in time when the Investigator becomes aware of the SAE. As additional information becomes available, the designated electronic report form must be updated within one working day. In addition, all SAEs that occur up to and including 30 days after administration of study drug must be reported within one working day from when the Investigator becomes aware of the SAE.</p>	<p>All new SAEs that come to the Investigator and/or Sponsor's notice during the course of the study (<b>up to and including the last study visit</b>) must be reported by the Investigator on the designated electronic report form within <b>24 hours</b> of the point in time when the Investigator becomes aware of the SAE. As additional information becomes available, the designated electronic report form must be updated within <b>24 hours</b>.</p>	<p><i>Clarification on SAE Reporting requirements/time lines.</i></p>

Section number and title in Protocol Ver. 1 (09 MAR 15)	Section number and title in Amendment 1 (27 MAY 15)	Original text:	Changed to:	Rationale
14.2.2 Data Safety Monitoring Board	14.2.2 Data Safety Monitoring Board	An independent DSMB will monitor the clinical, PK and PD data for safety signals throughout the study and will be asked to assess efficacy at the time of the interim analysis to determine study continuation. In order to perform their monitoring function the DSMB will have access to un-blinded data as necessary.	An independent DSMB will monitor the clinical, PK and PD data for safety signals throughout the study and will be asked to assess <b>the placebo response rate</b> at the time of the interim analysis to determine <b>final sample size</b> . In order to perform their monitoring function the DSMB will have access to un-blinded <b>safety</b> data as necessary.	<i>Changes in response to FDA SPA letter re: clarification of data available for the DSMB review of the interim analysis</i>
Appendices	Appendices	NA	<i>Status Epilepticus Severity Score (STESS) added as <a href="#">Appendix 6</a></i>	<i>Previous omission.</i>

**Summary of Changes**  
**Protocol-547-SSE-301**  
**Amendment One (Italy Specific) Dated 02 DEC 2015**

The following changes were made to the attached protocol in this amendment. All other changes were administrative in nature.

<b>Section number and title in Protocol Amendment One Dated 27 MAY 15</b>	<b>Section number and title in Amendment One (Italy Specific) Dated 02 DEC 15</b>	<b>Original text:</b>	<b>Changed to:</b>	<b>Rationale</b>
2. Study Synopsis/Study Population	2. Study Synopsis/Study Population	Subjects will be aged two years or more in SRSE <sup>1</sup> (as defined in the Inclusion Criteria Section 8.1), and being managed in an intensive care setting.	Subjects will be aged two years or more in SRSE <sup>1</sup> (as defined in the Inclusion Criteria Section 8.1), and being managed in an intensive care setting. <b>Pediatric patients (those &lt; 14 years of age) will be managed in a pediatric intensive care setting.</b>	<i>Specifies study setting for pediatrics under 14 years of age.</i>
7.1 Overview of Study Design	7.1 Overview of Study Design	This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE.	This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE. <b>Pediatric patients (those &lt; 14 years of age) will be managed in a pediatric intensive care setting.</b>	<i>Specifies study setting for pediatrics under 14 years of age.</i>

**Summary of Changes**  
**Protocol-547-SSE-301**  
**Dated 17 NOV 2015**

The following changes were made to the attached protocol in this amendment. Minor typographical/editorial errors throughout the document were also corrected.

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
2. Study Synopsis/Study Sites	2. Study Synopsis/Study Sites	Up to 150 sites in the USA, Europe, and Canada.	Up to <b>180</b> sites in the USA, Europe, and Canada.  <i>Change also featured on pages 5 &amp; 43</i>	<i>Oversight in Amendment 1, addition of EU sites to yield 180 total sites</i>
2. Study Synopsis/Study Design	2. Study Synopsis/Study Design	Burst suppression must be maintained for the first 12 hours of the infusion of study drug.	Burst suppression must be maintained for the first 12 hours of the infusion of <b>blinded</b> study drug.  <i>Change also featured on pages 5-6, &amp; 38-39</i>	<i>Clarification on mandatory burst suppression time frame during blinded infusion treatment phase only</i>
2. Study Synopsis/Study Design	2. Study Synopsis/Study Design	The randomization will be stratified by concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).	The randomization will be stratified by concomitant pentobarbital/ <b>thiopental</b> use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).	<i>Thiopental added as accepted Third Line Agent barbiturate comparable to Pentobarbital. Randomization will be stratified</i>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
			<i>References to concomitant thiopental use also featured on pages 6, 11, 39-40, 41, 70, &amp; 72</i>	<i>by concomitant barbiturate use (pentobarbital and thiopental), along with prior third-line agent wean attempts.</i>
Table 2: Schedule of Assessments: Two Infusions of Study Drug (one blinded, one open-label)	Table 2: Schedule of Assessments: Two Infusions of Study Drug (one blinded, one open-label)	NA	Additional assessment added to Visit 9R (145h-168h):  <b>TW Success and Physiologic Brain Activity</b>	<i>Previous omission, corrected for consistency with Sec. 12.5.1 Visit 9/9R</i>
Figure 1: Study Design	Figure 1: Study Design	Visit 2 ( $\leq 30$ h before V3)	Visit 2 ( $\leq 54$ h before V3)	<i>Previous omission, corrected for consistency with Tables 1 – 3 and Sec. 12.2</i>
Figure 2: Details of Treatment Administration and Follow-up	Figure 2: Details of Treatment Administration and Follow-up	Screening Period / V1-2/ -36h	Screening Period / V1-2/ -84h	<i>Previous omission, corrected for consistency with Tables 1 – 3, Figure 1, and Sec. 12.1 &amp; 12.2</i>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
11.1.1.1 Weaning	11.1.1.1 Weaning	<ul style="list-style-type: none"> <li>• Pentobarbital: 1 mg/kg/hour</li> <li>• Midazolam: 0.1 mg/kg/hour</li> <li>• Propofol: 3 mg/kg/hour</li> <li>• Ketamine 1.2 mg/kg/hour</li> </ul>	<ul style="list-style-type: none"> <li>• Pentobarbital: 1 mg/kg/hour</li> <li>• <b>Thiopental: 3 mg/kg/hour</b></li> <li>• Midazolam: 0.1 mg/kg/hour</li> <li>• Propofol: 3 mg/kg/hour</li> <li>• Ketamine 1.2 mg/kg/hour</li> </ul>	<i>Thiopental added as accepted Third Line Agent</i>
11.1.1.1 Weaning	11.1.1.1 Weaning	The Clinical Standardization Team will be able to review EEGs in real time related to key study timepoints (qualifying wean, terminal wean, and the period after the end of the blinded study drug infusion) in order to provide advice about compliance with the Clinical Standardization Guidelines.	The Clinical Standardization Team will be able to <b>discuss EEGs related to key study</b> timepoints (qualifying wean, terminal wean, and the period after the end of the blinded study drug infusion <b>if the terminal wean was successful</b> ) in <b>a timely manner</b> in order to provide advice about compliance with the Clinical Standardization Guidelines.	<i>Clarification on the CST communication process and CST expectations on advising sites on the CSGs</i>
11.1.1.2 EEG	11.1.1.2 EEG	<ul style="list-style-type: none"> <li>• A six-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the</li> </ul>	<ul style="list-style-type: none"> <li>• A <b>24-hour</b> duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that</li> </ul>	<i>Extended the Consent EEG to capture as much of the burst suppression period prior to the Qualifying</i>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
		<p>study for that patient; patterns would be seizure activity for the first path to eligibility, burst suppression for the second path to eligibility, and a variable pattern for the third path to eligibility.</p> <ul style="list-style-type: none"> <li>• EEG will be performed to cover the qualifying wean (QWEEG). EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for the one hour after the end of the QW. The duration of the QWEEG will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s) or the decision to re-institute a third-line agent(s) at doses intended to induce burst suppression.</li> </ul>	<p>patient; patterns would be seizure activity for the first path to eligibility, burst suppression for the second path to eligibility, and a variable pattern for the third path to eligibility. <b>This EEG will capture as much as possible of the burst suppression pattern that precedes the QW.</b></p> <ul style="list-style-type: none"> <li>• EEG will be performed to cover the qualifying wean (QWEEG). EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for <b>up to 24 hours</b> after the end of the QW. The duration of the QWEEG will be up to <b>48.5</b> hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s), the decision to re-institute a third-</li> </ul>	<p><i>Wean as possible.</i></p> <p><i>Extended the QWEEG to match QW Guidance in Sec. 11.1.1.1 for Investigators to allow 24 hours to lapse after the end of QW before declaring QW success.</i></p> <p><i>Extended the BIEEG to capture the burst suppression period during the initial 12 hours of the blinded infusion.</i></p>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
		<ul style="list-style-type: none"> <li>• EEG will be performed from three hours prior to the start of the blinded infusion to five hours after the start of the blinded infusion. This will be called the BIEEG. The intent of this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG.</li> </ul>	<p>line agent(s) at doses intended to induce burst suppression, <b>and the decision that the QW is a success.</b></p> <ul style="list-style-type: none"> <li>• EEG will be performed from three hours prior to the start of the blinded infusion to <b>12</b> hours after the start of the blinded infusion. This will be called the BIEEG. The intent of this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG <b>and to assess the depth of burst suppression in the first 12 hours of blinded study drug infusion.</b></li> </ul>	
11.1.1.2 EEG	11.1.1.2 EEG	<ul style="list-style-type: none"> <li>• For the QWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the</li> </ul>	<ul style="list-style-type: none"> <li>• For the QWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the</li> </ul>	<i>Clarification on Investigator assessment of the Qualifying Wean and the duration of the QWEEG.</i>



Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
		subject was a failure on the qualifying wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the qualifying wean)	subject was a failure <b>or success</b> on the qualifying wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the qualifying wean <b>constitutes a failure</b> ); <b>the QWEEG will extend to cover the 24 hours after the end of third line agents in order to confirm that the QW was a success.</b>	
11.1.1.2 EEG	11.1.1.2 EEG	A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period (average EEG power at the end of Visit 9 of more than two	A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm <b>the depth of burst suppression prior to the QW and during the first 12 hours of the blinded study drug infusion, the</b> PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain	<i>Added the Consent EEG (CEEG) and Blinded Infusion EEG (BIEEG) to the EEG records to be read centrally to capture the depth of burst suppression prior to Qualifying Wean and during</i>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
		<p>microvolts):</p> <ul style="list-style-type: none"> <li>• All subjects will have the CEEG and QWEEG collected and stored, and the QWEEG read;</li> <li>• Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;</li> <li>• Those subjects randomized who are not retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read;</li> <li>• Those subjects randomized who are retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion</li> </ul>	<p>activity at the end of the primary endpoint assessment period (average EEG power at the end of Visit 9 of more than two microvolts):</p> <ul style="list-style-type: none"> <li>• All subjects will have the CEEG and QWEEG collected and stored, and the <b>CEEG and</b> QWEEG read;</li> <li>• Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;</li> <li>• Those subjects randomized who are not retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the <b>BIEEG, QWEEG, TWEEG, and PAEEG</b> related to the blinded study drug infusion read;</li> <li>• Those subjects randomized who are retreated will have the</li> </ul>	<p><i>the first 12 hours of the blinded infusion.</i></p>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
		and the TWEEG, TAEED, and PAEEG related to the open-label study drug infusion collected and stored, and the QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read.	BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion and the TWEEG, TAEED, and PAEEG related to the open-label study drug infusion collected and stored, and the <b>BIEEG</b> , QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read.	
11.2.2 Clinical Laboratory Tests	11.2.2 Clinical Laboratory Tests	These samples will be analyzed at a central laboratory; hour-to-hour medical decisions will be based on sampling for laboratory testing done outside the protocol as part of normal standard of care. GFR will be calculated by the local laboratory.	<b>For adults and children <math>\geq 30</math> kg, these samples will be analyzed at a central laboratory; hour-to-hour medical decisions will be based on sampling for laboratory testing done outside the protocol as part of normal standard of care. GFR will be calculated by the central laboratory. For children under 30 kg, results of local laboratory testing undertaken at the protocolled timepoints may be sent to the central laboratory for inclusion in the central study</b>	<i>Clarified that central laboratory will calculate the GFR for subjects 30 kg or larger, and that all subjects under 30 kg will have local laboratory results sent to the central laboratory for entry in the laboratory database in order to reduce the</i>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
			<b>laboratory database; this obviates the need for additional blood sampling for central laboratory testing.</b>	<i>overall volume of blood collected for subjects under 30 kg</i>
11.2.2.1. Hematology and Serum Chemistry	11.2.2.1. Hematology and Serum Chemistry	Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose.	Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose. <b>In addition triglycerides will be measured in serum chemistry samples (to aid assessment of lipemia in pharmacokinetic samples).</b>	<i>Addition of Triglycerides to Serum Chemistry panel to assist with PK sample analysis</i>
11.2.4. Weight and Height	11.2.4. Weight and Height	Weight and height will be measured at Visit 1 and weight will also be measured once during each 24 hour period of the first infusion of study drug, and of the second infusion of SAGE-547	Weight and height will be measured at Visit 1 and weight will also be measured once during each 24 hour period of the first infusion of study drug, and of the second infusion of SAGE-547 should the subject	<i>Clarification on process for obtaining daily weight for dosing.</i>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
		should the subject qualify for the second infusion of SAGE-547. These daily weights will be used to modify the dose of SAGE-547 if required.	qualify for the second infusion of SAGE-547. These daily weights will be used to modify the dose of SAGE-547 if required. <b>If it is not possible to weigh the subject daily, an actual weight must be obtained prior to starting the blinded study drug, and that weight used to calculate the dose of study drug to be administered. If this is not possible, permission from the Monitor must be obtained to use another method to obtain the subject's weight (such as information from the LAR or estimating using an established local protocol).</b>	
11.2.8.1. Pharmacokinetic Data	11.2.8.1. Pharmacokinetic Data	Formal plasma <b>and urine</b> analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS))	Formal plasma analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS))	<i>Deletion of urine PK analysis; inadvertent carry-over from Protocol ver. 1 to Protocol Amendment 1</i>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
11.2.8.1. Pharmacokinetic Data	11.2.8.1. Pharmacokinetic Data	Each blood sample will be 3 ml in volume for adults and children weighing 30 kg or more, and 2 ml in volume for children weighing less than 30 kg. Separate aliquots will be obtained from each sample to service the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum blood draw for PK analysis for a subject having two infusions of study drug will be 99 ml (66 ml for children weighing less than 30 kg).	Each blood sample will be 3 ml in volume for adults and children weighing 30 kg or more, and <b>1</b> ml in volume for children weighing less than 30 kg. Separate aliquots will be obtained from each sample to service the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum blood draw for PK analysis for a subject having two infusions of study drug will be 99 ml ( <b>33</b> ml for children weighing less than 30 kg).	<i>PK blood draw volume reduced from 2 mL to 1 mL per timepoint, and from 66 mL to 33 mL for subjects under 30 kg.</i>
11.2.8.1. Pharmacokinetic Data	11.2.8.1. Pharmacokinetic Data	<u>Other Analysis</u> If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations.	<u>Other Analysis</u> If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations. <b>The minimum volume of cerebrospinal fluid for</b>	<i>Specification of the minimum volume of cerebrospinal fluid.</i>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
			<b>analysis is 100 microlitres.</b>	
12.3.1. Visit 3/3R	12.3.1. Visit 3/3R	<ul style="list-style-type: none"> <li>• Completion of the FOUR Score</li> <li>– +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the end of the QW)</li> </ul>	<ul style="list-style-type: none"> <li>• Completion of the FOUR Score</li> <li>– +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the end of the <b>24 hour observation period following the QW</b>)</li> </ul>	<i>Clarification on FOUR Score assessment timeframe for Qualifying Wean Successes (QWS)</i>
12.5.2. Visit 10/10R	12.5.2. Visit 10/10R	<ul style="list-style-type: none"> <li>• At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine retreatment with higher dose of study drug. All patients for retreatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.</li> </ul>	<ul style="list-style-type: none"> <li>• At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine <b>eligibility for</b> retreatment with <b>the</b> higher dose of study drug. <b>This determination may occur at any point during Visit 10: the retreatment infusion must begin within the Visit 10 window.</b> All patients for retreatment must have an eligibility form agreed and signed by the medical</li> </ul>	<i>Clarification on Visit 10 retreatment eligibility and retreatment infusion window.</i>

<b>Section number and title in Protocol Amendment 1 (27 MAY 15)</b>	<b>Section number and title in Amendment 2 (17 NOV 15)</b>	<b>Original text:</b>	<b>Changed to:</b>	<b>Rationale</b>
			monitor before the open-label infusion begins.	



**Summary of Changes**  
**Protocol-547-SSE-301 (Adults Only)**  
**Dated 17 NOV 2015**

The following changes were made to the attached protocol in this amendment. Minor typographical/editorial errors throughout the document were also corrected.

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
2. Study Synopsis/Study Sites	2. Study Synopsis/Study Sites	Up to 150 sites in the USA, Europe, and Canada.	Up to <b>180</b> sites in the USA, Europe, and Canada.  <i>Change also featured on pages 5 &amp; 43</i>	<i>Oversight in Amendment 1, addition of EU sites to yield 180 total sites</i>
2. Study Synopsis/Study Design	2. Study Synopsis/Study Design	Subjects will be aged two years or more, in SRSE	Subjects will be aged <b>18</b> years or more, in SRSE  <i>Changes also featured on pages 9 and 42</i>	<i>Amended to remove pediatric patients and only enroll adult population</i>
2. Study Synopsis/Study Design	2. Study Synopsis/Study Design	Burst suppression must be maintained for the first 12 hours of the infusion of study drug.	Burst suppression must be maintained for the first 12 hours of the infusion of <b>blinded</b> study drug.  <i>Change also featured on pages 5-6, &amp; 38-39</i>	<i>Clarification on mandatory burst suppression time frame during blinded infusion treatment phase only</i>
2. Study Synopsis/Study Design	2. Study Synopsis/Study Design	The randomization will be stratified by concomitant pentobarbital use (yes or no) and	The randomization will be stratified by concomitant pentobarbital/ <b>thiopental</b> use (yes or	<i>Thiopental added as accepted Third Line Agent</i>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
		number of previous third-line agent wean attempts prior to randomization (one vs two or more).	no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).  <i>References to concomitant thiopental use also featured on pages 6, 11, 39-40, 41, 70, &amp; 72</i>	<i>barbiturate comparable to Pentobarbital. Randomization will be stratified by concomitant barbiturate use (pentobarbital and thiopental), along with prior third-line agent wean attempts.</i>
2. Study Synopsis/Study Objectives	2. Study Synopsis/Study Objectives	To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult and pediatric subjects with SRSE	To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in <b>adult and pediatric</b> subjects with SRSE  <i>Change also featured on page 35</i>	<i>Amended to remove pediatric patients and only enroll adult population</i>
2. Study Synopsis/Study Objectives	2. Study Synopsis/Study Objectives	To evaluate the Modified Rankin Score (mRS) (age $\geq 17$ years)	To evaluate the Modified Rankin Score (mRS) ( <del>age <math>\geq 17</math> years</del> )  <i>Changes also featured on pages 9, 37, 38, and 61</i>	<i>Removed redundant text; mRS evaluated in all subjects given inclusion of adults only</i>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
2. Study Synopsis/Exclusion Criteria	2. Study Synopsis/Exclusion Criteria	4. Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing underlying neurological disorder	<del>4. Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing underlying neurological disorder</del>  Change also featured on page 42	<i>Exclusion deleted; not relevant given removal of pediatric patients</i>
Table 2: Schedule of Assessments: Two Infusions of Study Drug (one blinded, one open-label)	Table 2: Schedule of Assessments: Two Infusions of Study Drug (one blinded, one open-label)	NA	Additional assessment added to Visit 9R (145h-168h):  <b>TW Success and Physiologic Brain Activity</b>	<i>Previous omission, corrected for consistency with Sec. 12.5.1 Visit 9/9R</i>
Figure 1: Study Design	Figure 1: Study Design	Visit 2 ( $\leq 30$ h before V3)	Visit 2 ( $\leq 54$ h before V3)	<i>Previous omission, corrected for consistency with Tables 1 – 3 and Sec. 12.2</i>
Figure 2: Details of Treatment Administration and Follow-up	Figure 2: Details of Treatment Administration and Follow-up	Screening Period / V1-2/ -36h	Screening Period / V1-2/ -84h	<i>Previous omission, corrected for consistency with Tables 1 – 3, Figure 1, and Sec. 12.1 &amp; 12.2</i>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
11.1.1.1 Weaning	11.1.1.1 Weaning	<ul style="list-style-type: none"> <li>• Pentobarbital: 1 mg/kg/hour</li> <li>• Midazolam: 0.1 mg/kg/hour</li> <li>• Propofol: 3 mg/kg/hour</li> <li>• Ketamine 1.2 mg/kg/hour</li> </ul>	<ul style="list-style-type: none"> <li>• Pentobarbital: 1 mg/kg/hour</li> <li>• <b>Thiopental: 3 mg/kg/hour</b></li> <li>• Midazolam: 0.1 mg/kg/hour</li> <li>• Propofol: 3 mg/kg/hour</li> <li>• Ketamine 1.2 mg/kg/hour</li> </ul>	<i>Thiopental added as accepted Third Line Agent</i>
11.1.1.1 Weaning	11.1.1.1 Weaning	The Clinical Standardization Team will be able to review EEGs in real time related to key study timepoints (qualifying wean, terminal wean, and the period after the end of the blinded study drug infusion) in order to provide advice about compliance with the Clinical Standardization Guidelines.	The Clinical Standardization Team will be able to <b>discuss EEGs related to key study</b> timepoints (qualifying wean, terminal wean, and the period after the end of the blinded study drug infusion <b>if the terminal wean was successful</b> ) <b>in a timely manner</b> in order to provide advice about compliance with the Clinical Standardization Guidelines.	<i>Clarification on the CST communication process and CST expectations on advising sites on the CSGs</i>
11.1.1.2 EEG	11.1.1.2 EEG	<ul style="list-style-type: none"> <li>• A six-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the</li> </ul>	<ul style="list-style-type: none"> <li>• A <b>24-hour</b> duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that</li> </ul>	<i>Extended the Consent EEG to capture as much of the burst suppression period prior to the Qualifying</i>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
		<p>study for that patient; patterns would be seizure activity for the first path to eligibility, burst suppression for the second path to eligibility, and a variable pattern for the third path to eligibility.</p> <ul style="list-style-type: none"> <li>• EEG will be performed to cover the qualifying wean (QWEEG). EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for the one hour after the end of the QW. The duration of the QWEEG will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s) or the decision to re-institute a third-line agent(s) at doses intended to induce burst suppression.</li> </ul>	<p>patient; patterns would be seizure activity for the first path to eligibility, burst suppression for the second path to eligibility, and a variable pattern for the third path to eligibility. <b>This EEG will capture as much as possible of the burst suppression pattern that precedes the QW.</b></p> <ul style="list-style-type: none"> <li>• EEG will be performed to cover the qualifying wean (QWEEG). EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for <b>up to 24 hours</b> after the end of the QW. The duration of the QWEEG will be up to <b>48.5</b> hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s), the decision to re-institute a third-</li> </ul>	<p><i>Wean as possible.</i></p> <p><i>Extended the QWEEG to match QW Guidance in Sec. 11.1.1.1 for Investigators to allow 24 hours to lapse after the end of QW before declaring QW success.</i></p> <p><i>Extended the BIEEG to capture the burst suppression period during the initial 12 hours of the blinded infusion.</i></p>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
		<ul style="list-style-type: none"> <li>• EEG will be performed from three hours prior to the start of the blinded infusion to five hours after the start of the blinded infusion. This will be called the BIEEG. The intent of this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG.</li> </ul>	<p>line agent(s) at doses intended to induce burst suppression, <b>and the decision that the QW is a success.</b></p> <ul style="list-style-type: none"> <li>• EEG will be performed from three hours prior to the start of the blinded infusion to <b>12</b> hours after the start of the blinded infusion. This will be called the BIEEG. The intent of this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG <b>and to assess the depth of burst suppression in the first 12 hours of blinded study drug infusion.</b></li> </ul>	
11.1.1.2 EEG	11.1.1.2 EEG	<ul style="list-style-type: none"> <li>• For the QWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the</li> </ul>	<ul style="list-style-type: none"> <li>• For the QWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the</li> </ul>	<i>Clarification on Investigator assessment of the Qualifying Wean and the duration of the QWEEG.</i>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
		subject was a failure on the qualifying wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the qualifying wean)	subject was a failure <b>or success</b> on the qualifying wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the qualifying wean <b>constitutes a failure</b> ); <b>the QWEEG will extend to cover the 24 hours after the end of third line agents in order to confirm that the QW was a success.</b>	
11.1.1.2 EEG	11.1.1.2 EEG	A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period (average EEG power at the end of Visit 9 of more than two	A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm <b>the depth of burst suppression prior to the QW and during the first 12 hours of the blinded study drug infusion, the</b> PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain	<i>Added the Consent EEG (CEEG) and Blinded Infusion EEG (BIEEG) to the EEG records to be read centrally to capture the depth of burst suppression prior to Qualifying Wean and during</i>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
		<p>microvolts):</p> <ul style="list-style-type: none"> <li>• All subjects will have the CEEG and QWEEG collected and stored, and the QWEEG read;</li> <li>• Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;</li> <li>• Those subjects randomized who are not retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read;</li> <li>• Those subjects randomized who are retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion</li> </ul>	<p>activity at the end of the primary endpoint assessment period (average EEG power at the end of Visit 9 of more than two microvolts):</p> <ul style="list-style-type: none"> <li>• All subjects will have the CEEG and QWEEG collected and stored, and the <b>CEEG and</b> QWEEG read;</li> <li>• Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;</li> <li>• Those subjects randomized who are not retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the <b>BIEEG, QWEEG, TWEEG, and PAEEG</b> related to the blinded study drug infusion read;</li> <li>• Those subjects randomized who are retreated will have the</li> </ul>	<p><i>the first 12 hours of the blinded infusion.</i></p>



Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
		and the TWEEG, TAEED, and PAEEG related to the open-label study drug infusion collected and stored, and the QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read.	BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion and the TWEEG, TAEED, and PAEEG related to the open-label study drug infusion collected and stored, and the <b>BIEEG</b> , QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read.	
11.2.2.1. Hematology and Serum Chemistry	11.2.2.1. Hematology and Serum Chemistry	Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose.	Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose. <b>In addition triglycerides will be measured in serum chemistry samples (to aid assessment of lipemia in pharmacokinetic samples).</b>	<i>Addition of Triglycerides to Serum Chemistry panel to assist with PK sample analysis</i>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
11.2.2.2. Pregnancy Test	11.2.2.2. Pregnancy Test	“child-bearing potential” is taken to mean any female aged 10 years to 55 years	<p>“child-bearing potential” is taken to mean any female aged <b>18</b> years to 55 years</p> <p><i>Change also featured on page 61</i></p>	<i>Amended since no inclusion of subjects less than 18 years</i>
11.2.4. Weight and Height	11.2.4. Weight and Height	Weight and height will be measured at Visit 1 and weight will also be measured once during each 24 hour period of the first infusion of study drug, and of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547. These daily weights will be used to modify the dose of SAGE-547 if required.	Weight and height will be measured at Visit 1 and weight will also be measured once during each 24 hour period of the first infusion of study drug, and of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547. These daily weights will be used to modify the dose of SAGE-547 if required. <b>If it is not possible to weigh the subject daily, an actual weight must be obtained prior to starting the blinded study drug, and that weight used to calculate the dose of study drug to be administered. If this is not possible, permission from the Monitor must be</b>	<i>Clarification on process for obtaining daily weight for dosing.</i>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
			<b>obtained to use another method to obtain the subject's weight (such as information from the LAR or estimating using an established local protocol).</b>	
11.2.8.1. Pharmacokinetic Data	11.2.8.1. Pharmacokinetic Data	Formal plasma <b>and urine</b> analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS))	Formal plasma analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS))	<i>Deletion of urine PK analysis; inadvertent carry-over from Protocol ver. 1 to Protocol Amendment 1</i>
11.2.8.1. Pharmacokinetic Data	11.2.8.1. Pharmacokinetic Data	Each blood sample will be 3 ml in volume for adults and children weighing 30 kg or more, and 2 ml in volume for children weighing less than 30 kg. Separate aliquots will be obtained from each sample to service the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum blood draw for PK analysis for a subject having two infusions of	Each blood sample will be 3 ml in volume for adults and children weighing 30 kg or more, and 1 ml in volume for children weighing less than 30 kg. Separate aliquots will be obtained from each sample to service the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum blood draw for PK analysis for a subject having two infusions of study drug will be	<i>PK blood draw volume reduced from 2 mL to 1 mL per timepoint, and from 66 mL to 33 mL for subjects under 30 kg.</i>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
		study drug will be 99 ml (66 ml for children weighing less than 30 kg).	99 ml ( <b>33</b> ml for children weighing less than 30 kg).	
11.2.8.1. Pharmacokinetic Data	11.2.8.1. Pharmacokinetic Data	<p><u>Other Analysis</u></p> <p>If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations.</p>	<p><u>Other Analysis</u></p> <p>If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations. <b>The minimum volume of cerebrospinal fluid for analysis is 100 microlitres.</b></p>	<i>Specification of the minimum volume of cerebrospinal fluid.</i>
12.3.1. Visit 3/3R	12.3.1. Visit 3/3R	<ul style="list-style-type: none"> <li>• Completion of the FOUR Score</li> <li>– +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the end of the QW)</li> </ul>	<ul style="list-style-type: none"> <li>• Completion of the FOUR Score <ul style="list-style-type: none"> <li>– +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the end of the <b>24 hour observation period following the QW</b>)</li> </ul> </li> </ul>	<i>Clarification on FOUR Score assessment timeframe for Qualifying Wean Successes (QWS)</i>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
12.5.2. Visit 10/10R	12.5.2. Visit 10/10R	<ul style="list-style-type: none"> <li>At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine retreatment with higher dose of study drug. All patients for retreatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.</li> </ul>	<ul style="list-style-type: none"> <li>At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine <b>eligibility for</b> retreatment with <b>the</b> higher dose of study drug. <b>This determination may occur at any point during Visit 10: the retreatment infusion must begin within the Visit 10 window.</b> All patients for retreatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.</li> </ul>	<i>Clarification on Visit 10 retreatment eligibility and retreatment infusion window.</i>

**Summary of Changes****Protocol-547-SSE-301 (Adults Only, Sweden)****Dated 07 DEC 2015**

The following changes were made to the attached protocol in this amendment. Minor typographical/editorial errors throughout the document were also corrected.

<b>Section number and title in Protocol Amendment 1 (27 MAY 15)</b>	<b>Section number and title in Amendment 2 (17 NOV 15)</b>	<b>Original text:</b>	<b>Changed to:</b>	<b>Rationale</b>
2. Study Synopsis/Study Sites	2. Study Synopsis/Study Sites	Up to 150 sites in the USA, Europe, and Canada.	Up to <b>180</b> sites in the USA, Europe, and Canada.  <i>Change also featured on pages 5 &amp; 43</i>	<i>Oversight in Amendment 1, addition of EU sites to yield 180 total sites</i>
2. Study Synopsis/Study Design	2. Study Synopsis/Study Design	Subjects will be aged two years or more, in SRSE	Subjects will be aged <b>18</b> years or more, in SRSE  <i>Changes also featured on pages 9 and 42</i>	<i>Amended to remove pediatric patients and only enroll adult population</i>
2. Study Synopsis/Study Design	2. Study Synopsis/Study Design	consent will be obtained from their legally authorized representative (LAR)	consent will be obtained from their legally authorized representative (LAR) <b>already appointed by the Court for their well-being, and closest relatives</b>  <i>Changes also featured on pages 6, 35, 38, 39, 57, and 59</i>	<i>Added to meet legal requirements of Swedish Medicinal Products Act</i>
2. Study Synopsis/Study	2. Study Synopsis/Study	Burst suppression must be maintained for the first 12 hours	Burst suppression must be maintained for the first 12 hours of	<i>Clarification on mandatory burst</i>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
Design	Design	of the infusion of study drug.	the infusion of <b>blinded</b> study drug.  <i>Change also featured on pages 5-6, &amp; 38-39</i>	<i>suppression time frame during blinded infusion treatment phase only</i>
2. Study Synopsis/Study Design	2. Study Synopsis/Study Design	The randomization will be stratified by concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).	The randomization will be stratified by concomitant pentobarbital/ <b>thiopental</b> use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).  <i>References to concomitant thiopental use also featured on pages 6, 11, 39-40, 41, 70, &amp; 72</i>	<i>Thiopental added as accepted Third Line Agent barbiturate comparable to Pentobarbital. Randomization will be stratified by concomitant barbiturate use (pentobarbital and thiopental), along with prior third-line agent wean attempts.</i>
2. Study Synopsis/Study Objectives	2. Study Synopsis/Study Objectives	To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult and pediatric subjects with	To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in <b>adult and pediatric</b> subjects with SRSE	<i>Amended to remove pediatric patients and only enroll adult population</i>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
		SRSE	<i>Change also featured on page 35</i>	
2. Study Synopsis/Study Objectives	2. Study Synopsis/Study Objectives	To evaluate the Modified Rankin Score (mRS) (age $\geq 17$ years)	To evaluate the Modified Rankin Score (mRS) ( <del>age <math>\geq 17</math> years</del> )  <i>Changes also featured on pages 9, 37, 38, and 61</i>	<i>Removed redundant text; mRS evaluated in all subjects given inclusion of adults only</i>
2. Study Synopsis/Exclusion Criteria	2. Study Synopsis/Exclusion Criteria	4. Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing underlying neurological disorder	<del>4. Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing underlying neurological disorder</del>  <i>Change also featured on page 42</i>	<i>Exclusion deleted; not relevant given removal of pediatric patients</i>
2. Study Synopsis/Exclusion Criteria	2. Study Synopsis/Exclusion Criteria	c. fulminant hepatic failure	<b>c. severe hepatic impairment</b>  <i>Change also featured on page 42</i>	<i>In response to Swedish Medical Products Agency comments</i>
Table 2: Schedule of Assessments: Two Infusions of Study Drug (one blinded, one open-label)	Table 2: Schedule of Assessments: Two Infusions of Study Drug (one blinded, one open-label)	NA	Additional assessment added to Visit 9R (145h-168h):  <b>TW Success and Physiologic Brain Activity</b>	<i>Previous omission, corrected for consistency with Sec. 12.5.1 Visit 9/9R</i>
4, Ethics/Subject Information and	4, Ethics/Subject Information and	Subjects prospectively enrolled in this study will be unable to give	Subjects prospectively enrolled in this study will be unable to give	<i>Added to meet legal</i>



Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
Informed Consent	Informed Consent	consent. Therefore, consent will be given by proxy by a legally authorized representative (LAR).	consent. Therefore, consent will be given by proxy by a legally authorized representative (LAR) <b>already appointed by the Court for their well-being, and closest relatives. According to Swedish Medicinal Products Act (Läkemedelslagen 1992:859), consent will be obtained by both the LAR and the closest relatives of the patients. Only patients with a previously appointed LAR by the Court will be included in the study, providing also the closest relatives consent to the study.</b>	<i>requirements of Swedish Medicinal Products Act</i>
Figure 1: Study Design	Figure 1: Study Design	Visit 2 ( $\leq 30$ h before V3)	Visit 2 ( $\leq 54$ h before V3)	<i>Previous omission, corrected for consistency with Tables 1 – 3 and Sec. 12.2</i>
Figure 2: Details of Treatment Administration and Follow-up	Figure 2: Details of Treatment Administration and Follow-up	Screening Period / V1-2/ -36h	Screening Period / V1-2/ -84h	<i>Previous omission, corrected for consistency with Tables 1 – 3, Figure 1, and</i>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
				<i>Sec. 12.1 &amp; 12.2</i>
10.5 Concomitant Medications, Procedures and Treatments	10.5 Concomitant Medications, Procedures and Treatments	SAGE-547 has demonstrated inhibitory effects on cytochrome P450 isoenzyme 2C9 (CYP2C9). Therefore, AEDs such as phenytoin and phenobarbital that are primarily metabolized by CYP2C9 should be closely monitored during SAGE-547 administration to ensure target exposures are maintained	SAGE-547 has demonstrated inhibitory effects on cytochrome P450 isoenzyme 2C9 (CYP2C9). Therefore, AEDs such as phenytoin and phenobarbital that are primarily metabolized by CYP2C9 should be closely monitored during SAGE-547 administration to ensure target exposures are maintained. <b>A list of drugs which are inhibitors/inducers of CYP2C9 (as well as CYP2C8, CYP2C19, CYP3A4, UGT2B7, and UGT2B17) is provided in Appendix 7. In the absence of formal drug-drug interaction studies of SAGE-547, Investigators should ensure that co-administration is performed with caution.</b>  <i>Changes also feature addition of Appendix 7</i>	<i>In response to Swedish Medical Products Agency comments</i>
11.1.1.1 Weaning	11.1.1.1 Weaning	<ul style="list-style-type: none"> <li>Pentobarbital: 1 mg/kg/hour</li> </ul>	<ul style="list-style-type: none"> <li>Pentobarbital: 1 mg/kg/hour</li> </ul>	<i>Thiopental added as accepted Third</i>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
		<ul style="list-style-type: none"> <li>• Midazolam: 0.1 mg/kg/hour</li> <li>• Propofol: 3 mg/kg/hour</li> <li>• Ketamine 1.2 mg/kg/hour</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Thiopental: 3 mg/kg/hour</b></li> <li>• Midazolam: 0.1 mg/kg/hour</li> <li>• Propofol: 3 mg/kg/hour</li> <li>• Ketamine 1.2 mg/kg/hour</li> </ul>	<i>Line Agent</i>
11.1.1.1 Weaning	11.1.1.1 Weaning	The Clinical Standardization Team will be able to review EEGs in real time related to key study timepoints (qualifying wean, terminal wean, and the period after the end of the blinded study drug infusion) in order to provide advice about compliance with the Clinical Standardization Guidelines.	The Clinical Standardization Team will be able to <b>discuss EEGs related to key study</b> timepoints (qualifying wean, terminal wean, and the period after the end of the blinded study drug infusion <b>if the terminal wean was successful</b> ) in <b>a timely manner</b> in order to provide advice about compliance with the Clinical Standardization Guidelines.	<i>Clarification on the CST communication process and CST expectations on advising sites on the CSGs</i>
11.1.1.2 EEG	11.1.1.2 EEG	<ul style="list-style-type: none"> <li>• A six-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for</li> </ul>	<ul style="list-style-type: none"> <li>• A <b>24-hour</b> duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path</li> </ul>	<i>Extended the Consent EEG to capture as much of the burst suppression period prior to the <u>Qualifying Wean</u> as possible.</i>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
		<p>the first path to eligibility, burst suppression for the second path to eligibility, and a variable pattern for the third path to eligibility.</p> <ul style="list-style-type: none"> <li>• EEG will be performed to cover the qualifying wean (QWEEG). EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for the one hour after the end of the QW. The duration of the QWEEG will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s) or the decision to re-institute a third-line agent(s) at doses intended to induce burst suppression.</li> <li>• EEG will be performed from three hours prior to the start</li> </ul>	<p>to eligibility, burst suppression for the second path to eligibility, and a variable pattern for the third path to eligibility. <b>This EEG will capture as much as possible of the burst suppression pattern that precedes the QW.</b></p> <ul style="list-style-type: none"> <li>• EEG will be performed to cover the qualifying wean (QWEEG). EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for <b>up to 24 hours</b> after the end of the QW. The duration of the QWEEG will be up to <b>48.5</b> hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s), the decision to re-institute a third-line agent(s) at doses intended to induce burst suppression,</li> </ul>	<p><i>Extended the QWEEG to match QW Guidance in Sec. 11.1.1.1 for Investigators to allow 24 hours to lapse after the end of QW before declaring QW success.</i></p> <p><i>Extended the BIEEG to capture the burst suppression period during the initial 12 hours of the blinded infusion.</i></p>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
		of the blinded infusion to five hours after the start of the blinded infusion. This will be called the BIEEG. The intent of this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG.	<p><b>and the decision that the QW is a success.</b></p> <ul style="list-style-type: none"> <li>EEG will be performed from three hours prior to the start of the blinded infusion to <b>12</b> hours after the start of the blinded infusion. This will be called the BIEEG. The intent of this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG <b>and to assess the depth of burst suppression in the first 12 hours of blinded study drug infusion.</b></li> </ul>	
11.1.1.2 EEG	11.1.1.2 EEG	<ul style="list-style-type: none"> <li>For the QWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure on the qualifying wean (inability to</li> </ul>	<ul style="list-style-type: none"> <li>For the QWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure <b>or success</b> on the qualifying wean</li> </ul>	<i>Clarification on Investigator assessment of the Qualifying Wean and the duration of the QWEEG.</i>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
		wean off the third-line agent or the third-line agent reinstituted for burst suppression during the qualifying wean)	(inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the qualifying wean <b>constitutes a failure</b> ); the QWEEG will extend to cover the 24 hours after the end of third line agents in order to confirm that the QW was a success.	
11.1.1.2 EEG	11.1.1.2 EEG	<p>A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period (average EEG power at the end of Visit 9 of more than two microvolts):</p> <ul style="list-style-type: none"> <li>All subjects will have the</li> </ul>	<p>A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm <b>the depth of burst suppression prior to the QW and during the first 12 hours of the blinded study drug infusion, the</b> PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period</p>	<p><i>Added the Consent EEG (CEEG) and Blinded Infusion EEG (BIEEG) to the EEG records to be read centrally to capture the depth of burst suppression prior to Qualifying Wean and during the first 12 hours of the blinded</i></p>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
		<p>CEEG and QWEEG collected and stored, and the QWEEG read;</p> <ul style="list-style-type: none"> <li>Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;</li> <li>Those subjects randomized who are not retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read;</li> <li>Those subjects randomized who are retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion and the TWEEG, TAEED, and PAEEG related to the open-label study drug infusion</li> </ul>	<p>(average EEG power at the end of Visit 9 of more than two microvolts):</p> <ul style="list-style-type: none"> <li>All subjects will have the CEEG and QWEEG collected and stored, and the <b>CEEG and</b> QWEEG read;</li> <li>Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;</li> <li>Those subjects randomized who are not retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the <b>BIEEG</b>, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read;</li> <li>Those subjects randomized who are retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded</li> </ul>	<i>infusion.</i>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
		collected and stored, and the QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read.	study drug infusion and the TWEEG, TAEFG, and PAEEG related to the open-label study drug infusion collected and stored, and the <b>BIEEG</b> , QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read.	
11.2.2.1. Hematology and Serum Chemistry	11.2.2.1. Hematology and Serum Chemistry	Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose.	Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose. <b>In addition triglycerides will be measured in serum chemistry samples (to aid assessment of lipemia in pharmacokinetic samples).</b>	<i>Addition of Triglycerides to Serum Chemistry panel to assist with PK sample analysis</i>
11.2.2.2. Pregnancy Test	11.2.2.2. Pregnancy Test	“child-bearing potential” is taken to mean any female aged 10 years	“child-bearing potential” is taken to mean any female aged <b>18</b> years to	<i>Amended since no inclusion of</i>



Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
		to 55 years	55 years  <i>Change also featured on page 61</i>	<i>subjects less than 18 years</i>
11.2.4. Weight and Height	11.2.4. Weight and Height	Weight and height will be measured at Visit 1 and weight will also be measured once during each 24 hour period of the first infusion of study drug, and of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547. These daily weights will be used to modify the dose of SAGE-547 if required.	Weight and height will be measured at Visit 1 and weight will also be measured once during each 24 hour period of the first infusion of study drug, and of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547. These daily weights will be used to modify the dose of SAGE-547 if required. <b>If it is not possible to weigh the subject daily, an actual weight must be obtained prior to starting the blinded study drug, and that weight used to calculate the dose of study drug to be administered. If this is not possible, permission from the Monitor must be obtained to use another method to obtain the subject's weight</b>	<i>Clarification on process for obtaining daily weight for dosing.</i>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
			(such as information from the LAR or estimating using an established local protocol).	
11.2.8.1. Pharmacokinetic Data	11.2.8.1. Pharmacokinetic Data	Formal plasma <b>and urine</b> analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS))	Formal plasma analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS))	<i>Deletion of urine PK analysis; inadvertent carry-over from Protocol ver. 1 to Protocol Amendment 1</i>
11.2.8.1. Pharmacokinetic Data	11.2.8.1. Pharmacokinetic Data	Each blood sample will be 3 ml in volume for adults and children weighing 30 kg or more, and 2 ml in volume for children weighing less than 30 kg. Separate aliquots will be obtained from each sample to service the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum blood draw for PK analysis for a subject having two infusions of study drug will be 99 ml (66 ml for children weighing less than 30	Each blood sample will be 3 ml in volume for <b>subjects</b> weighing 30 kg or more, and <b>1</b> ml in volume for <b>subjects</b> weighing less than 30 kg. Separate aliquots will be obtained from each sample to service the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum blood draw for PK analysis for a subject having two infusions of study drug will be 99 ml ( <b>33</b> ml for <b>subjects</b> weighing less than 30 kg).	<i>PK blood draw volume reduced from 2 mL to 1 mL per timepoint, and from 66 mL to 33 mL for subjects under 30 kg.</i>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
		kg).		
11.2.8.1. Pharmacokinetic Data	11.2.8.1. Pharmacokinetic Data	<u>Other Analysis</u> If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations.	<u>Other Analysis</u> If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations. <b>The minimum volume of cerebrospinal fluid for analysis is 100 microlitres.</b>	<i>Specification of the minimum volume of cerebrospinal fluid.</i>
12.3.1. Visit 3/3R	12.3.1. Visit 3/3R	<ul style="list-style-type: none"> <li>Completion of the FOUR Score</li> <li>– +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the end of the QW)</li> </ul>	<ul style="list-style-type: none"> <li>Completion of the FOUR Score               <ul style="list-style-type: none"> <li>– +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the end of the <b>24 hour observation period following the QW</b>)</li> </ul> </li> </ul>	<i>Clarification on FOUR Score assessment timeframe for Qualifying Wean Successes (QWS)</i>
12.5.2. Visit 10/10R	12.5.2. Visit 10/10R	<ul style="list-style-type: none"> <li>At Visit 10 only (not Visit</li> </ul>	<ul style="list-style-type: none"> <li>At Visit 10 only (not Visit</li> </ul>	<i>Clarification on</i>

Section number and title in Protocol Amendment 1 (27 MAY 15)	Section number and title in Amendment 2 (17 NOV 15)	Original text:	Changed to:	Rationale
		10R), if subject failed the terminal wean, determine retreatment with higher dose of study drug. All patients for retreatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.	10R), if subject failed the terminal wean, determine <b>eligibility for</b> retreatment with <b>the</b> higher dose of study drug. <b>This determination may occur at any point during Visit 10: the retreatment infusion must begin within the Visit 10 window.</b> All patients for retreatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.	<i>Visit 10 retreatment eligibility and retreatment infusion window.</i>

**Summary of Changes**  
**Protocol-547-SSE-301**  
**Dated 04 Feb 2016**

The following changes were made to the attached protocol in this amendment. Minor typographical/editorial errors throughout the document were also corrected.

Section number and title in Protocol Amendment 1 (27 MAY 2015)	Section number and title in Amendment 2 (04 FEB 2016)	Original text:	Changed to:	Rationale
2. Study Synopsis/Study Sites	2. Study Synopsis/Study Sites	Up to 150 sites in the USA, Europe, and Canada.	Up to <b>180</b> sites in the USA, Europe, and Canada.  <i>Change also featured on pages 5 &amp; 43</i>	<i>Oversight in Amendment 1, addition of EU sites to yield 180 total sites</i>
2. Study Synopsis/Study Sites	2. Study Synopsis/Study Sites	Subjects will be aged two years or more, in SRSE (as defined in the Inclusion Criteria Section 8.1), and being managed in an intensive care setting.	Subjects will be aged two years or more, in SRSE (as defined in the Inclusion Criteria Section 8.1), and being managed in an intensive care setting. <b>Pediatric patients (those &lt; 14 years of age) will be managed in a pediatric intensive care setting.</b>	<i>Specifies study setting for pediatrics under 14 years of age</i>
2. Study Synopsis/Study Design	2. Study Synopsis/Study Design	Burst suppression must be maintained for the first 12 hours of the infusion of study drug.	Burst suppression must be maintained for the first 12 hours of the infusion of <b>blinded</b> study drug.  <i>Change also featured on pages 5-6, &amp; 38-39</i>	<i>Clarification on mandatory burst suppression time frame during blinded infusion treatment phase only</i>

Section number and title in Protocol Amendment 1 (27 MAY 2015)	Section number and title in Amendment 2 (04 FEB 2016)	Original text:	Changed to:	Rationale
2. Study Synopsis/Study Design	2. Study Synopsis/Study Design	The randomization will be stratified by concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).	The randomization will be stratified by concomitant pentobarbital/ <b>thiopental</b> use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).  <i>References to concomitant thiopental use also featured on pages 6, 11, 39-40, 41, 70, &amp; 72</i>	<i>Thiopental added as accepted Third Line Agent barbiturate comparable to Pentobarbital. Randomization will be stratified by concomitant barbiturate use (pentobarbital and thiopental), along with prior third-line agent wean attempts.</i>
Table 2: Schedule of Assessments: Two Infusions of Study Drug (one blinded, one open-label)	Table 2: Schedule of Assessments: Two Infusions of Study Drug (one blinded, one open-label)	NA	Additional assessment added to Visit 9R (145h-168h):  <b>TW Success and Physiologic Brain Activity</b>	<i>Previous omission, corrected for consistency with Sec. 12.5.1 Visit 9/9R</i>
7.1 Overview of Study Design	7.1 Overview of Study Design	This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in	This is a randomized, double-blind, placebo-controlled trial, designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion to subjects in SRSE. <b>Pediatric</b>	<i>Specifies study setting for pediatrics under 14 years of age</i>

Section number and title in Protocol Amendment 1 (27 MAY 2015)	Section number and title in Amendment 2 (04 FEB 2016)	Original text:	Changed to:	Rationale
		SRSE.	<b>patients (those &lt; 14 years of age) will be managed in a pediatric intensive care setting.</b>	
Figure 1: Study Design	Figure 1: Study Design	Visit 2 ( $\leq$ 30 h before V3)	Visit 2 ( $\leq$ <b>54</b> h before V3)	<i>Previous omission, corrected for consistency with Tables 1 – 3 and Sec. 12.2</i>
Figure 2: Details of Treatment Administration and Follow-up	Figure 2: Details of Treatment Administration and Follow-up	Screening Period / V1-2/ -36h	Screening Period / V1-2/ <b>-84h</b>	<i>Previous omission, corrected for consistency with Tables 1 – 3, Figure 1, and Sec. 12.1 &amp; 12.2</i>
11.1.1.1 Weaning	11.1.1.1 Weaning	<ul style="list-style-type: none"> <li>• Pentobarbital: 1 mg/kg/hour</li> <li>• Midazolam: 0.1 mg/kg/hour</li> <li>• Propofol: 3 mg/kg/hour</li> <li>• Ketamine 1.2 mg/kg/hour</li> </ul>	<ul style="list-style-type: none"> <li>• Pentobarbital: 1 mg/kg/hour</li> <li>• <b>Thiopental: 3 mg/kg/hour</b></li> <li>• Midazolam: 0.1 mg/kg/hour</li> <li>• Propofol: 3 mg/kg/hour</li> <li>• Ketamine 1.2 mg/kg/hour</li> </ul>	<i>Thiopental added as accepted Third Line Agent</i>
11.1.1.1 Weaning	11.1.1.1 Weaning	The Clinical Standardization Team will be able to review EEGs	The Clinical Standardization Team will be able to <b>discuss EEGs</b>	<i>Clarification on the CST</i>

Section number and title in Protocol Amendment 1 (27 MAY 2015)	Section number and title in Amendment 2 (04 FEB 2016)	Original text:	Changed to:	Rationale
		in real time related to key study timepoints (qualifying wean, terminal wean, and the period after the end of the blinded study drug infusion) in order to provide advice about compliance with the Clinical Standardization Guidelines.	<b>related to key study</b> timepoints (qualifying wean, terminal wean, and the period after the end of the blinded study drug infusion <b>if the terminal wean was successful</b> ) <b>in a timely manner</b> in order to provide advice about compliance with the Clinical Standardization Guidelines.	<i>communication process and CST expectations on advising sites on the CSGs</i>
11.1.1.2 EEG	11.1.1.2 EEG	<ul style="list-style-type: none"> <li>A six-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst suppression for the second path to eligibility, and a variable pattern for the third path to eligibility.</li> <li>EEG will be performed to cover the qualifying wean (QWEEG). EEG will start 30</li> </ul>	<ul style="list-style-type: none"> <li>A <b>24-hour</b> duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst suppression for the second path to eligibility, and a variable pattern for the third path to eligibility. <b>This EEG will capture as much as possible of the burst suppression pattern that precedes the</b></li> </ul>	<p><i>Extended the Consent EEG to capture as much of the burst suppression period prior to the Qualifying Wean as possible.</i></p> <p><i>Extended the QWEEG to match QW Guidance in Sec. 11.1.1.1 for Investigators to allow 24 hours to lapse after the end of QW before declaring QW</i></p>



Section number and title in Protocol Amendment 1 (27 MAY 2015)	Section number and title in Amendment 2 (04 FEB 2016)	Original text:	Changed to:	Rationale
		<p>minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for the one hour after the end of the QW. The duration of the QWEEG will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s) or the decision to re-institute a third-line agent(s) at doses intended to induce burst suppression.</p> <ul style="list-style-type: none"> <li>• EEG will be performed from three hours prior to the start of the blinded infusion to five hours after the start of the blinded infusion. This will be called the BIEEG. The intent of this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG.</li> </ul>	<p><b>QW.</b></p> <ul style="list-style-type: none"> <li>• EEG will be performed to cover the qualifying wean (QWEEG). EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for <b>up to 24 hours</b> after the end of the QW. The duration of the QWEEG will be up to <b>48.5</b> hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s), the decision to re-institute a third-line agent(s) at doses intended to induce burst suppression, <b>and the decision that the QW is a success.</b></li> <li>• EEG will be performed from three hours prior to the start of the blinded infusion to <b>12</b> hours after the start of the blinded infusion. This will be called</li> </ul>	<p><i>success.</i></p> <p><i>Extended the BIEEG to capture the burst suppression period during the initial 12 hours of the blinded infusion.</i></p>

Section number and title in Protocol Amendment 1 (27 MAY 2015)	Section number and title in Amendment 2 (04 FEB 2016)	Original text:	Changed to:	Rationale
			the BIEEG. The intent of this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG <b>and to assess the depth of burst suppression in the first 12 hours of blinded study drug infusion.</b>	
11.1.1.2 EEG	11.1.1.2 EEG	<ul style="list-style-type: none"> <li>For the QWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure on the qualifying wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the qualifying wean)</li> </ul>	<ul style="list-style-type: none"> <li>For the QWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure <b>or success</b> on the qualifying wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the qualifying wean <b>constitutes a failure); the QWEEG will extend to cover the 24 hours after the end of third line</b></li> </ul>	<i>Clarification on Investigator assessment of the Qualifying Wean and the duration of the QWEEG.</i>

Section number and title in Protocol Amendment 1 (27 MAY 2015)	Section number and title in Amendment 2 (04 FEB 2016)	Original text:	Changed to:	Rationale
			<b>agents in order to confirm that the QW was a success.</b>	
11.1.1.2 EEG	11.1.1.2 EEG	<p>A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period (average EEG power at the end of Visit 9 of more than two microvolts):</p> <ul style="list-style-type: none"> <li>• All subjects will have the CEEG and QWEEG collected and stored, and the QWEEG read;</li> <li>• Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;</li> </ul>	<p>A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm <b>the depth of burst suppression prior to the QW and during the first 12 hours of the blinded study drug infusion, the</b> PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period (average EEG power at the end of Visit 9 of more than two microvolts):</p> <ul style="list-style-type: none"> <li>• All subjects will have the CEEG and QWEEG collected and stored, and the <b>CEEG and</b> QWEEG read;</li> </ul>	<p><i>Added the Consent EEG (CEEG) and Blinded Infusion EEG (BIEEG) to the EEG records to be read centrally to capture the depth of burst suppression prior to Qualifying Wean and during the first 12 hours of the blinded infusion.</i></p>

Section number and title in Protocol Amendment 1 (27 MAY 2015)	Section number and title in Amendment 2 (04 FEB 2016)	Original text:	Changed to:	Rationale
		<ul style="list-style-type: none"> <li>Those subjects randomized who are not retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read;</li> <li>Those subjects randomized who are retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion and the TWEEG, TAEED, and PAEEG related to the open-label study drug infusion collected and stored, and the QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read.</li> </ul>	<ul style="list-style-type: none"> <li>Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;</li> <li>Those subjects randomized who are not retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the <b>BIEEG</b>, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read;</li> <li>Those subjects randomized who are retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion and the TWEEG, TAEED, and PAEEG related to the open-label study drug infusion collected and stored, and the <b>BIEEG</b>, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read.</li> </ul>	

Section number and title in Protocol Amendment 1 (27 MAY 2015)	Section number and title in Amendment 2 (04 FEB 2016)	Original text:	Changed to:	Rationale
11.2.2 Clinical Laboratory Tests	11.2.2 Clinical Laboratory Tests	These samples will be analyzed at a central laboratory; hour-to-hour medical decisions will be based on sampling for laboratory testing done outside the protocol as part of normal standard of care. GFR will be calculated by the local laboratory.	<b>For adults and children <math>\geq 30</math> kg, these samples will be analyzed at a central laboratory; hour-to-hour medical decisions will be based on sampling for laboratory testing done outside the protocol as part of normal standard of care. GFR will be calculated by the central laboratory. For children under 30 kg, results of local laboratory testing undertaken at the protocolled timepoints may be sent to the central laboratory for inclusion in the central study laboratory database; this obviates the need for additional blood sampling for central laboratory testing.</b>	<i>Clarified that central laboratory will calculate the GFR for subjects 30 kg or larger, and that all subjects under 30 kg will have local laboratory results sent to the central laboratory for entry in the laboratory database in order to reduce the overall volume of blood collected for subjects under 30 kg</i>
11.2.2.1. Hematology and Serum Chemistry	11.2.2.1. Hematology and Serum Chemistry	Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total),	Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN),	<i>Addition of Triglycerides to Serum Chemistry panel to assist with PK sample</i>

Section number and title in Protocol Amendment 1 (27 MAY 2015)	Section number and title in Amendment 2 (04 FEB 2016)	Original text:	Changed to:	Rationale
		blood urea nitrogen (BUN), calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose.	calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose. <b>In addition triglycerides will be measured in serum chemistry samples (to aid assessment of lipemia in pharmacokinetic samples).</b>	<i>analysis</i>
11.2.4. Weight and Height	11.2.4. Weight and Height	Weight and height will be measured at Visit 1 and weight will also be measured once during each 24 hour period of the first infusion of study drug, and of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547. These daily weights will be used to modify the dose of SAGE-547 if required.	Weight and height will be measured at Visit 1 and weight will also be measured once during each 24 hour period of the first infusion of study drug, and of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547. These daily weights will be used to modify the dose of SAGE-547 if required. <b>If it is not possible to weigh the subject daily, an actual weight must be obtained prior to starting the blinded study drug, and that weight used to calculate the dose of study drug to be administered.</b>	<i>Clarification on process for obtaining daily weight for dosing.</i>

Section number and title in Protocol Amendment 1 (27 MAY 2015)	Section number and title in Amendment 2 (04 FEB 2016)	Original text:	Changed to:	Rationale
			<b>If this is not possible, permission from the Monitor must be obtained to use another method to obtain the subject's weight (such as information from the LAR or estimating using an established local protocol).</b>	
11.2.8.1. Pharmacokinetic Data	11.2.8.1. Pharmacokinetic Data	Formal plasma <b>and urine</b> analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS))	Formal plasma analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS))	<i>Deletion of urine PK analysis; inadvertent carry-over from Protocol ver. 1 to Protocol Amendment 1</i>
11.2.8.1. Pharmacokinetic Data	11.2.8.1. Pharmacokinetic Data	Each blood sample will be 3 ml in volume for adults and children weighing 30 kg or more, and 2 ml in volume for children weighing less than 30 kg. Separate aliquots will be obtained from each sample to service the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum	Each blood sample will be 3 ml in volume for adults and children weighing 30 kg or more, and <b>1</b> ml in volume for children weighing less than 30 kg. Separate aliquots will be obtained from each sample to service the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum blood draw	<i>PK blood draw volume reduced from 2 mL to 1 mL per timepoint, and from 66 mL to 33 mL for subjects under 30 kg.</i>

Section number and title in Protocol Amendment 1 (27 MAY 2015)	Section number and title in Amendment 2 (04 FEB 2016)	Original text:	Changed to:	Rationale
		blood draw for PK analysis for a subject having two infusions of study drug will be 99 ml (66 ml for children weighing less than 30 kg).	for PK analysis for a subject having two infusions of study drug will be 99 ml ( <b>33</b> ml for children weighing less than 30 kg).	
11.2.8.1. Pharmacokinetic Data	11.2.8.1. Pharmacokinetic Data	<u>Other Analysis</u> If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations.	<u>Other Analysis</u> If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations. <b>The minimum volume of cerebrospinal fluid for analysis is 100 microlitres.</b>	<i>Specification of the minimum volume of cerebrospinal fluid.</i>
12.3.1. Visit 3/3R	12.3.1. Visit 3/3R	<ul style="list-style-type: none"> <li>• Completion of the FOUR Score</li> <li>– +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the end</li> </ul>	<ul style="list-style-type: none"> <li>• Completion of the FOUR Score</li> <li>– +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the end of the <b>24 hour observation period</b></li> </ul>	<i>Clarification on FOUR Score assessment timeframe for Qualifying Wean Successes (QWS)</i>



Section number and title in Protocol Amendment 1 (27 MAY 2015)	Section number and title in Amendment 2 (04 FEB 2016)	Original text:	Changed to:	Rationale
		of the QW)	<b>following the QW)</b>	
12.5.2. Visit 10/10R	12.5.2. Visit 10/10R	<ul style="list-style-type: none"> <li>At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine retreatment with higher dose of study drug. All patients for retreatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.</li> </ul>	<ul style="list-style-type: none"> <li>At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine <b>eligibility for</b> retreatment with <b>the</b> higher dose of study drug. <b>This determination may occur at any point during Visit 10: the retreatment infusion must begin within the Visit 10 window.</b> All patients for retreatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.</li> </ul>	<i>Clarification on Visit 10 retreatment eligibility and retreatment infusion window.</i>
13.1.4 Analysis of Primary Endpoint	13.1.4 Analysis of Primary Endpoint	An additional analysis of the primary endpoint will also be performed on the MITT population. In addition sensitivity analyses of the primary endpoint will be	An additional analysis of the primary endpoint will also be performed on the MITT population. In addition sensitivity analyses of the primary endpoint will be performed using the ITT	<i>Additional analysis added at the request of AIFA</i>

Section number and title in Protocol Amendment 1 (27 MAY 2015)	Section number and title in Amendment 2 (04 FEB 2016)	Original text:	Changed to:	Rationale
		<p>performed using the ITT population based on:</p> <ul style="list-style-type: none"> <li>the number of third-line agents (one, two, or three) subjects were administered post-randomization; and</li> <li>which third line agent was the subject of the first TW.</li> </ul>	<p>population based on:</p> <ul style="list-style-type: none"> <li>the number of third-line agents (one, two, or three) subjects were administered post-randomization; and</li> <li>which third line agent was the subject of the first TW.</li> </ul> <p><b>As requested by Italian regulators, the primary endpoint will also be summarized by the cause of status epilepticus being or not being an autoimmune disorder as defined by medical history and prior and/or concurrent medication use.</b></p>	

**Summary of Changes****Protocol-547-SSE-301****Dated 22 April 2016**

The following changes were made to the attached protocol in this amendment. Minor typographical/editorial errors were corrected and administrative revisions addressed throughout the document.

<b>Section number and title in Protocol Version 4.0 (Amendment 3 [22 April 2016])</b>	<b>Section number and title in Version 3.0 (Amendment 2 [17 November 2015])</b>	<b>Original text:</b>	<b>Changed to:</b>	<b>Rationale</b>
Synopsis	Synopsis	Up to 180 sites in the USA, Europe, and Canada.	Up to 180 sites in the USA, <b>Israel</b> , Europe, and Canada.	<i>Adding Israel to list of countries, previous omission.</i>
Synopsis	Synopsis	To evaluate the impact of retreatment with a higher dose SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;	To evaluate the impact of treatment with a higher dose SAGE-547 infusion;	<i>Revised the nomenclature in other objectives from retreatment to open-label treatment.</i>
Synopsis	Synopsis	The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who fail to respond to their randomized double blind treatment and are retreated with a higher dose of SAGE-547.	The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who are treated with a higher dose of SAGE-547.	<i>Revised the nomenclature in other endpoints to reflect change from retreatment to treatment.</i>

Synopsis	Synopsis	Exclusion 5a:  a GFR low enough to warrant dialysis for whatever reason, but dialysis is not planned or non-continuous dialysis is planned (that would not adequately remove Captisol®)	Exclusion 5a:  a GFR low enough to warrant dialysis <b>but</b> for whatever reason, dialysis <b>that would adequately remove Captisol® is not planned.</b>	<i>Revised to clarify the intent of Ex.#5a (also revised in Sec. 8.2 - Exclusion Criteria)</i>
Synopsis	Synopsis <b>NEW</b>	Exclusion 9:  Subjects who have been enrolled in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not withdraw or complete and then re-enroll).	Exclusion 9:  Subjects who have been <b>treated or randomized</b> in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not <b>have received study drug/placebo</b> and then re-enroll).	<i>Revised to clarify the intent of Ex.#9 (also revised in Sec. 8.2 - Exclusion Criteria)</i>
Synopsis	Synopsis	Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are retreated with SAGE-547.	Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who <b>are treated with a higher dose</b> of SAGE-547.	<i>Revised the nomenclature in statistical methods to reflect change from retreatment to treatment with a higher dose of SAGE-547.</i>
Section 3.4.2 / SAGE-547 Clinical Program in the Treatment of SRSE	Section 3.4.2 / SAGE-547 Clinical Program in the Treatment of SRSE	an ongoing Phase 2 open-label trial, Study 547-SSE-201; a planned open-label, expanded access protocol, Study 547-SSE-302;	<b>a completed</b> Phase 2 open-label trial, Study 547-SSE-201; <b>an ongoing</b> open-label, expanded access protocol, Study 547-SSE-302;	<i>Revised introduction based on current status of clinical program.</i>

Section 5.4 / Other Objectives	Section 5.4 / Other Objectives	To evaluate the impact of retreatment with a higher dose SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;	To evaluate the impact of treatment with a higher dose SAGE-547 infusion;	<i>Revised the nomenclature in other objectives from retreatment to open-label treatment.</i>
Section 6.4 / Other Endpoints	Section 6.4 / Other Endpoints	The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who fail to respond to their randomized double blind treatment and are retreated with a higher dose of SAGE-547.	The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who are treated with a higher dose of SAGE-547.	<i>Revised the nomenclature in other endpoints to reflect change from retreatment to treatment.</i>
Section 7.3 / Blinding and Randomization	Section 7.3 / Blinding and Randomization	The second infusion of SAGE-547 will be administered on an open-label basis to subjects who failed the primary endpoint wean.	The second infusion of SAGE-547 will be administered on an open-label basis to subjects who <b>meet the criteria for open-label treatment</b> .	<i>Revised second infusion criteria.</i>
Section 10.1 / Dosing Schedule (Blinded Infusions)	Section 10.1 / Dosing Schedule (Blinded Infusions)	The infusion rates to accomplish these µg/kg/h doses will be calculated according to the weight of the subject.	The infusion rates to accomplish these µg/kg/h doses will be calculated according to the weight of the subject <b>obtained within the six-hour window that follows the declaration of the QW failure at V2 and prior to dosing at V3.</b>	<i>The study drug dose is based on the initial pre-dose weight for each six-day infusion.</i>

Section 10.2 / Dosing Schedule (Open-Label Infusions)	Section 10.2 / Dosing Schedule (Open-Label Infusions)	If a subject fails wean from third-line agent(s) or requires re-instatement of third-line therapy within 24 hours of discontinuing the initial infusion of study drug, SAGE-547 Injection will be re-administered according to the dosing schedule in Table 6. The infusion rates to accomplish these $\mu\text{g/kg/h}$ doses will be calculated according to the weight of the subject. These infusion rates will be applied to SAGE-547 re-treatment for the open-label second infusions of study medication.	<b>Those subjects that qualify for the open-label study drug will be administered SAGE-547 Injection according to the dosing schedule in Table 6. The dose will be administered on a <math>\mu\text{g/kg/h}</math> basis, and the subject's weight measured prior to dosing during V10 will be used to calculate the doses.</b>	
Section 10.4 / Treatment Period	Section 10.4 / Treatment Period	The retreatment period is of identical duration.	The <b>open-label study drug treatment</b> period is of identical duration.	<i>Revised the nomenclature from retreatment to open-label treatment.</i>

Section 11.1.1.1/Weaning	Section 11.1.1.1/Weaning	The following guidance for weaning applies to all weans of third-line agents undertaken during the study. These weans include the qualifying wean (QW); ...	The following guidance for weaning applies to all weans of third-line agents undertaken during the study. <b>Continued determined efforts to liberate subjects from sedation must be undertaken for the entire duration of the blinded study drug infusion. Each failed wean from third-line agents should be followed by a 6-24 hour period of suppression and then another wean attempt, with further optimization of the AED regimen.</b>  <b>Weans</b> include the qualifying wean (QW); ...	<i>Additional guidance provided for third-line agent weaning during blinded and open-label treatment courses.</i>
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Section 11.1.1.2 / EEG	Section 11.1.1.2 / EEG	<p>A 24-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst suppression for the second path to eligibility, and a variable pattern for the third path to eligibility. This EEG will capture as much as possible of the burst suppression pattern that precedes the QW.</p>	<p>A 24-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst suppression for the second path to eligibility, and a variable pattern for the third path to eligibility. This EEG <b>also aims to</b> capture the burst suppression pattern <b>during the 24 hours</b> that precede the QW. <b>If the CEEG does not capture the 24 hours that precede the QW, additional EEG data collected as standard of care after the CEEG and prior to the QW may be collected to assess the depth of burst suppression prior to the QW.</b></p>	<p><i>Clarification on the intent of the 24 hour consent EEG, aimed at capturing the period of burst suppression required prior to initiating the qualifying wean.</i></p>
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Section 11.1.1.2 / EEG	Section 11.1.1.2 / EEG	Those subjects randomized who are not retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the BIEEG, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read;	Those subjects randomized who are not <b>administered the open-label study drug</b> will have the <b>QWEEG</b> , BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the BIEEG, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read;	<i>Revised the nomenclature from retreatment to open-label treatment.</i>  <i>Included QWEEG, previous omission.</i>
Section 11.1.1.2 / EEG	Section 11.1.1.2 / EEG	Those subjects randomized who are retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion and the TWEEG, TAEED, and PAEEG related to the open-label study drug infusion collected and stored, and the BIEEG, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read.	Those subjects randomized who <b>later undergo the open-label infusion</b> will have the <b>QWEEG</b> , BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion and the TWEEG, TAEED, and PAEEG related to the open-label study drug infusion collected and stored, and the BIEEG, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read.	<i>Revised the nomenclature from retreatment to open-label treatment.</i>  <i>Included QWEEG, previous omission.</i>
Section 11.1.2.2 / Epilepsy Status	Section 11.1.2.2 / Epilepsy Status	N/A	N/A	<i>Clarified the timing of status epilepticus history collection.</i>

Section 11.2.4 / Weight and Height	Section 11.2.4 / Weight and Height	Weight and height will be measured at Visit 1 and weight will also be measured once during each 24 hour period of the first infusion of study drug, and of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547. These daily weights will be used to modify the dose of SAGE-547 if required. If it is not possible to weigh the subject daily, an actual weight must be obtained prior to starting the blinded study drug, and that weight used to calculate the dose of study drug to be administered. If this is not possible, permission from the Monitor must be obtained to use another method to obtain the subject's weight (such as information from the LAR or estimating using an established local protocol).	Weight and height will be measured at Visit 1. Weight will also be obtained at <b>V2, within the six hour window that follows the declaration of the QW failure and prior to the initiation of the blinded infusion loading dose at H0 of V3, and will be used to calculate the infusion rates throughout the entire blinded treatment course. If a subject qualifies for open-label study drug, the infusion rates for the open-label infusion will be calculated using the subject's weight measured prior to dosing during V10.</b> If it is not possible to obtain an actual weight <b>at the above-referenced time points</b> , permission from the <b>Clinical Monitor</b> must be obtained to use another method to obtain the subject's weight (such as information from the LAR or estimating using an established local protocol). <b>In addition, a daily weight will be obtained and recorded if this is easily obtained, such as the use of a scale bed.</b>	<i>Revised the recording of weight to align with availability of scale beds and to define the weight collection used to calculate the infusion rates for each treatment course.</i>
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Sec. 11.2.5 ECG	Sec. 11.2.5 ECG	All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours; at other times the allowed time window for ECGs is +/- 2 hours:	All efforts must be made to perform ECGs immediately after the PK samples up to 160 hours. <b>If it is not possible to perform ECG immediately after the collection of PK samples up to 160 hours, ECG must be performed within 15 minutes prior to the collection of PK samples up to 160 hours;</b> at other times the allowed time window for ECGs is +/- 2 hours:	<i>Clarified timing of ECG in relation to PK sampling (also specified in footnotes to Tables 1 – 3 and Sec. 12 - Study Procedures)</i>
Section 12.3.1 through Section 12.4.1	Section 12.3.1 through Section 12.4.1	N/A	N/A	<i>Removed requirement for weight measurement and replaced with if easily obtained.</i>
Section 13.1.11	Section 13.1.11	N/A	N/A	<i>Revised the nomenclature from retreatment to open-label treatment.</i>

**Summary of Changes****Protocol-547-SSE-301****Dated 12 August 2016**

The following changes were made to the attached protocol in this amendment. Minor typographical/editorial errors were corrected and administrative revisions were addressed within the document.

<b>Section number and title in Version 4.0 (Amendment 3 [22 April 2016])</b>	<b>Section number and title in Version 5.0 (Amendment 4 [12 August 2016])</b>	<b>Original text:</b>	<b>Changed to:</b>	<b>Rationale</b>
Signature Page	Signature Page	N/A	New signature page added to include signature spaces for the Sponsor protocol review team.	<i>Previous omission.</i>
Synopsis: Study Design	Synopsis: Study Design	The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst suppression with a third-line agent.	The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst <b>or seizure</b> suppression with a third-line agent.  <i>Note: 'seizure suppression' revised throughout document with regards to EEG suppression goals for managing RSE and SRSE patients, as well as permitting 'seizure suppression' during screening period, prior to initiation of qualifying wean (QW).</i>	<i>Allowing burst or seizure suppression during screening period, prior to initiation of QW, allows sites to use a less restrictive approach achieving EEG suppression and one more typical to sites' standard of care when screening patients.</i>

Section number and title in Version 4.0 (Amendment 3 [22 April 2016])	Section number and title in Version 5.0 (Amendment 4 [12 August 2016])	Original text:	Changed to:	Rationale
Synopsis: Study Design	Synopsis: Study Design	These subjects will be consented for the study after admission to the intensive care unit, but before any third-line agents are administered for burst suppression.	These subjects will be consented for the study after admission to the intensive care unit, before <b>or after</b> any third-line agents are administered for burst <b>or seizure</b> suppression.  <i>Note: revision also appears in Sec. 7.1.</i>	<i>Clarification that subjects may be administered third-line anesthetic agents for EEG burst or seizure suppression prior to or following the consent procedure.</i>
Synopsis: Study Design	Synopsis: Study Design	Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within six hours of the investigator's determination that they failed the QW.	Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within <b>eight</b> hours of the investigator's determination that they failed the QW.  <i>Note: revision also appears in Sections 7.1, 10.1, 11.2.4, and 12.2.</i>	<i>Extending time frame from failure of QW to when blinded infusion begins will provide greater flexibility for study teams to mobilize and coordinate pre-treatment activities.</i>

Section number and title in Version 4.0 (Amendment 3 [22 April 2016])	Section number and title in Version 5.0 (Amendment 4 [12 August 2016])	Original text:	Changed to:	Rationale
Synopsis: Inclusion Criteria	Synopsis: Inclusion Criteria	<p>Inclusion criterion # 2, sub-bullet # 3:</p> <p>Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst suppression pattern;</p>	<p>Inclusion criterion # 2, sub-bullet # 3:</p> <p>Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed <b>zero</b>, one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst <b>or seizure</b> suppression pattern;</p> <p><u>Note:</u> revision also appears in Section 8.1.</p>	<p><i>Clarified that some patients may enter the study having never failed a prior third-line agent wean. These patients will enter the study in Refractory Status Epilepticus (RSE) and the outcome of the protocol-specific QW will determine whether or not they are in Super-Refractory Status Epilepticus (SRSE).</i></p>

Section number and title in Version 4.0 (Amendment 3 [22 April 2016])	Section number and title in Version 5.0 (Amendment 4 [12 August 2016])	Original text:	Changed to:	Rationale
Synopsis: Exclusion Criteria	Synopsis: Exclusion Criteria	Exclusion criterion # 3:  Subjects with SRSE due to anoxic/hypoxic encephalopathy	Exclusion criterion # 3:  Subjects with SRSE due to anoxic/hypoxic encephalopathy <b>with highly malignant/malignant EEG features (Westhall, Rosetti et al. 2016)</b>  <i>Note: revision also appears in Section 8.2.</i>	<i>Clarified EEG features indicative of patients with anoxic/hypoxic encephalopathy to aid Investigator/Sponsor determination to exclude patients meeting this criterion.</i>
Synopsis: Exclusion Criteria	Synopsis: Exclusion Criteria	N/A	Removed Exclusion criterion # 5, sub-bullet 'e':  'a do not resuscitate (DNR) order.'  <i>Note: revision also appears in Section 8.2 and DNR removed from List of Abbreviations and Definitions of Terms.</i>	<i>Removed DNR as exclusion criterion due to variations of interpretations of DNR across sites.</i>

Section number and title in Version 4.0 (Amendment 3 [22 April 2016])	Section number and title in Version 5.0 (Amendment 4 [12 August 2016])	Original text:	Changed to:	Rationale
Figure 1: Study Design	Figure 1: Study Design	Visit 1 consent and eligibility section:  (Re)administration of 3 <sup>rd</sup> line agent(s) $\geq$ 24h burst suppression on 3 <sup>rd</sup> line agent(s)	Visit 1 consent and eligibility section:  (Re)administration of 3 <sup>rd</sup> line agent(s) $\geq$ 24h burst <b>or seizure suppression</b> on 3 <sup>rd</sup> line agent(s)	<i>As referenced above, allowing burst or seizure suppression during screening period, prior to initiation of QW.</i>
Figure 2: Details of Treatment Administration and Follow-up	Figure 2: Details of Treatment Administration and Follow-up	N/A	'Failure' arrow, with regards to subjects who are considered failures of the blinded infusion, moved from beneath V6 to V10, as V10 is timepoint when decision for open-label treatment is made.	<i>Previous oversight, the modified figure clarifies the timepoint when open-label treatment is determined, at V10.</i>



Section number and title in Version 4.0 (Amendment 3 [22 April 2016])	Section number and title in Version 5.0 (Amendment 4 [12 August 2016])	Original text:	Changed to:	Rationale
10.5 Concomitant Medications, Procedures and Treatments	10.5 Concomitant Medications, Procedures and Treatments	Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. All concomitant medications, procedures, and treatments should be documented throughout the study from Screening through Visit 12/12R and recorded on the eCRF.	Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. <b>For all randomized and the first 50 qualifying wean success (QWS) subjects, detailed information on all concomitant medications (concomitant AEDs, third-line agents, pressors, and other concomitant medications), procedures, and treatments should be documented throughout the study from Screening through Visit 12/12R, as described below, and recorded on the eCRF. For subsequent QWS subjects, after the detailed information on all concomitant AEDs, pressors, third-line agents, procedures, and treatments collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant AED or pressor, third-line agent, procedure, and/or treatment, and the start and stop dates and times) from Visit 3 through Visit 12 will be recorded in the eCRF. For subsequent QWS subjects, after the detailed information on all concomitant medications collected during the screening period (Visits 1 and 2) has been recorded, only minimal information, to include the name of the concomitant medications and indication only will be recorded from Visit 3 through Visit 12.</b>  <i>Note: revision appears in SOA footnotes</i>	<i>Specified the intent to collect minimal data on QWS subjects, following enrollment of 50 QWS subjects.</i>

Section number and title in Version 4.0 (Amendment 3 [22 April 2016])	Section number and title in Version 5.0 (Amendment 4 [12 August 2016])	Original text:	Changed to:	Rationale
Sec. 11.1.1.1 Weaning	Sec. 11.1.1.1 Weaning	The following are considered to be minimum maintenance doses of these agents that may be expected alone or in combination to achieve EEG burst suppression. If subjects are on lower doses than these and are not in EEG burst suppression for <b>the 24 hours prior to the QW</b> or the first 12 hours of the blinded study drug infusion, they will be considered to be <b>screen failures</b> /protocol violators and will exit the study.	The following are considered to be minimum maintenance doses of these agents that may be expected alone or in combination to achieve EEG burst suppression. If subjects are on lower doses than these and are not in EEG burst suppression for the first 12 hours of the blinded study drug infusion, they will be considered to be protocol violators and will exit the study.	<i>Removed requirement for patients to be in EEG burst suppression in the 24 hours prior to the QW. Clarified that burst suppression is required only during the first 12 hours of the blinded study drug infusion. Patients in seizure suppression for 24 hours pre-QW will not be considered screen failures.</i>

Section number and title in Version 4.0 (Amendment 3 [22 April 2016])	Section number and title in Version 5.0 (Amendment 4 [12 August 2016])	Original text:	Changed to:	Rationale
Sec. 11.1.1.1 Weaning	Sec. 11.1.1.1 Weaning	The Clinical Standardization Team will be able to discuss EEGs related to key study timepoints ( <b>qualifying wean</b> , terminal wean, and the period after the end of the blinded study drug infusion if the terminal wean was successful) in a timely manner in order to provide advice about compliance with the Clinical Standardization Guidelines.	The Clinical Standardization Team will be able to discuss EEGs related to key study timepoints (terminal wean and the period after the end of the blinded study drug infusion if the terminal wean was successful) in a timely manner in order to provide advice about compliance with the Clinical Standardization Guidelines.	<i>Removed guidelines for CST review of QWEEG, providing clarification on guidelines for sites to contact CST during TW and the Primary Endpoint Assessment period.</i>
Sec. 11.1.1.2 EEG	Sec. 11.1.1.2 EEG	First bullet point:  This EEG also aims to capture the burst or seizure suppression pattern during the 24 hours that precede the QW. If the CEEG does not capture the 24 hours that precede the QW, additional EEG data collected as standard of care after the CEEG and prior to the QW may be collected to assess the depth of burst suppression prior to the QW.	First bullet point:  This EEG also aims to capture the burst or seizure suppression pattern during the 24 hours that precede the QW. If the CEEG does not capture the 24 hours that precede the QW, additional EEG data collected as standard of care <b>prior to</b> the CEEG and prior to the QW may be collected to assess the depth of burst <b>or seizure suppression in the 24 hour period</b> prior to the QW.	<i>Previous editorial oversight, intention is to permit collection of SOC EEG data that may precede CEEG, in order to collect EEG data on the depth of EEG suppression in the 24 hrs prior to QW.</i>

Section number and title in Version 4.0 (Amendment 3 [22 April 2016])	Section number and title in Version 5.0 (Amendment 4 [12 August 2016])	Original text:	Changed to:	Rationale
Sec. 11.2.5 ECG	Sec. 11.2.5 ECG	12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug...	<p><b>For the first 50 subjects randomized in the study,</b> 12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug...</p> <p><b>For the subsequent subjects randomized in the study, the following timepoints for ECG will be used:</b></p> <ul style="list-style-type: none"> <li>• pre-dose and at +1 +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the blinded (first) study drug infusion</li> <li>• pre-dose and at +1 +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the open-label (second) study drug infusion</li> </ul> <p><b>It is not necessary to collect these ECGs with the PK samples at these timepoints and, apart from the +1h ECG, there is +/- 2 hour time window for these ECGs.</b></p> <p><i>Note: revision also made to SOA footnotes and throughout Sec. 12</i></p>	<i>Clarified the number of ECG timepoints required based on order of randomization, including the window for ECG collection and relation to PK draws.</i>

Section number and title in Version 4.0 (Amendment 3 [22 April 2016])	Section number and title in Version 5.0 (Amendment 4 [12 August 2016])	Original text:	Changed to:	Rationale
Sec. 11.2.8.1 Pharmacokinetic Data	Sec. 11.2.8.1 Pharmacokinetic Data	Plasma Analysis section, bullet # 4:  All samples will also be analyzed for plasma concentrations of Captisol®.	Plasma Analysis section, bullet # 4:  All samples <b>from the first 50 subjects randomized</b> will also be analyzed for plasma concentrations of Captisol®.	<i>Created an upper limit on Captisol® samples that will be analyzed by PK vendor.</i>

Section number and title in Version 4.0 (Amendment 3 [22 April 2016])	Section number and title in Version 5.0 (Amendment 4 [12 August 2016])	Original text:	Changed to:	Rationale
Sec. 14.1.4 Medical Monitor and Emergency Contact Information	Sec. 14.1.4 Medical Monitor and Emergency Contact Information	[REDACTED], MD [REDACTED]	[REDACTED], MD [REDACTED]  In a study related medical emergency situation, when the assigned Medical Monitor cannot be reached by a caller, an on-call Physician can be reached 24 hours per day, 7 days per week via an [REDACTED] Call-Center:  <ul style="list-style-type: none"> <li>Telephone: [REDACTED] (this is a chargeable telephone number allowing a global reach from both landlines and mobile phones)</li> <li>[REDACTED]</li> </ul> On this internet page a list of country-specific toll-free telephone numbers is provided. It should be noted that not all countries globally have access to toll-free numbers as indicated on the “24/7 Medical Help desk” index. Countries without toll-free numbers need to dial the chargeable number as indicated above. Furthermore, toll-free numbers are not available from mobile phones.	<i>Updated [REDACTED] global 24/7 Medical Monitor and on-call physician contact information.</i>

Section number and title in Version 4.0 (Amendment 3 [22 April 2016])	Section number and title in Version 5.0 (Amendment 4 [12 August 2016])	Original text:	Changed to:	Rationale
N/A	Sec. 14.2.4 Reporting to European Regulatory Authorities	N/A	<p><b>14.2.4 Reporting to European Regulatory Authorities</b></p> <p>The Sponsor or its designee is responsible for SUSAR notification to the relevant regulatory authorities as outlined in the ICH Guidelines. All investigators participating in the study will also be informed as required by regulations.</p> <p>Any SUSAR is subject to expedited reporting in the EU. The Sponsor or its designee, will report any single SUSAR to the appropriate National CAs and IECs within 7 days if the SUSAR is life-threatening or fatal (with the relevant follow-up information subsequently communicated within an additional eight days), and within 15 days if the SUSAR is neither life-threatening nor fatal. SUSARs reported will be those that have arisen in the present clinical trial and SUSARs that have arisen in other clinical trials conducted by the Sponsor with the same medicinal product.</p> <p>In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to competent authorities of the concerned Member States and to IEC(s)/IRBs as required by national laws.</p>	<i>Section on EU Regulatory Reporting was omitted from previous amendment and added due to trial occurring throughout EU.</i>

**Summary of Changes**  
**Protocol-547-SSE-301 (Adults Only)**  
**Dated 18 AUG 2016**

The following changes were made to the attached protocol in this amendment. Minor typographical/editorial errors throughout the document were also corrected.

Section number and title in Protocol Amendment 2, Adults Only (17 NOV 15)	Section number and title in Protocol Amendment 4, Adults Only (18 AUG 16)	Original text:	Changed to:	Rationale
2. Study Synopsis/Study Sites/Number of Subjects	2. Study Synopsis/Study Sites/Number of Subjects	Up to 180 sites in the USA, Europe, and Canada.	Up to 180 sites in the USA, <b>Israel</b> , Europe, and Canada.	<i>Addition of Israel to country list</i>
2. Synopsis: Study Design	2. Synopsis: Study Design	The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst suppression with a third-line agent.	The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst <b>or seizure</b> suppression with a third-line agent.  <i>Note: 'seizure suppression' revised throughout document with regards to EEG suppression goals for managing RSE and SRSE patients, as well as permitting 'seizure suppression' during screening period, prior to initiation of</i>	<i>Allowing burst or seizure suppression during screening period, prior to initiation of QW, allows sites to use a less restrictive approach achieving EEG suppression and one more typical to sites' standard of care when screening</i>



Section number and title in Protocol Amendment 2, Adults Only (17 NOV 15)	Section number and title in Protocol Amendment 4, Adults Only (18 AUG 16)	Original text:	Changed to:	Rationale
			<i>qualifying wean (QW).</i>	<i>patients.</i>
2. Study Synopsis/Study Design	2. Study Synopsis/Study Design	These subjects will be consented for the study after admission to the intensive care unit, but before any third-line agents are administered for burst suppression.	These subjects will be consented for the study after admission to the intensive care unit, before <b>or after</b> any third-line agents are administered for burst <b>or seizure</b> suppression.  <i>Note: revision also appears in Sec. 7.1.</i>	<i>Clarification that subjects may be administered third-line anesthetic agents for EEG burst or seizure suppression prior to or following the consent procedure.</i>
2. Study Synopsis/Study Design	2. Study Synopsis/Study Design	Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within six hours of the investigator's determination that they failed the QW.	Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within <b>eight</b> hours of the investigator's determination that they failed the QW.  <i>Note: revision also appears in Sections 7.1, 10.1, 11.2.4, and 12.2.</i>	<i>Extending time frame from failure of QW to when blinded infusion begins will provide greater flexibility for study teams to mobilize and coordinate pre-treatment activities.</i>
2. Study Synopsis/Study	2. Study Synopsis/Study	To evaluate the impact of retreatment with a higher dose	To evaluate the impact of <del>re</del> reatment with a higher dose	<i>Revised the nomenclature in</i>

Section number and title in Protocol Amendment 2, Adults Only (17 NOV 15)	Section number and title in Protocol Amendment 4, Adults Only (18 AUG 16)	Original text:	Changed to:	Rationale
Objectives	Objectives	SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;	<del>SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;</del>	<i>other objectives from retreatment to open-label treatment.</i>
2. Study Synopsis/Endpoints	2. Study Synopsis/Endpoints	The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who fail to respond to their randomized double blind treatment and are retreated with a higher dose of SAGE-547.	The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects <del>who fail to respond to their randomized double blind treatment and</del> are retreated with a higher dose of SAGE-547.	<i>Revised the nomenclature in other endpoints to reflect change from retreatment to treatment.</i>
2. Study Synopsis/Inclusion Criteria	2. Study Synopsis/Inclusion Criteria	Inclusion criterion # 2, sub-bullet # 3:  Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst suppression pattern;	Inclusion criterion # 2, sub-bullet # 3:  Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed <b>zero</b> , one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst <b>or seizure</b> suppression pattern;	<i>Clarified that some patients may enter the study having never failed a prior third-line agent wean. These patients will enter the study in Refractory Status Epilepticus (RSE) and the outcome of the protocol-specific QW will</i>

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			<i>Note: revision also appears in Section 8.1.</i>	<i>determine whether or not they are in Super-Refractory Status Epilepticus (SRSE).</i>
2. Study Synopsis/Exclusion Criteria	2. Study Synopsis/Exclusion Criteria	Exclusion criterion # 3:  Subjects with SRSE due to anoxic/hypoxic encephalopathy	Exclusion criterion # 3:  Subjects with SRSE due to anoxic/hypoxic encephalopathy <b>with highly malignant/malignant EEG features (Westhall, Rosetti et al. 2016)</b>  <i>Note: revision also appears in Section 8.2.</i>	<i>Clarified EEG features indicative of patients with anoxic/hypoxic encephalopathy to aid Investigator/Sponsor determination to exclude patients meeting this criterion.</i>
2. Study Synopsis/Exclusion Criteria	2. Study Synopsis/Exclusion Criteria	Exclusion 5a:  a GFR low enough to warrant dialysis for whatever reason, but dialysis is not planned or non-continuous dialysis is planned (that would not adequately remove Captisol®)	Exclusion 5a:  a GFR low enough to warrant dialysis <b>but</b> for whatever reason, dialysis <b>that would adequately remove Captisol® is not planned.</b>	<i>Revised to clarify the intent of Ex.#5a (also revised in Sec. 8.2 - Exclusion Criteria)</i>

Section number and title in Protocol Amendment 2, Adults Only (17 NOV 15)	Section number and title in Protocol Amendment 4, Adults Only (18 AUG 16)	Original text:	Changed to:	Rationale
2. Study Synopsis/Exclusion Criteria	2. Study Synopsis/Exclusion Criteria	Exclusion criterion # 5, sub-bullet 'e':  a do not resuscitate (DNR) order.	Exclusion criterion # 5, sub-bullet 'e':  <del>a do not resuscitate (DNR) order.</del>  <i>Note: revision also appears in Section 8.2 and DNR removed from List of Abbreviations and Definitions of Terms.</i>	<i>Removed DNR as exclusion criterion due to variations of interpretations of DNR across sites.</i>
2. Study Synopsis/Exclusion Criteria	2. Study Synopsis/Exclusion Criteria	Exclusion 8:  Subjects who have been enrolled in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not withdraw or complete and then re-enroll).	Exclusion 8:  Subjects who have been <b>treated or randomized</b> in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not <b>have received study drug/placebo</b> and then re-enroll).  <i>Note: also revised in Sec. 8.2 - Exclusion Criteria</i>	<i>Revised to clarify the intent of Ex.#8</i>
2. Study Synopsis/Analysis of Secondary Efficacy Endpoints	2. Study Synopsis/Analysis of Secondary Efficacy Endpoints	Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are retreated with SAGE-547.	Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who <b>are</b> treated with <b>a higher dose</b> of SAGE-547.	<i>Revised the nomenclature in statistical methods to reflect change from retreatment to</i>

Section number and title in Protocol Amendment 2, Adults Only (17 NOV 15)	Section number and title in Protocol Amendment 4, Adults Only (18 AUG 16)	Original text:	Changed to:	Rationale
				<i>treatment with a higher dose of SAGE-547.</i>
Section 3.4.2 / SAGE-547 Clinical Program in the Treatment of SRSE	Section 3.4.2 / SAGE-547 Clinical Program in the Treatment of SRSE	an ongoing Phase 2 open-label trial, Study 547-SSE-201; a planned open-label, expanded access protocol, Study 547-SSE-302;	<b>a completed</b> Phase 2 open-label trial, Study 547-SSE-201; <b>an ongoing</b> open-label, expanded access protocol, Study 547-SSE-302;	<i>Revised introduction based on current status of clinical program.</i>
Section 7.3 / Blinding and Randomization	Section 7.3 / Blinding and Randomization	The second infusion of SAGE-547 will be administered on an open-label basis to subjects who failed the primary endpoint wean.	The second infusion of SAGE-547 will be administered on an open-label basis to subjects who <b>meet the criteria for open-label treatment.</b>	<i>Revised second infusion criteria.</i>
Figure 2: Details of Treatment Administration and Follow-up	Figure 2: Details of Treatment Administration and Follow-up	N/A	'Failure' arrow, with regards to subjects who are considered failures of the blinded infusion, moved from beneath V6 to V10, as V10 is timepoint when decision for open-label treatment is made.	<i>Previous oversight, the modified figure clarifies the timepoint when open-label treatment is determined, at V10.</i>
Section 10.1 / Dosing Schedule (Blinded Infusions)	Section 10.1 / Dosing Schedule (Blinded Infusions)	The infusion rates to accomplish these $\mu\text{g/kg/h}$ doses will be calculated according to the weight of the subject.	The infusion rates to accomplish these $\mu\text{g/kg/h}$ doses will be calculated according to the weight of the subject <b>obtained within the</b>	<i>The study drug dose is based on the initial pre-dose weight for</i>

Section number and title in Protocol Amendment 2, Adults Only (17 NOV 15)	Section number and title in Protocol Amendment 4, Adults Only (18 AUG 16)	Original text:	Changed to:	Rationale
			<b>eight-hour window that follows the declaration of the QW failure at V2 and prior to dosing at V3.</b>	<i>each six-day infusion.</i>
Section 10.2 / Dosing Schedule (Open-Label Infusions)	Section 10.2 / Dosing Schedule (Open-Label Infusions)	If a subject fails wean from third-line agent(s) or requires re-instatement of third-line therapy within 24 hours of discontinuing the initial infusion of study drug, SAGE-547 Injection will be re-administered according to the dosing schedule in Table 6. The infusion rates to accomplish these $\mu\text{g/kg/h}$ doses will be calculated according to the weight of the subject. These infusion rates will be applied to SAGE-547 re-treatment for the open-label second infusions of study medication.	<b>Those subjects that qualify for the open-label study drug will be administered SAGE-547 Injection according to the dosing schedule in Table 6. The dose will be administered on a <math>\mu\text{g/kg/h}</math> basis, and the subject's weight measured prior to dosing during V10 will be used to calculate the doses.</b>	<i>The study drug dose is based on the initial pre-dose weight for each six-day infusion.</i>
10.5 Concomitant Medications, Procedures and Treatments	10.5 Concomitant Medications, Procedures and Treatments	Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the	Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the	<i>Specified the intent to collect minimal data on QWS subjects, following enrollment of 50 QWS subjects.</i>

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		Investigator at any time during the study. All concomitant medications, procedures, and treatments should be documented throughout the study from Screening through Visit 12/12R and recorded on the eCRF.	Investigator at any time during the study. <b>For all randomized and the first 50 qualifying wean success (QWS) subjects, detailed information on all concomitant medications (concomitant AEDs, third-line agents, pressors, and other concomitant medications),</b> procedures, and treatments should be documented throughout the study from Screening through Visit 12/12R, <b>as described below,</b> and recorded on the eCRF. <b>For subsequent QWS subjects, after the detailed information on all concomitant AEDs, pressors, third-line agents, procedures, and treatments collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant AED or pressor, third-line agent, procedure, and/or</b>	

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			<p>treatment, and the start and stop dates and times) from Visit 3 through Visit 12 will be recorded in the eCRF. For subsequent QWS subjects, after the detailed information on all concomitant medications collected during the screening period (Visits 1 and 2) has been recorded, only minimal information, to include the name of the concomitant medications and indication only will be recorded from Visit 3 through Visit 12.</p> <p><i>Note: revision appears in SOA footnotes</i></p>	
Section 11.1.1.1/Weaning	Section 11.1.1.1/Weaning	The following guidance for weaning applies to all weans of third-line agents undertaken during the study.	The following guidance for weaning applies to all weans of third-line agents undertaken during the study. <b>Continued determined efforts to liberate subjects from sedation must be undertaken for the entire duration of the blinded study drug infusion. Each failed</b>	<i>Additional guidance provided for third-line agent weaning during blinded and open-label treatment courses</i>



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			<b>wean from third-line agents should be followed by a 6-24 hour period of suppression and then another wean attempt, with further optimization of the AED regimen.</b>	
11.1.1.2 EEG	11.1.1.2 EEG	A 24-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst suppression for the second path to eligibility, and a variable pattern for the third path to eligibility.	A 24-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst <b>or seizure</b> suppression for the second path to eligibility, and a variable pattern for the third path to eligibility. <b>This EEG also aims to capture the burst or seizure suppression pattern during the 24 hours that precede the QW. If the CEEG does not capture the 24 hours that precede the QW, additional EEG data collected as standard of care prior to the CEEG and prior to the QW may</b>	<i>Extended the QWEEG to match QW Guidance in Sec. 11.1.1.1 for Investigators to allow 24 hours to lapse after the end of QW before declaring QW success.</i>

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			be collected to assess the depth of burst or seizure suppression in the 24 hour period prior to the QW.	
11.2.4. Weight and Height	11.2.4. Weight and Height	Weight and height will be measured at Visit 1 and weight will also be measured once during each 24 hour period of the first infusion of study drug, and of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547. These daily weights will be used to modify the dose of SAGE-547 if required.	Weight and height will be measured at Visit 1. <b>Weight will also be obtained at V2, within the eight hour window that follows the declaration of the QW failure and prior to the initiation of the blinded infusion loading dose at H0 of V3, and will be used to calculate the infusion rates throughout the entire blinded treatment course. If a subject qualifies for open-label study drug, the infusion rates for the open-label infusion will be calculated using the subject's weight measured prior to dosing during V10. If it is not possible to obtain the actual weight at the above-referenced timepoints, permission</b>	<i>Clarification on process for obtaining daily weight for dosing.</i>

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			<p>from the Clinical Monitor must be obtained to use another method to obtain the subject's weight (such as information from the LAR or estimating using an established local protocol). In addition, a daily weight will be obtained and recorded if this is easily obtained, such as the use of a scale bed.</p>	
11.2.5 ECG	11.2.5 ECG	12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug...	<p><b>For the first 50 subjects randomized in the study</b>, 12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug...</p> <p><b>For the subsequent subjects randomized in the study, the following timepoints for ECG will be used:</b></p> <ul style="list-style-type: none"> <li>• pre-dose and at +1 +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the blinded (first) study drug infusion</li> </ul>	<p><i>Clarified the number of ECG timepoints required based on order of randomization, including the window for ECG collection and relation to PK draws.</i></p>

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			<ul style="list-style-type: none"> <li>• <b>pre-dose and at +1 +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the open-label (second) study drug infusion</b></li> </ul> <p><b>It is not necessary to collect these ECGs with the PK samples at these timepoints and, apart from the +1h ECG, there is +/- 2 hour time window for these ECGs.</b></p> <p><i>Note: revision also made to SOA footnotes and throughout Sec. 12</i></p>	
Sec. 11.2.8.1 Pharmacokinetic Data	Sec. 11.2.8.1 Pharmacokinetic Data	All samples will also be analyzed for plasma concentrations of Captisol®.	All samples <b>from the first 50 subjects randomized</b> will also be analyzed for plasma concentrations of Captisol®.	<i>Created an upper limit on Captisol® samples that will be analyzed by PK vendor.</i>
12.3.1. Visit 3/3R	12.3.1. Visit 3/3R	<ul style="list-style-type: none"> <li>• Completion of the FOUR Score</li> <li>– +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in</li> </ul>	<ul style="list-style-type: none"> <li>• Completion of the FOUR Score</li> <li>– +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following <b>the final declaration</b></li> </ul>	<i>Clarification on FOUR Score assessment timeframe for Qualifying Wean Successes (QWS)</i>

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		the 24 hours following the end of the QW)	<b>of QW success)</b>	
12.5.2. Visit 10/10R	12.5.2. Visit 10/10R	<ul style="list-style-type: none"> <li>At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine retreatment with higher dose of study drug. All patients for retreatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.</li> </ul>	<ul style="list-style-type: none"> <li>At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine eligibility for <b>the open-label treatment</b> with the higher dose of study drug. <b>This determination may occur at any point during Visit 10: the higher dose open-label infusion must begin within the Visit 10 window.</b> All patients receiving the higher dose open-label treatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.</li> </ul>	<i>Clarification on Visit 10 retreatment eligibility and retreatment infusion window.</i>
14.1.4 Medical Monitor and Emergency Contact Information	14.1.4 Medical Monitor and Emergency Contact Information	[REDACTED], MD	[REDACTED], MD	<i>Updated [REDACTED] global 24/7 Medical Monitor and on-call physician contact</i>

Section number and title in Protocol Amendment 2, Adults Only (17 NOV 15)	Section number and title in Protocol Amendment 4, Adults Only (18 AUG 16)	Original text:	Changed to:	Rationale
		<div data-bbox="745 430 1186 506" style="background-color: black; height: 47px; width: 100%;"></div>	<div data-bbox="1211 430 1654 506" style="background-color: black; height: 47px; width: 100%;"></div> <p data-bbox="1220 537 1688 792"><b>In a study related medical emergency situation, when the assigned Medical Monitor cannot be reached by a caller, an on-call Physician can be reached 24 hours per day, 7 days per week via an [REDACTED] Call-Center:</b></p> <ul data-bbox="1220 829 1688 1105" style="list-style-type: none"> <li>• <b>Telephone: [REDACTED]</b> (this is a chargeable telephone number allowing a global reach from both landlines and mobile phones)</li> <li>• [REDACTED]</li> </ul> <p data-bbox="1220 1122 1688 1367"><b>On this internet page a list of country-specific toll-free telephone numbers is provided. It should be noted that not all countries globally have access to toll-free numbers as indicated on the “24/7 Medical Help desk”</b></p>	<p data-bbox="1713 430 1873 467"><i>information.</i></p>

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			<b>index. Countries without toll-free numbers need to dial the chargeable number as indicated above. Furthermore, toll-free numbers are not available from mobile phones.</b>	
N/A	14.2.4 Reporting to European Regulatory Authorities	N/A	<p><b>14.2.4. Reporting to European Regulatory Authorities</b></p> <p><b>The Sponsor or its designee is responsible for SUSAR notification to the relevant regulatory authorities as outlined in the ICH Guidelines. All investigators participating in the study will also be informed as required by regulations.</b></p> <p><b>Any SUSAR is subject to expedited reporting in the EU. The Sponsor or its designee, will report any single SUSAR to the appropriate National CAs and IECs within 7 days if the SUSAR is life-threatening or fatal (with</b></p>	<i>Section on EU Regulatory Reporting was omitted from previous amendment and added due to trial occurring throughout EU.</i>

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			<p><b>the relevant follow-up information subsequently communicated within an additional eight days), and within 15 days if the SUSAR is neither life-threatening nor fatal. SUSARs reported will be those that have arisen in the present clinical trial and SUSARs that have arisen in other clinical trials conducted by the Sponsor with the same medicinal product.</b></p> <p><b>In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to competent authorities of the concerned Member States and to IEC(s)/IRBs as required by national laws.</b></p>	



**Summary of Changes**  
**Protocol-547-SSE-301 (Adults Only)**  
**Dated 18 AUG 2016**

The following changes were made to the attached protocol in this amendment. Minor typographical/editorial errors throughout the document were also corrected.

<b>Section number and title in Protocol Amendment 1, (27 MAY 15)</b>	<b>Section number and title in Protocol Amendment 4, Adults Only (18 AUG 16)</b>	<b>Original text:</b>	<b>Changed to:</b>	<b>Rationale</b>
2. Study Synopsis/Study Sites/Number of Subjects	2. Study Synopsis/Study Sites/Number of Subjects	Up to 150 sites in the USA, Europe, and Canada.  The study will randomize 140 subjects at up to 150 sites.	Up to <b>180</b> sites in the USA, <b>Israel</b> , Europe, and Canada.  The study will randomize 140 subjects at up to <b>180</b> sites  <i>Change also featured on page 44</i>	<i>Oversight in Amendment 1, addition of Israel to country list to yield 180 total sites</i>
2. Study synopsis / population	2. Study synopsis / population	Subjects will be aged two years or more, in SRSE (as defined in the Inclusion Criteria Section 8.1), and being managed in an intensive care setting.	Subjects will be aged 18 years or more, in SRSE (as defined in the Inclusion Criteria Section 8.1), and being managed in an intensive care setting.  <i>Note: revision also appears in Section 8.1.</i>	<i>According to request from the Ethics Committee to exclude children</i>
2. Synopsis: Study Design	2. Synopsis: Study Design	The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a	The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view	<i>Allowing burst or seizure suppression during screening period, prior to</i>

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		view to initiating burst suppression with a third-line agent.	to initiating burst <b>or seizure</b> suppression with a third-line agent.  <i>Note: 'seizure suppression' revised throughout document with regards to EEG suppression goals for managing RSE and SRSE patients, as well as permitting 'seizure suppression' during screening period, prior to initiation of qualifying wean (QW).</i>	<i>initiation of QW, allows sites to use a less restrictive approach achieving EEG suppression and one more typical to sites' standard of care when screening patients.</i>
2. Study Synopsis/Study Design	2. Study Synopsis/Study Design	Burst suppression must be maintained for the first 12 hours of the infusion of study drug.	Burst suppression must be maintained for the first 12 hours of the infusion of <b>blinded</b> study drug.  <i>Change also featured on pages 5-6, &amp; 40-41</i>	<i>Clarification on mandatory burst suppression time frame during blinded infusion treatment phase only</i>
2. Study Synopsis/Study Design	2. Study Synopsis/Study Design	These subjects will be consented for the study after admission to the intensive care unit, but before any third-line agents are administered for burst suppression.	These subjects will be consented for the study after admission to the intensive care unit, before <b>or after</b> any third-line agents are administered for burst <b>or seizure</b> suppression.  <i>Note: revision also appears in Sec.</i>	<i>Clarification that subjects may be administered third-line anesthetic agents for EEG burst or seizure suppression prior</i>

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			7.1.	<i>to or following the consent procedure.</i>
2. Study Synopsis/Study Design	2. Study Synopsis/Study Design	Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within six hours of the investigator's determination that they failed the QW.	Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within <b>eight</b> hours of the investigator's determination that they failed the QW.  <i>Note: revision also appears in Sections 7.1, 10.1, 11.2.4, and 12.2.</i>	<i>Extending time frame from failure of QW to when blinded infusion begins will provide greater flexibility for study teams to mobilize and coordinate pre-treatment activities.</i>
2. Study Synopsis/Study Design	2. Study Synopsis/Study Design	The randomization will be stratified by concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).	The randomization will be stratified by concomitant pentobarbital/ <b>thiopental</b> use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).  <i>References to concomitant thiopental use also featured on pages 6, 11, 41-42, 41, 72, &amp; 73</i>	<i>Thiopental added as accepted Third Line Agent barbiturate comparable to Pentobarbital. Randomization will be stratified by concomitant barbiturate use (pentobarbital</i>

Section number and title in Protocol Amendment 1, (27 MAY 15)	Section number and title in Protocol Amendment 4, Adults Only (18 AUG 16)	Original text:	Changed to:	Rationale
				<i>and thiopental), along with prior third-line agent wean attempts.</i>
2. Study synopsis / study objectives	2. Study synopsis / study objectives	To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult and pediatric subjects with SRSE	To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult subjects with SRSE  <i>Note: revision also appears in Section 5.1.</i>	<i>According to request from the Ethics Committee to exclude children</i>
2. Study Synopsis/Study Objectives	2. Study Synopsis/Study Objectives	To evaluate the impact of retreatment with a higher dose SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;	To evaluate the impact of retreatment with a higher dose SAGE-547 infusion in <del>subjects who initially fail to respond to double blind study medication;</del>	<i>Revised the nomenclature in other objectives from retreatment to open-label treatment.</i>
2. Study synopsis / study objectives / endpoints		To evaluate the Modified Rankin Score (mRS) (age $\geq 17$ years).	To evaluate the Modified Rankin Score (mRS)  <i>Note: revision also appears in Sections 5.4, 6.4, 11.2.8.8</i>	<i>According to request from the Ethics Committee to exclude children</i>
2. Study Synopsis/Endpoints	2. Study Synopsis/Endpoints	The same endpoints as described for the primary and secondary	The same endpoints as described for the primary and secondary	<i>Revised the nomenclature in</i>

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		endpoints will be calculated for those subjects who fail to respond to their randomized double blind treatment and are retreated with a higher dose of SAGE-547.	endpoints will be calculated for those subjects <del>who fail to respond to their randomized double blind treatment</del> and are retreated with a higher dose of SAGE-547.	<i>other endpoints to reflect change from retreatment to treatment.</i>
2. Study synopsis / Inclusion criteria	2. Study synopsis / Inclusion criteria	Inclusion criterion # 1: Subjects two (2) years of age and older	Inclusion criterion # 1: Subjects 18 years of age and older  <i><u>Note:</u> revision also appears in Section 8.1</i>	<i>According to request from the Ethics Committee to exclude children</i>
2. Study Synopsis/Inclusion Criteria	2. Study Synopsis/Inclusion Criteria	Inclusion criterion # 2, sub-bullet # 3:  Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst suppression pattern;	Inclusion criterion # 2, sub-bullet # 3:  Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed <b>zero</b> , one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst <b>or seizure</b> suppression pattern;	<i>Clarified that some patients may enter the study having never failed a prior third-line agent wean. These patients will enter the study in Refractory Status Epilepticus (RSE) and the outcome of the protocol-specific QW will determine</i>

Section number and title in Protocol Amendment 1, (27 MAY 15)	Section number and title in Protocol Amendment 4, Adults Only (18 AUG 16)	Original text:	Changed to:	Rationale
			<i>Note: revision also appears in Section 8.1.</i>	<i>whether or not they are in Super-Refractory Status Epilepticus (SRSE).</i>
2. Study Synopsis/Exclusion Criteria	2. Study Synopsis/Exclusion Criteria	Exclusion criterion # 3:  Subjects with SRSE due to anoxic/hypoxic encephalopathy	Exclusion criterion # 3:  Subjects with SRSE due to anoxic/hypoxic encephalopathy <b>with highly malignant/malignant EEG features (Westhall, Rosetti et al. 2016)</b>  <i>Note: revision also appears in Section 8.2.</i>	<i>Clarified EEG features indicative of patients with anoxic/hypoxic encephalopathy to aid Investigator/Sponsor determination to exclude patients meeting this criterion.</i>
2. Study synopsis / Exclusion criteria		Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing underlying neurological disorder	<del>Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing underlying neurological disorder</del>  <i>Note: revision also appears in Section 8.1.</i>	<i>According to request from the Ethics Committee to exclude children</i>
2. Study Synopsis/Exclusion	2. Study Synopsis/Exclusion	Exclusion 5a:	Exclusion 4a:	<i>Revised to clarify the intent of</i>

Section number and title in Protocol Amendment 1, (27 MAY 15)	Section number and title in Protocol Amendment 4, Adults Only (18 AUG 16)	Original text:	Changed to:	Rationale
Criteria	Criteria	a GFR low enough to warrant dialysis for whatever reason, but dialysis is not planned or non-continuous dialysis is planned (that would not adequately remove Captisol®)	a GFR low enough to warrant dialysis <b>but</b> for whatever reason, dialysis <b>that would adequately remove Captisol® is not planned.</b>	<i>Ex.#4a (formerly 5a) (also revised in Sec. 8.2 - Exclusion Criteria)</i>
2. Study Synopsis/Exclusion Criteria	2. Study Synopsis/Exclusion Criteria	Exclusion criterion # 5, sub-bullet 'e':  a do not resuscitate (DNR) order.	Exclusion criterion # 4, sub-bullet 'e':  <del>a do not resuscitate (DNR) order.</del>  <i>Note: revision also appears in Section 8.2 and DNR removed from List of Abbreviations and Definitions of Terms.</i>	<i>Removed DNR as exclusion criterion due to variations of interpretations of DNR across sites.</i>
2. Study Synopsis/Exclusion Criteria	2. Study Synopsis/Exclusion Criteria	Exclusion 9:  Subjects who have been enrolled in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not withdraw or complete and then re-enroll).	Exclusion 8:  Subjects who have been <b>treated or randomized</b> in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not <b>have received study drug/placebo</b> and then re-enroll).  <i>Note: also revised in Sec. 8.2 - Exclusion Criteria</i>	<i>Revised to clarify the intent of Ex.#8</i>

Section number and title in Protocol Amendment 1, (27 MAY 15)	Section number and title in Protocol Amendment 4, Adults Only (18 AUG 16)	Original text:	Changed to:	Rationale
2. Study Synopsis/Analysis of Secondary Efficacy Endpoints	2. Study Synopsis/Analysis of Secondary Efficacy Endpoints	Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are retreated with SAGE-547.	Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who <b>are</b> treated with <b>a higher dose</b> of SAGE-547.	<i>Revised the nomenclature in statistical methods to reflect change from retreatment to treatment with a higher dose of SAGE-547.</i>
Table 2: Schedule of Assessments: Two Infusions of Study Drug (one blinded, one open-label)	Table 2: Schedule of Assessments: Two Infusions of Study Drug (one blinded, one open-label)	NA	Additional assessment added to Visit 9R (145h-168h):  <b>TW Success and Physiologic Brain Activity</b>	<i>Previous omission, corrected for consistency with Sec. 12.5.1 Visit 9/9R</i>
Section 3.4.2 / SAGE-547 Clinical Program in the Treatment of SRSE	Section 3.4.2 / SAGE-547 Clinical Program in the Treatment of SRSE	an ongoing Phase 2 open-label trial, Study 547-SSE-201; a planned open-label, expanded access protocol, Study 547-SSE-302;	<b>a completed</b> Phase 2 open-label trial, Study 547-SSE-201; <b>an ongoing</b> open-label, expanded access protocol, Study 547-SSE-302;	<i>Revised introduction based on current status of clinical program.</i>
Section 7.3 / Blinding and Randomization	Section 7.3 / Blinding and Randomization	The second infusion of SAGE-547 will be administered on an open-label basis to subjects who failed the primary endpoint wean.	The second infusion of SAGE-547 will be administered on an open-label basis to subjects who <b>meet the criteria for open-label treatment.</b>	<i>Revised second infusion criteria.</i>



Section number and title in Protocol Amendment 1, (27 MAY 15)	Section number and title in Protocol Amendment 4, Adults Only (18 AUG 16)	Original text:	Changed to:	Rationale
Figure 2: Details of Treatment Administration and Follow-up	Figure 2: Details of Treatment Administration and Follow-up	N/A	'Failure' arrow, with regards to subjects who are considered failures of the blinded infusion, moved from beneath V6 to V10, as V10 is timepoint when decision for open-label treatment is made.	<i>Previous oversight, the modified figure clarifies the timepoint when open-label treatment is determined, at V10.</i>
Section 10.1 / Dosing Schedule (Blinded Infusions)	Section 10.1 / Dosing Schedule (Blinded Infusions)	The infusion rates to accomplish these $\mu\text{g/kg/h}$ doses will be calculated according to the weight of the subject.	The infusion rates to accomplish these $\mu\text{g/kg/h}$ doses will be calculated according to the weight of the subject <b>obtained within the eight-hour window that follows the declaration of the QW failure at V2 and prior to dosing at V3.</b>	<i>The study drug dose is based on the initial pre-dose weight for each six-day infusion.</i>
Section 10.2 / Dosing Schedule (Open-Label Infusions)	Section 10.2 / Dosing Schedule (Open-Label Infusions)	If a subject fails wean from third-line agent(s) or requires re-instatement of third-line therapy within 24 hours of discontinuing the initial infusion of study drug, SAGE-547 Injection will be re-administered according to the dosing schedule in Table 6. The infusion rates to accomplish these $\mu\text{g/kg/h}$ doses will be calculated	<b>Those subjects that qualify for the open-label study drug will be administered SAGE-547 Injection according to the dosing schedule in Table 6. The dose will be administered on a <math>\mu\text{g/kg/h}</math> basis, and the subject's weight measured prior to dosing during V10 will be used to calculate the doses.</b>	<i>The study drug dose is based on the initial pre-dose weight for each six-day infusion.</i>

Section number and title in Protocol Amendment 1, (27 MAY 15)	Section number and title in Protocol Amendment 4, Adults Only (18 AUG 16)	Original text:	Changed to:	Rationale
		according to the weight of the subject. These infusion rates will be applied to SAGE-547 re-treatment for the open-label second infusions of study medication.		
10.5 Concomitant Medications, Procedures and Treatments	10.5 Concomitant Medications, Procedures and Treatments	Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. All concomitant medications, procedures, and treatments should be documented throughout the study from Screening through Visit 12/12R and recorded on the eCRF.	Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. <b>For all randomized and the first 50 qualifying wean success (QWS) subjects, detailed information on all concomitant medications (concomitant AEDs, third-line agents, pressors, and other concomitant medications), procedures, and treatments should be documented throughout the study from Screening through Visit 12/12R, as described</b>	<i>Specified the intent to collect minimal data on QWS subjects, following enrollment of 50 QWS subjects.</i>

<b>Section number and title in Protocol Amendment 1, (27 MAY 15)</b>	<b>Section number and title in Protocol Amendment 4, Adults Only (18 AUG 16)</b>	<b>Original text:</b>	<b>Changed to:</b>	<b>Rationale</b>
			<b>below, and recorded on the eCRF. For subsequent QWS subjects, after the detailed information on all concomitant AEDs, pressors, third-line agents, procedures, and treatments collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant AED or pressor, third-line agent, procedure, and/or treatment, and the start and stop dates and times) from Visit 3 through Visit 12 will be recorded in the eCRF. For subsequent QWS subjects, after the detailed information on all concomitant medications collected during the screening period (Visits 1 and 2) has been recorded, only minimal information, to include the name of the concomitant medications and indication only</b>	

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			<b>will be recorded from Visit 3 through Visit 12.</b>  <i>Note: revision appears in SOA footnotes</i>	
11.1.1.1 Weaning	11.1.1.1 Weaning	<ul style="list-style-type: none"> <li>• Pentobarbital: 1 mg/kg/hour</li> <li>• Midazolam: 0.1 mg/kg/hour</li> <li>• Propofol: 3 mg/kg/hour</li> <li>• Ketamine 1.2 mg/kg/hour</li> </ul>	<ul style="list-style-type: none"> <li>• Pentobarbital: 1 mg/kg/hour</li> <li>• <b>Thiopental: 3 mg/kg/hour</b></li> <li>• Midazolam: 0.1 mg/kg/hour</li> <li>• Propofol: 3 mg/kg/hour</li> <li>• Ketamine 1.2 mg/kg/hour</li> </ul>	<i>Thiopental added as accepted Third Line Agent</i>
11.1.1.1 Weaning	11.1.1.1 Weaning	The Clinical Standardization Team will be able to review EEGs in real time related to key study timepoints (qualifying wean, terminal wean, and the period after the end of the blinded study drug infusion) in order to provide advice about compliance with the Clinical Standardization Guidelines.	The Clinical Standardization Team will be able to <b>discuss</b> EEGs related to key study timepoints ( <del>qualifying wean</del> , terminal wean, and the period after the end of the blinded study drug infusion <b>if the terminal wean was successful</b> ) in a <b>timely manner</b> in order to provide advice about compliance with the Clinical Standardization Guidelines.	<i>Removed guidelines for CST review of QWEEG; Clarification on the CST communication process and CST expectations on advising sites on the CSGs</i>
Section 11.1.1.1/Weaning	Section 11.1.1.1/Weaning	The following guidance for weaning applies to all weans of	The following guidance for weaning applies to all weans of	<i>Additional guidance</i>

Section number and title in Protocol Amendment 1, (27 MAY 15)	Section number and title in Protocol Amendment 4, Adults Only (18 AUG 16)	Original text:	Changed to:	Rationale
		third-line agents undertaken during the study.	third-line agents undertaken during the study. <b>Continued determined efforts to liberate subjects from sedation must be undertaken for the entire duration of the blinded study drug infusion. Each failed wean from third-line agents should be followed by a 6-24 hour period of suppression and then another wean attempt, with further optimization of the AED regimen.</b>	<i>provided for third-line agent weaning during blinded and open-label treatment courses</i>
11.1.1.2 EEG	11.1.1.2 EEG	A six-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst suppression for the second path to eligibility, and a variable pattern for the third path to eligibility. EEG will be performed to cover the qualifying wean (QWEEG).	A <b>24</b> -hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst <b>or seizure</b> suppression for the second path to eligibility, and a variable pattern for the third path to eligibility. <b>This EEG also aims to capture the burst or seizure suppression pattern during the 24</b>	<i>Extended the Consent EEG to capture as much of the burst suppression period prior to the Qualifying Wean as possible.</i>  <i>Extended the QWEEG to match QW Guidance in Sec. 11.1.1.1 for Investigators to</i>

Section number and title in Protocol Amendment 1, (27 MAY 15)	Section number and title in Protocol Amendment 4, Adults Only (18 AUG 16)	Original text:	Changed to:	Rationale
		<p>EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for the one hour after the end of the QW. The duration of the QWEEG will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s) or the decision to re-institute a third-line agent(s) at doses intended to induce burst suppression. EEG will be performed from three hours prior to the start of the blinded infusion to five hours after the start of the blinded infusion. This will be called the BIEEG. The intent of this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG.</p>	<p><b>hours that precede the QW. If the CEEG does not capture the 24 hours that precede the QW, additional EEG data collected as standard of care prior to the CEEG and prior to the QW may be collected to assess the depth of burst or seizure suppression in the 24 hour period prior to the QW.</b></p> <ul style="list-style-type: none"> <li>• EEG will be performed to cover the qualifying wean (QWEEG). EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for <b>up to 24 hours</b> after the end of the QW. The duration of the QWEEG will be up to <b>48.5</b> hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s), the decision to re-institute a third-</li> </ul>	<p><i>allow 24 hours to lapse after the end of QW before declaring QW success.</i></p> <p><i>Extended the BIEEG to capture the burst suppression period during the initial 12 hours of the blinded infusion.</i></p>

Section number and title in Protocol Amendment 1, (27 MAY 15)	Section number and title in Protocol Amendment 4, Adults Only (18 AUG 16)	Original text:	Changed to:	Rationale
			<p>line agent(s) at doses intended to induce burst <b>or seizure</b> suppression, <b>and the decision that the QW is a success.</b></p> <ul style="list-style-type: none"> <li>• EEG will be performed from three hours prior to the start of the blinded infusion to <b>12</b> hours after the start of the blinded infusion. This will be called the BIEEG. The intent of this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG <b>and to assess the depth of burst suppression in the first 12 hours of blinded study drug infusion.</b></li> </ul>	
11.1.1.2 EEG	11.1.1.2 EEG	to provide relief to the scalp from the irritating effects of the electrodes are advised particularly in children, according to local practice	to provide relief to the scalp from the irritating effects of the electrodes are advised, according to local practice	<i>According to request from the Ethics Committee to exclude children</i>
11.1.1.2 EEG	11.1.1.2 EEG	<ul style="list-style-type: none"> <li>• For the QWEEG, the PI will note the date and time of the</li> </ul>	<ul style="list-style-type: none"> <li>• For the QWEEG, the PI will note the date and time of the</li> </ul>	<i>Clarification on Investigator</i>

Section number and title in Protocol Amendment 1, (27 MAY 15)	Section number and title in Protocol Amendment 4, Adults Only (18 AUG 16)	Original text:	Changed to:	Rationale
		start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure on the qualifying wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the qualifying wean)	start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure <b>or success</b> on the qualifying wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst <b>or seizure</b> suppression during the qualifying wean <b>constitutes a failure</b> ); <b>the QWEEG will extend to cover the 24 hours after the end of third line agents in order to confirm that the QW was a success.</b>	<i>assessment of the Qualifying Wean and the duration of the QWEEG.</i>
11.1.1.2 EEG	11.1.1.2 EEG	A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period	A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm <b>the depth of burst suppression prior to the QW and during the first 12 hours of the blinded study drug infusion, the</b> PI assessment of response or non-response to blinded study	<i>Added the Consent EEG (CEEG) and Blinded Infusion EEG (BIEEG) to the EEG records to be read centrally to capture the depth of burst</i>



Section number and title in Protocol Amendment 1, (27 MAY 15)	Section number and title in Protocol Amendment 4, Adults Only (18 AUG 16)	Original text:	Changed to:	Rationale
		<p>(average EEG power at the end of Visit 9 of more than two microvolts):</p> <ul style="list-style-type: none"> <li>• All subjects will have the CEEG and QWEEG collected and stored, and the QWEEG read;</li> <li>• Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;</li> <li>• Those subjects randomized who are not retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read;</li> <li>• Those subjects randomized who are retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the</li> </ul>	<p>medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period (average EEG power at the end of Visit 9 of more than two microvolts):</p> <ul style="list-style-type: none"> <li>• All subjects will have the CEEG and QWEEG collected and stored, and the <b>CEEG and</b> QWEEG read;</li> <li>• Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;</li> <li>• Those subjects randomized who are not <b>administered the open-label study drug</b> will have the <b>QWEEG</b>, BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the <b>BIEEG</b>, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read;</li> </ul>	<p><i>suppression prior to Qualifying Wean and during the first 12 hours of the blinded infusion.</i></p>

Section number and title in Protocol Amendment 1, (27 MAY 15)	Section number and title in Protocol Amendment 4, Adults Only (18 AUG 16)	Original text:	Changed to:	Rationale
		blinded study drug infusion and the TWEEG, TAEED, and PAEEG related to the open-label study drug infusion collected and stored, and the QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read.	<ul style="list-style-type: none"> <li>Those subjects randomized who <b>later undergo the open-label infusion</b> will have the <b>QWEEG</b>, BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion and the TWEEG, TAEED, and PAEEG related to the open-label study drug infusion collected and stored, and the <b>BIEEG</b>, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read.</li> </ul>	
11.2.2.1. Hematology and Serum Chemistry	11.2.2.1. Hematology and Serum Chemistry	Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose.	Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose. <b>In addition triglycerides will be measured in serum chemistry samples (to aid</b>	<i>Addition of Triglycerides to Serum Chemistry panel to assist with PK sample analysis</i>

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			<b>assessment of lipemia in pharmacokinetic samples).</b>	
11.2.2.2. Pregnancy Test		Blood will be collected from female subjects 10 years to 55 years	Blood will be collected from female subjects 18 years to 55 years  <i>Note: revision also appears in Sections 12.1.</i>	<i>According to request from the Ethics Committee to exclude children</i>
11.2.4. Weight and Height	11.2.4. Weight and Height	Weight and height will be measured at Visit 1 and weight will also be measured once during each 24 hour period of the first infusion of study drug, and of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547. These daily weights will be used to modify the dose of SAGE-547 if required.	Weight and height will be measured at Visit 1. <b>Weight will also be obtained at V2, within the eight hour window that follows the declaration of the QW failure and prior to the initiation of the blinded infusion loading dose at H0 of V3, and will be used to calculate the infusion rates throughout the entire blinded treatment course. If a subject qualifies for open-label study drug, the infusion rates for the open-label infusion will be calculated using the subject's weight measured prior to dosing during V10. If it is not possible to obtain the</b>	<i>Clarification on process for obtaining daily weight for dosing.</i>

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			actual weight at the above-referenced timepoints, permission from the Clinical Monitor must be obtained to use another method to obtain the subject's weight (such as information from the LAR or estimating using an established local protocol). In addition, a daily weight will be obtained and recorded if this is easily obtained, such as the use of a scale bed.	
11.2.5 ECG	11.2.5 ECG	12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug...	<p><b>For the first 50 subjects randomized in the study</b>, 12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug...</p> <p><b>For the subsequent subjects randomized in the study, the following timepoints for ECG will be used:</b></p> <ul style="list-style-type: none"> <li>• pre-dose and at +1 +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start</li> </ul>	<i>Clarified the number of ECG timepoints required based on order of randomization, including the window for ECG collection and relation to PK draws.</i>

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			<p><b>of the blinded (first) study drug infusion</b></p> <ul style="list-style-type: none"> <li><b>pre-dose and at +1 +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the open-label (second) study drug infusion</b></li> </ul> <p><b>It is not necessary to collect these ECGs with the PK samples at these timepoints and, apart from the +1h ECG, there is +/- 2 hour time window for these ECGs.</b></p> <p><i>Note: revision also made to SOA footnotes and throughout Sec. 12</i></p>	
11.2.8.1. Pharmacokinetic Data	11.2.8.1. Pharmacokinetic Data	Formal plasma <b>and urine</b> analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS))	Formal plasma analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS))	<i>Deletion of urine PK analysis; inadvertent carry-over from Protocol ver. 1 to Protocol Amendment 1</i>
11.2.8.1 Pharmacokinetic	11.2.8.1 Pharmacokinetic	All samples will also be analyzed for plasma concentrations of	All samples <b>from the first 50 subjects randomized</b> will also be	<i>Created an upper limit on Captisol®</i>

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Data	Data	Captisol®.	analyzed for plasma concentrations of Captisol®.	<i>samples that will be analyzed by PK vendor.</i>
11.2.8.1. Pharmacokinetic Data		Each blood sample will be 3 ml in volume for adults and children subjects weighing 30 kg or more, and 12 ml in volume for children subjects weighing less than 30 kg.	Each blood sample will be 3 ml in volume for adults subjects weighing 30 kg or more, and 12 ml in volume for subjects weighing less than 30 kg	<i>According to request from the Ethics Committee to exclude children</i>
11.2.8.1. Pharmacokinetic Data	11.2.8.1. Pharmacokinetic Data	<u>Other Analysis</u> If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations.	<u>Other Analysis</u> If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations. <b>The minimum volume of cerebrospinal fluid for analysis is 100 microlitres.</b>	<i>Specification of the minimum volume of cerebrospinal fluid.</i>
12.3.1. Visit 3/3R	12.3.1. Visit 3/3R	<ul style="list-style-type: none"> <li>Completion of the FOUR Score</li> <li>– +24 hours (+/- 2 hours) after the start of the infusion</li> </ul>	<ul style="list-style-type: none"> <li>Completion of the FOUR Score</li> <li>– +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score</li> </ul>	<i>Clarification on FOUR Score assessment timeframe for Qualifying Wean</i>

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		(QWS subjects complete FOUR Score at some time in the 24 hours following the end of the QW)	at some time in the 24 hours following <b>the final declaration of QW success</b> )	<i>Successes (QWS)</i>
12.5.2. Visit 10/10R	12.5.2. Visit 10/10R	<ul style="list-style-type: none"> <li>At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine retreatment with higher dose of study drug. All patients for retreatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.</li> </ul>	<ul style="list-style-type: none"> <li>At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine <b>eligibility for the open-label treatment</b> with the higher dose of study drug. <b>This determination may occur at any point during Visit 10: the higher dose open-label infusion must begin within the Visit 10 window.</b> All patients receiving the higher dose open-label treatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.</li> </ul>	<i>Clarification on Visit 10 retreatment eligibility and retreatment infusion window.</i>
14.1.4 Medical Monitor and Emergency Contact	14.1.4 Medical Monitor and Emergency Contact	[REDACTED], MD [REDACTED]	[REDACTED], MD [REDACTED]	<i>Updated [REDACTED] global 24/7 Medical Monitor</i>

Section number and title in Protocol Amendment 1, (27 MAY 15)	Section number and title in Protocol Amendment 4, Adults Only (18 AUG 16)	Original text:	Changed to:	Rationale
Information	Information	<div data-bbox="745 427 1205 581" style="background-color: black; height: 95px; width: 100%;"></div>	<div data-bbox="1215 427 1696 581" style="background-color: black; height: 95px; width: 100%;"></div> <p data-bbox="1220 613 1692 862"><b>In a study related medical emergency situation, when the assigned Medical Monitor cannot be reached by a caller, an on-call Physician can be reached 24 hours per day, 7 days per week via an [REDACTED] Call-Center:</b></p> <ul data-bbox="1220 906 1692 1182" style="list-style-type: none"> <li>• <b>Telephone:</b> [REDACTED] (this is a chargeable telephone number allowing a global reach from both landlines and mobile phones)</li> <li>• [REDACTED]</li> </ul> <p data-bbox="1220 1198 1692 1365"><b>On this internet page a list of country-specific toll-free telephone numbers is provided. It should be noted that not all countries globally have access to</b></p>	<p data-bbox="1711 427 1950 532"><i>and on-call physician contact information.</i></p>



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			<b>toll-free numbers as indicated on the “24/7 Medical Help desk” index. Countries without toll-free numbers need to dial the chargeable number as indicated above. Furthermore, toll-free numbers are not available from mobile phones.</b>	
N/A	14.2.4 Reporting to European Regulatory Authorities	N/A	<p><b>14.2.4. Reporting to European Regulatory Authorities</b></p> <p><b>The Sponsor or its designee is responsible for SUSAR notification to the relevant regulatory authorities as outlined in the ICH Guidelines. All investigators participating in the study will also be informed as required by regulations.</b></p> <p><b>Any SUSAR is subject to expedited reporting in the EU. The Sponsor or its designee, will report any single SUSAR to the appropriate National CAs and</b></p>	<i>Section on EU Regulatory Reporting was omitted from previous amendment and added due to trial occurring throughout EU.</i>

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			<p><b>IECs within 7 days if the SUSAR is life-threatening or fatal (with the relevant follow-up information subsequently communicated within an additional eight days), and within 15 days if the SUSAR is neither life-threatening nor fatal. SUSARs reported will be those that have arisen in the present clinical trial and SUSARs that have arisen in other clinical trials conducted by the Sponsor with the same medicinal product.</b></p> <p><b>In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to competent authorities of the concerned Member States and to IEC(s)/IRBs as required by national laws.</b></p>	

**Summary of Changes****Protocol-547-SSE-301 (Adults Only) Denmark specific****Dated 18 AUG 2016**

The following changes were made to the attached protocol in this amendment. Minor typographical/editorial errors throughout the document were also corrected.

<b>Section number and title in Protocol Amendment 1, Denmark specific (01 MAR 16)</b>	<b>Section number and title in Protocol Amendment 4, Adults Only Denmark specific (18 AUG 16)</b>	<b>Original text:</b>	<b>Changed to:</b>	<b>Rationale</b>
2. Study Synopsis/Study Sites/Number of Subjects	2. Study Synopsis/Study Sites/Number of Subjects	Up to 150 sites in the USA, Europe, and Canada.  The study will randomize 140 subjects at up to 150 sites.	Up to <b>180</b> sites in the USA, <b>Israel</b> , Europe, and Canada.  The study will randomize 140 subjects at up to <b>180</b> sites  <i>Change also featured on page 44</i>	<i>Oversight in Amendment 1, addition of Israel to country list to yield 180 total sites</i>
2. Study synopsis / population	2. Study synopsis / population	Subjects will be aged two years or more, in SRSE (as defined in the Inclusion Criteria Section 8.1), and being managed in an intensive care setting.	Subjects will be aged 18 years or more, in SRSE (as defined in the Inclusion Criteria Section 8.1), and being managed in an intensive care setting. <i>Note: revision also appears in Section 8.1.</i>	<i>According to Danish Medicine Agency request to exclude children</i>
2. Synopsis: Study Design	2. Synopsis: Study Design	The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first-	The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and	<i>Allowing burst or seizure suppression during screening</i>

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		and second-line therapies, with a view to initiating burst suppression with a third-line agent.	second-line therapies, with a view to initiating burst <b>or seizure</b> suppression with a third-line agent.  <i>Note: 'seizure suppression' revised throughout document with regards to EEG suppression goals for managing RSE and SRSE patients, as well as permitting 'seizure suppression' during screening period, prior to initiation of qualifying wean (QW).</i>	<i>period, prior to initiation of QW, allows sites to use a less restrictive approach achieving EEG suppression and one more typical to sites' standard of care when screening patients.</i>
2. Study Synopsis/Study Design	2. Study Synopsis/Study Design	Burst suppression must be maintained for the first 12 hours of the infusion of study drug.	Burst suppression must be maintained for the first 12 hours of the infusion of <b>blinded</b> study drug.  <i>Change also featured on pages 5-6, &amp; 40-41</i>	<i>Clarification on mandatory burst suppression time frame during blinded infusion treatment phase only</i>
2. Study Synopsis/Study Design	2. Study Synopsis/Study Design	These subjects will be consented for the study after admission to the intensive care unit, but before any third-line agents are administered for burst suppression.	These subjects will be consented for the study after admission to the intensive care unit, before <b>or after</b> any third-line agents are administered for burst <b>or seizure</b> suppression.	<i>Clarification that subjects may be administered third-line anesthetic agents for EEG burst or</i>

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			<i>Note: revision also appears in Sec. 7.1.</i>	<i>seizure suppression prior to or following the consent procedure.</i>
2. Study Synopsis/Study Design	2. Study Synopsis/Study Design	Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within six hours of the investigator's determination that they failed the QW.	Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within <b>eight</b> hours of the investigator's determination that they failed the QW.  <i>Note: revision also appears in Sections 7.1, 10.1, 11.2.4, and 12.2.</i>	<i>Extending time frame from failure of QW to when blinded infusion begins will provide greater flexibility for study teams to mobilize and coordinate pre-treatment activities.</i>
2. Study Synopsis/Study Design	2. Study Synopsis/Study Design	The randomization will be stratified by concomitant pentobarbital use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).	The randomization will be stratified by concomitant pentobarbital/ <b>thiopental</b> use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs two or more).	<i>Thiopental added as accepted Third Line Agent barbiturate comparable to Pentobarbital. Randomization will be stratified</i>

Section number and title in Protocol Amendment 1, Denmark specific (01 MAR 16)	Section number and title in Protocol Amendment 4, Adults Only Denmark specific (18 AUG 16)	Original text:	Changed to:	Rationale
			<i>References to concomitant thiopental use also featured on pages 6, 11, 41-42, 41, 72, &amp; 73</i>	<i>by concomitant barbiturate use (pentobarbital and thiopental), along with prior third-line agent wean attempts.</i>
2. Study synopsis / study objectives	2. Study synopsis / study objectives	To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult and pediatric subjects with SRSE	To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult subjects with SRSE  <i>Note: revision also appears in Section 5.1.</i>	<i>According to Danish Medicine Agency request to exclude children</i>
2. Study Synopsis/Study Objectives	2. Study Synopsis/Study Objectives	To evaluate the impact of retreatment with a higher dose SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;	To evaluate the impact of retreatment with a higher dose SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;	<i>Revised the nomenclature in other objectives from retreatment to open-label treatment.</i>
2. Study synopsis / study objectives / endpoints		To evaluate the Modified Rankin Score (mRS) (age $\geq 17$ years).	To evaluate the Modified Rankin Score (mRS)	<i>According to Danish Medicine Agency request to</i>

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			<i>Note: revision also appears in Sections 5.4, 6.4, 11.2.8.8</i>	<i>exclude children</i>
2. Study Synopsis/Endpoints	2. Study Synopsis/Endpoints	The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who fail to respond to their randomized double blind treatment and are retreated with a higher dose of SAGE-547.	The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects <del>who fail to respond to their randomized double blind treatment and</del> are retreated with a higher dose of SAGE-547.	<i>Revised the nomenclature in other endpoints to reflect change from retreatment to treatment.</i>
2. Study synopsis / Inclusion criteria	2. Study synopsis / Inclusion criteria	Inclusion criterion # 1: Subjects two (2) years of age and older	Inclusion criterion # 1: Subjects 18 years of age and older  <i>Note: revision also appears in Section 8.1</i>	<i>According to Danish Medicine Agency request to exclude children</i>
2. Study Synopsis/Inclusion Criteria	2. Study Synopsis/Inclusion Criteria	Inclusion criterion # 2, sub-bullet # 3:  Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed one or more wean attempts from third-line	Inclusion criterion # 2, sub-bullet # 3:  Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed <b>zero</b> , one or more wean attempts from third-line agents and	<i>Clarified that some patients may enter the study having never failed a prior third-line agent wean. These patients will enter the study in Refractory Status</i>

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		agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst suppression pattern;	are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst <b>or seizure</b> suppression pattern;  <i>Note: revision also appears in Section 8.1.</i>	<i>Epilepticus (RSE) and the outcome of the protocol-specific QW will determine whether or not they are in Super-Refractory Status Epilepticus (SRSE).</i>
2. Study Synopsis/Exclusion Criteria	2. Study Synopsis/Exclusion Criteria	Exclusion criterion # 3:  Subjects with SRSE due to anoxic/hypoxic encephalopathy	Exclusion criterion # 3:  Subjects with SRSE due to anoxic/hypoxic encephalopathy <b>with highly malignant/malignant EEG features (Westhall, Rosetti et al. 2016)</b>  <i>Note: revision also appears in Section 8.2.</i>	<i>Clarified EEG features indicative of patients with anoxic/hypoxic encephalopathy to aid Investigator/Sponsor determination to exclude patients meeting this criterion.</i>
2. Study synopsis / Exclusion criteria		Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing	<del>Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing underlying</del>	<i>According to Danish Medicine Agency request to</i>



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		underlying neurological disorder	<del>neurological disorder</del> <i>Note: revision also appears in Section 8.1.</i>	<i>exclude children</i>
2. Study Synopsis/Exclusion Criteria	2. Study Synopsis/Exclusion Criteria	Exclusion 5a:  a GFR low enough to warrant dialysis for whatever reason, but dialysis is not planned or non-continuous dialysis is planned (that would not adequately remove Captisol®)	Exclusion 4a:  a GFR low enough to warrant dialysis <b>but</b> for whatever reason, dialysis <b>that would adequately remove Captisol® is not planned.</b>	<i>Revised to clarify the intent of Ex.#4a (formerly 5a) (also revised in Sec. 8.2 - Exclusion Criteria)</i>
2. Study Synopsis/Exclusion Criteria	2. Study Synopsis/Exclusion Criteria	Exclusion criterion # 5, sub-bullet 'e':  a do not resuscitate (DNR) order.	Exclusion criterion # 4, sub-bullet 'e':  <del>a do not resuscitate (DNR) order.</del> <i>Note: revision also appears in Section 8.2 and DNR removed from List of Abbreviations and Definitions of Terms.</i>	<i>Removed DNR as exclusion criterion due to variations of interpretations of DNR across sites.</i>
2. Study Synopsis/Exclusion Criteria	2. Study Synopsis/Exclusion Criteria	Exclusion 9:  Subjects who have been enrolled in this trial or any other trial	Exclusion 8:  Subjects who have been <b>treated or randomized</b> in this trial or any	<i>Revised to clarify the intent of Ex.#8</i>

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		employing SAGE-547 previously (i.e., subjects may not withdraw or complete and then re-enroll).	other trial employing SAGE-547 previously (i.e., subjects may not <b>have received study drug/placebo</b> and then re-enroll).  <i>Note: also revised in Sec. 8.2 - Exclusion Criteria</i>	
2. Study Synopsis/Analysis of Secondary Efficacy Endpoints	2. Study Synopsis/Analysis of Secondary Efficacy Endpoints	Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are retreated with SAGE-547.	Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who <b>are</b> treated with a <b>higher dose</b> of SAGE-547.	<i>Revised the nomenclature in statistical methods to reflect change from retreatment to treatment with a higher dose of SAGE-547.</i>
Table 2: Schedule of Assessments: Two Infusions of Study Drug (one blinded, one open-label)	Table 2: Schedule of Assessments: Two Infusions of Study Drug (one blinded, one open-label)	NA	Additional assessment added to Visit 9R (145h-168h):  <b>TW Success and Physiologic Brain Activity</b>	<i>Previous omission, corrected for consistency with Sec. 12.5.1 Visit 9/9R</i>
Section 3.4.2 / SAGE-547 Clinical Program in the	Section 3.4.2 / SAGE-547 Clinical Program in the	an ongoing Phase 2 open-label trial, Study 547-SSE-201; a planned open-label, expanded	<b>a completed</b> Phase 2 open-label trial, Study 547-SSE-201; <b>an ongoing</b> open-label, expanded	<i>Revised introduction based on current</i>

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Treatment of SRSE	Treatment of SRSE	access protocol, Study 547-SSE-302;	access protocol, Study 547-SSE-302;	<i>status of clinical program.</i>
Section 7.3 / Blinding and Randomization	Section 7.3 / Blinding and Randomization	The second infusion of SAGE-547 will be administered on an open-label basis to subjects who failed the primary endpoint wean.	The second infusion of SAGE-547 will be administered on an open-label basis to subjects who <b>meet the criteria for open-label treatment.</b>	<i>Revised second infusion criteria.</i>
Figure 2: Details of Treatment Administration and Follow-up	Figure 2: Details of Treatment Administration and Follow-up	N/A	'Failure' arrow, with regards to subjects who are considered failures of the blinded infusion, moved from beneath V6 to V10, as V10 is timepoint when decision for open-label treatment is made.	<i>Previous oversight, the modified figure clarifies the timepoint when open-label treatment is determined, at V10.</i>
Section 10.1 / Dosing Schedule (Blinded Infusions)	Section 10.1 / Dosing Schedule (Blinded Infusions)	The infusion rates to accomplish these µg/kg/h doses will be calculated according to the weight of the subject.	The infusion rates to accomplish these µg/kg/h doses will be calculated according to the weight of the subject <b>obtained within the eight-hour window that follows the declaration of the QW failure at V2 and prior to dosing at V3.</b>	<i>The study drug dose is based on the initial pre-dose weight for each six-day infusion.</i>
Section 10.2 / Dosing Schedule	Section 10.2 / Dosing Schedule	If a subject fails wean from third-line agent(s) or requires re-	<b>Those subjects that qualify for the open-label study drug will be</b>	<i>The study drug dose is based on</i>

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(Open-Label Infusions)	(Open-Label Infusions)	instatement of third-line therapy within 24 hours of discontinuing the initial infusion of study drug, SAGE-547 Injection will be re-administered according to the dosing schedule in Table 6. The infusion rates to accomplish these µg/kg/h doses will be calculated according to the weight of the subject. These infusion rates will be applied to SAGE-547 re-treatment for the open-label second infusions of study medication.	<b>administered</b> SAGE-547 Injection according to the dosing schedule in Table 6. <b>The dose will be administered on a µg/kg/h basis, and the subject's weight measured prior to dosing during V10 will be used to calculate the doses.</b>	<i>the initial pre-dose weight for each six-day infusion.</i>
10.5 Concomitant Medications, Procedures and Treatments	10.5 Concomitant Medications, Procedures and Treatments	Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. All concomitant medications, procedures, and treatments should be documented	Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. <b>For all randomized and the first 50 qualifying wean success (QWS) subjects,</b>	<i>Specified the intent to collect minimal data on QWS subjects, following enrollment of 50 QWS subjects.</i>

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		throughout the study from Screening through Visit 12/12R and recorded on the eCRF.	<b>detailed information on all concomitant medications (concomitant AEDs, third-line agents, pressors, and other concomitant medications), procedures, and treatments should be documented throughout the study from Screening through Visit 12/12R, as described below, and recorded on the eCRF. For subsequent QWS subjects, after the detailed information on all concomitant AEDs, pressors, third-line agents, procedures, and treatments collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant AED or pressor, third-line agent, procedure, and/or treatment, and the start and stop dates and times) from Visit 3 through Visit 12 will be</b>	

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			<p>recorded in the eCRF. For subsequent QWS subjects, after the detailed information on all concomitant medications collected during the screening period (Visits 1 and 2) has been recorded, only minimal information, to include the name of the concomitant medications and indication only will be recorded from Visit 3 through Visit 12.</p> <p><i>Note: revision appears in SOA footnotes</i></p>	
11.1.1.1 Weaning	11.1.1.1 Weaning	<ul style="list-style-type: none"> <li>• Pentobarbital: 1 mg/kg/hour</li> <li>• Midazolam: 0.1 mg/kg/hour</li> <li>• Propofol: 3 mg/kg/hour</li> <li>• Ketamine 1.2 mg/kg/hour</li> </ul>	<ul style="list-style-type: none"> <li>• Pentobarbital: 1 mg/kg/hour</li> <li>• <b>Thiopental: 3 mg/kg/hour</b></li> <li>• Midazolam: 0.1 mg/kg/hour</li> <li>• Propofol: 3 mg/kg/hour</li> <li>• Ketamine 1.2 mg/kg/hour</li> </ul>	<i>Thiopental added as accepted Third Line Agent</i>
11.1.1.1 Weaning	11.1.1.1 Weaning	The Clinical Standardization Team will be able to review EEGs	The Clinical Standardization Team will be able to <b>discuss</b> EEGs related	<i>Removed guidelines for</i>

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		in real time related to key study timepoints (qualifying wean, terminal wean, and the period after the end of the blinded study drug infusion) in order to provide advice about compliance with the Clinical Standardization Guidelines.	to key study timepoints ( <del>qualifying wean</del> , terminal wean, and the period after the end of the blinded study drug infusion <b>if the terminal wean was successful</b> ) in a <b>timely manner</b> in order to provide advice about compliance with the Clinical Standardization Guidelines.	<i>CST review of QWEEG; Clarification on the CST communication process and CST expectations on advising sites on the CSGs</i>
Section 11.1.1.1/Weaning	Section 11.1.1.1/Weaning	The following guidance for weaning applies to all weans of third-line agents undertaken during the study.	The following guidance for weaning applies to all weans of third-line agents undertaken during the study. <b>Continued determined efforts to liberate subjects from sedation must be undertaken for the entire duration of the blinded study drug infusion. Each failed wean from third-line agents should be followed by a 6-24 hour period of suppression and then another wean attempt, with further optimization of the AED regimen.</b>	<i>Additional guidance provided for third-line agent weaning during blinded and open-label treatment courses</i>
11.1.1.2 EEG	11.1.1.2 EEG	A six-hour duration EEG will be performed from the time of	A <b>24</b> -hour duration EEG will be performed from the time of consent	<i>Extended the Consent EEG to</i>

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		<p>consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst suppression for the second path to eligibility, and a variable pattern for the third path to eligibility.</p> <p>EEG will be performed to cover the qualifying wean (QWEEG). EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for the one hour after the end of the QW. The duration of the QWEEG will be up to 25.5 hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s) or the decision to re-institute a third-line agent(s) at doses intended to</p>	<p>(CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst <b>or seizure</b> suppression for the second path to eligibility, and a variable pattern for the third path to eligibility. <b>This EEG also aims to capture the burst or seizure suppression pattern during the 24 hours that precede the QW. If the CEEG does not capture the 24 hours that precede the QW, additional EEG data collected as standard of care prior to the CEEG and prior to the QW may be collected to assess the depth of burst or seizure suppression in the 24 hour period prior to the QW.</b></p> <ul style="list-style-type: none"> <li>• EEG will be performed to cover the qualifying wean</li> </ul>	<p><i>capture as much of the burst suppression period prior to the Qualifying Wean as possible.</i></p> <p><i>Extended the QWEEG to match QW Guidance in Sec. 11.1.1.1 for Investigators to allow 24 hours to lapse after the end of QW before declaring QW success.</i></p> <p><i>Extended the BIEEG to capture the burst suppression period during the initial 12 hours of the blinded</i></p>



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		<p>induce burst suppression. EEG will be performed from three hours prior to the start of the blinded infusion to five hours after the start of the blinded infusion. This will be called the BIEEG. The intent of this EEG is to see the effect that the loading dose of blinded study drug infusion has on the EEG.</p>	<p>(QWEEG). EEG will start 30 minutes prior to the start of the QW, continue for up to 24 hours during the QW, and then continue for <b>up to 24 hours</b> after the end of the QW. The duration of the QWEEG will be up to <b>48.5</b> hours. The EEG will therefore include the EEG patterns that correspond to the decision to wean the subject off the third-line agent(s), the decision to re-institute a third-line agent(s) at doses intended to induce burst <b>or seizure</b> suppression, <b>and the decision that the QW is a success.</b></p> <ul style="list-style-type: none"> <li>• EEG will be performed from three hours prior to the start of the blinded infusion to <b>12</b> hours after the start of the blinded infusion. This will be called the BIEEG. The intent of this EEG is to see the effect that the</li> </ul>	<i>infusion.</i>

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			loading dose of blinded study drug infusion has on the EEG <b>and to assess the depth of burst suppression in the first 12 hours of blinded study drug infusion.</b>	
11.1.1.2 EEG	11.1.1.2 EEG	to provide relief to the scalp from the irritating effects of the electrodes are advised particularly in children, according to local practice	to provide relief to the scalp from the irritating effects of the electrodes are advised, according to local practice	<i>According to Danish Medicine Agency request to exclude children</i>
11.1.1.2 EEG	11.1.1.2 EEG	<ul style="list-style-type: none"> <li>For the QWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure on the qualifying wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst suppression during the qualifying wean)</li> </ul>	<ul style="list-style-type: none"> <li>For the QWEEG, the PI will note the date and time of the start of the EEG and the EEG pattern that supported the decision to determine that the subject was a failure <b>or success</b> on the qualifying wean (inability to wean off the third-line agent or the third-line agent reinstituted for burst <b>or seizure</b> suppression during the qualifying wean <b>constitutes a</b></li> </ul>	<i>Clarification on Investigator assessment of the Qualifying Wean and the duration of the QWEEG.</i>

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			<b>failure); the QWEEG will extend to cover the 24 hours after the end of third line agents in order to confirm that the QW was a success.</b>	
11.1.1.2 EEG	11.1.1.2 EEG	<p>A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period (average EEG power at the end of Visit 9 of more than two microvolts):</p> <ul style="list-style-type: none"> <li>• All subjects will have the CEEG and QWEEG collected and stored, and the QWEEG read;</li> <li>• Those subjects who are successful on the QW will not</li> </ul>	<p>A maximum of nine EEG records for each subject will be collected and stored centrally; of these, the following will be read centrally to confirm <b>the depth of burst suppression prior to the QW and during the first 12 hours of the blinded study drug infusion, the</b> PI assessment of response or non-response to blinded study medication, and confirm the presence of physiologic brain activity at the end of the primary endpoint assessment period (average EEG power at the end of Visit 9 of more than two microvolts):</p> <ul style="list-style-type: none"> <li>• All subjects will have the CEEG and QWEEG collected and</li> </ul>	<p><i>Added the Consent EEG (CEEG) and Blinded Infusion EEG (BIEEG) to the EEG records to be read centrally to capture the depth of burst suppression prior to Qualifying Wean and during the first 12 hours of the blinded infusion.</i></p>

Section number and title in Protocol Amendment 1, Denmark specific (01 MAR 16)	Section number and title in Protocol Amendment 4, Adults Only Denmark specific (18 AUG 16)	Original text:	Changed to:	Rationale
		<p>have any further EEGs collected, stored, or read;</p> <ul style="list-style-type: none"> <li>Those subjects randomized who are not retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read;</li> <li>Those subjects randomized who are retreated will have the BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion and the TWEEG, TAEED, and PAEEG related to the open-label study drug infusion collected and stored, and the QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read.</li> </ul>	<p>stored, and the <b>CEEED and</b> QWEEG read;</p> <ul style="list-style-type: none"> <li>Those subjects who are successful on the QW will not have any further EEGs collected, stored, or read;</li> <li>Those subjects randomized who are not <b>administered the open-label study drug</b> will have the <b>QWEEG</b>, BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion collected and stored, and the <b>BIEEG</b>, QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read;</li> <li>Those subjects randomized who <b>later undergo the open-label infusion</b> will have the <b>QWEEG</b>, BIEEG, TWEEG, TAEED and PAEEG related to the blinded study drug infusion and the TWEEG, TAEED, and PAEEG related to the open-</li> </ul>	

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			label study drug infusion collected and stored, and the <b>BIEEG</b> , QWEEG, TWEEG, and PAEEG related to the blinded study drug infusion read.	
11.2.2.1. Hematology and Serum Chemistry	11.2.2.1. Hematology and Serum Chemistry	Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose.	Serum chemistry will include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, bilirubin (total), blood urea nitrogen (BUN), calcium, chloride, creatine kinase, lipase, creatinine, magnesium, potassium, sodium, total protein, and glucose. <b>In addition triglycerides will be measured in serum chemistry samples (to aid assessment of lipemia in pharmacokinetic samples).</b>	<i>Addition of Triglycerides to Serum Chemistry panel to assist with PK sample analysis</i>
11.2.2.2. Pregnancy Test		Blood will be collected from female subjects 10 years to 55 years	Blood will be collected from female subjects 18 years to 55 years  <i>Note: revision also appears in Sections 12.1.</i>	<i>According to Danish Medicine Agency request to exclude children</i>

Section number and title in Protocol Amendment 1, Denmark specific (01 MAR 16)	Section number and title in Protocol Amendment 4, Adults Only Denmark specific (18 AUG 16)	Original text:	Changed to:	Rationale
11.2.4. Weight and Height	11.2.4. Weight and Height	Weight and height will be measured at Visit 1 and weight will also be measured once during each 24 hour period of the first infusion of study drug, and of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547. These daily weights will be used to modify the dose of SAGE-547 if required.	Weight and height will be measured at Visit 1. <b>Weight will also be obtained at V2, within the eight hour window that follows the declaration of the QW failure and prior to the initiation of the blinded infusion loading dose at H0 of V3, and will be used to calculate the infusion rates throughout the entire blinded treatment course. If a subject qualifies for open-label study drug, the infusion rates for the open-label infusion will be calculated using the subject's weight measured prior to dosing during V10. If it is not possible to obtain the actual weight at the above-referenced timepoints, permission from the Clinical Monitor must be obtained to use another method to obtain the subject's weight (such as information from the LAR or estimating using an</b>	<i>Clarification on process for obtaining daily weight for dosing.</i>

Section number and title in Protocol Amendment 1, Denmark specific (01 MAR 16)	Section number and title in Protocol Amendment 4, Adults Only Denmark specific (18 AUG 16)	Original text:	Changed to:	Rationale
			established local protocol). <b>In addition, a daily weight will be obtained and recorded if this is easily obtained, such as the use of a scale bed.</b>	
11.2.5 ECG	11.2.5 ECG	12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug...	<p><b>For the first 50 subjects randomized in the study</b>, 12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug...</p> <p><b>For the subsequent subjects randomized in the study, the following timepoints for ECG will be used:</b></p> <ul style="list-style-type: none"> <li>• pre-dose and at +1 +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the blinded (first) study drug infusion</li> <li>• pre-dose and at +1 +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the open-label (second)</li> </ul>	<i>Clarified the number of ECG timepoints required based on order of randomization, including the window for ECG collection and relation to PK draws.</i>

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			<p><b>study drug infusion</b></p> <p><b>It is not necessary to collect these ECGs with the PK samples at these timepoints and, apart from the +1h ECG, there is +/- 2 hour time window for these ECGs.</b></p> <p><i>Note: revision also made to SOA footnotes and throughout Sec. 12</i></p>	
11.2.8.1. Pharmacokinetic Data	11.2.8.1. Pharmacokinetic Data	Formal plasma <b>and urine</b> analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS))	Formal plasma analysis of SAGE-547 exposure will occur in a central bioanalytical lab with a validated detection method for SAGE-547 (high performance liquid chromatography tandem mass spectrometry (HPLC MS/MS))	<i>Deletion of urine PK analysis; inadvertent carry-over from Protocol ver. 1 to Protocol Amendment 1</i>
11.2.8.1 Pharmacokinetic Data	11.2.8.1 Pharmacokinetic Data	All samples will also be analyzed for plasma concentrations of Captisol®.	All samples <b>from the first 50 subjects randomized</b> will also be analyzed for plasma concentrations of Captisol®.	<i>Created an upper limit on Captisol® samples that will be analyzed by PK vendor.</i>
11.2.8.1. Pharmacokinetic		Each blood sample will be 3 ml in volume for adults and children	Each blood sample will be 3 ml in volume for adults subjects weighing	<i>According to Danish Medicine</i>



Section number and title in Protocol Amendment 1, Denmark specific (01 MAR 16)	Section number and title in Protocol Amendment 4, Adults Only Denmark specific (18 AUG 16)	Original text:	Changed to:	Rationale
Data		subjects weighing 30 kg or more, and 12 ml in volume for children subjects weighing less than 30 kg.	30 kg or more, and 12 ml in volume for subjects weighing less than 30 kg	<i>Agency request to exclude children</i>
11.2.8.1. Pharmacokinetic Data	11.2.8.1. Pharmacokinetic Data	<u>Other Analysis</u> If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations.	<u>Other Analysis</u> If a subject in the study is undergoing a spinal or ventricular tap at the same time as an infusion of study drug, they or their LAR will be asked if they would consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations. <b>The minimum volume of cerebrospinal fluid for analysis is 100 microlitres.</b>	<i>Specification of the minimum volume of cerebrospinal fluid.</i>
12.3.1. Visit 3/3R	12.3.1. Visit 3/3R	<ul style="list-style-type: none"> <li>Completion of the FOUR Score</li> <li>– +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the end of the QW)</li> </ul>	<ul style="list-style-type: none"> <li>Completion of the FOUR Score               <ul style="list-style-type: none"> <li>– +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following <b>the final declaration of QW success</b>)</li> </ul> </li> </ul>	<i>Clarification on FOUR Score assessment timeframe for Qualifying Wean Successes (QWS)</i>

Section number and title in Protocol Amendment 1, Denmark specific (01 MAR 16)	Section number and title in Protocol Amendment 4, Adults Only Denmark specific (18 AUG 16)	Original text:	Changed to:	Rationale
12.5.2. Visit 10/10R	12.5.2. Visit 10/10R	<ul style="list-style-type: none"> <li>At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine retreatment with higher dose of study drug. All patients for retreatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.</li> </ul>	<ul style="list-style-type: none"> <li>At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine <b>eligibility for the open-label treatment</b> with the higher dose of study drug. <b>This determination may occur at any point during Visit 10: the higher dose open-label infusion must begin within the Visit 10 window.</b> All patients receiving the higher dose open-label treatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.</li> </ul>	<i>Clarification on Visit 10 retreatment eligibility and retreatment infusion window.</i>
14.1.4 Medical Monitor and Emergency Contact Information	14.1.4 Medical Monitor and Emergency Contact Information	[REDACTED], MD	[REDACTED], MD	<i>Updated [REDACTED] global 24/7 Medical Monitor and on-call physician contact information.</i>

Section number and title in Protocol Amendment 1, Denmark specific (01 MAR 16)	Section number and title in Protocol Amendment 4, Adults Only Denmark specific (18 AUG 16)	Original text:	Changed to:	Rationale
			<p><b>In a study related medical emergency situation, when the assigned Medical Monitor cannot be reached by a caller, an on-call Physician can be reached 24 hours per day, 7 days per week via an [REDACTED] Call-Center:</b></p> <ul style="list-style-type: none"> <li>• <b>Telephone: [REDACTED]</b> (this is a chargeable telephone number allowing a global reach from both landlines and mobile phones)</li> <li>• [REDACTED]</li> </ul> <p><b>On this internet page a list of country-specific toll-free telephone numbers is provided. It should be noted that not all countries globally have access to toll-free numbers as indicated on the “24/7 Medical Help desk” index. Countries without toll-free</b></p>	

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			numbers need to dial the chargeable number as indicated above. Furthermore, toll-free numbers are not available from mobile phones.	
N/A	14.2.4 Reporting to European Regulatory Authorities	N/A	<p><b>14.2.4. Reporting to European Regulatory Authorities</b></p> <p><b>The Sponsor or its designee is responsible for SUSAR notification to the relevant regulatory authorities as outlined in the ICH Guidelines. All investigators participating in the study will also be informed as required by regulations.</b></p> <p><b>Any SUSAR is subject to expedited reporting in the EU. The Sponsor or its designee, will report any single SUSAR to the appropriate National CAs and IECs within 7 days if the SUSAR is life-threatening or fatal (with</b></p>	<i>Section on EU Regulatory Reporting was omitted from previous amendment and added due to trial occurring throughout EU.</i>

<b>Section number and title in Protocol Amendment 1, Denmark specific (01 MAR 16)</b>	<b>Section number and title in Protocol Amendment 4, Adults Only Denmark specific (18 AUG 16)</b>	<b>Original text:</b>	<b>Changed to:</b>	<b>Rationale</b>
			<p><b>the relevant follow-up information subsequently communicated within an additional eight days), and within 15 days if the SUSAR is neither life-threatening nor fatal. SUSARs reported will be those that have arisen in the present clinical trial and SUSARs that have arisen in other clinical trials conducted by the Sponsor with the same medicinal product.</b></p> <p><b>In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to competent authorities of the concerned Member States and to IEC(s)/IRBs as required by national laws.</b></p>	

**Summary of Changes****Protocol-547-SSE-301 (Adults Only, Germany Specific)****Dated 12 SEP 2016**

The following changes were made to the attached protocol in this amendment. Minor typographical/editorial errors throughout the document were also corrected.

<b>Section number and title in Protocol Amendment 2, Adults Only, Germany Specific (05 JUL 16)</b>	<b>Section number and title in Protocol Amendment 4, Adults Only, Germany Specific (12 SEP 16)</b>	<b>Original text:</b>	<b>Changed to:</b>	<b>Rationale</b>
2. Study Synopsis/Study Sites/Number of Subjects	2. Study Synopsis/Study Sites/Number of Subjects	Up to 180 sites in the USA, Europe, and Canada.	Up to 180 sites in the USA, <b>Israel</b> , Europe, and Canada.	<i>Addition of Israel to country list</i>
2. Synopsis: Study Design	2. Synopsis: Study Design	The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst suppression with a third-line agent.	The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst <b>or seizure</b> suppression with a third-line agent.  <i>Note: 'seizure suppression' revised throughout document with regards to EEG suppression goals for managing RSE and SRSE patients, as well as permitting 'seizure suppression' during screening</i>	<i>Allowing burst or seizure suppression during screening period, prior to initiation of QW, allows sites to use a less restrictive approach achieving EEG suppression and one more typical to sites' standard of care when</i>

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			<i>period, prior to initiation of qualifying wean (QW).</i>	<i>screening patients.</i>
2. Study Synopsis/Study Design	2. Study Synopsis/Study Design	These subjects will be consented for the study after admission to the intensive care unit, but before any third-line agents are administered for burst suppression.	These subjects will be consented for the study after admission to the intensive care unit, before <b>or after</b> any third-line agents are administered for burst <b>or seizure</b> suppression.  <i><u>Note:</u> revision also appears in Sec. 7.1.</i>	<i>Clarification that subjects may be administered third-line anesthetic agents for EEG burst or seizure suppression prior to or following the consent procedure.</i>
2. Study Synopsis/Study Design	2. Study Synopsis/Study Design	Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within six hours of the investigator's determination that they failed the QW.	Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within <b>eight</b> hours of the investigator's determination that they failed the QW.  <i><u>Note:</u> revision also appears in Sections 7.1, 10.1, 11.2.4, and 12.2.</i>	<i>Extending time frame from failure of QW to when blinded infusion begins will provide greater flexibility for study teams to mobilize and coordinate pre-treatment activities.</i>

Section number and title in Protocol Amendment 2, Adults Only, Germany Specific (05 JUL 16)	Section number and title in Protocol Amendment 4, Adults Only, Germany Specific (12 SEP 16)	Original text:	Changed to:	Rationale
2. Study Synopsis/Study Objectives	2. Study Synopsis/Study Objectives	To evaluate the impact of retreatment with a higher dose SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;	To evaluate the impact of <del>retreatment</del> with a higher dose SAGE-547 infusion <del>in subjects who initially fail to respond to double blind study medication;</del>	<i>Revised the nomenclature in other objectives from retreatment to open-label treatment.</i>
2. Study Synopsis/Endpoints	2. Study Synopsis/Endpoints	The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who fail to respond to their randomized double blind treatment and are retreated with a higher dose of SAGE-547.	The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects <del>who fail to respond to their randomized double blind treatment and</del> are retreated with a higher dose of SAGE-547.	<i>Revised the nomenclature in other endpoints to reflect change from retreatment to treatment.</i>
2. Study Synopsis/Inclusion Criteria	2. Study Synopsis/Inclusion Criteria	Inclusion criterion # 2, sub-bullet # 3:  Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed one or more wean attempts from third-line agents and are now on continuous	Inclusion criterion # 2, sub-bullet # 3:  Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed <b>zero</b> , one or more wean attempts from third-line agents and are now on continuous intravenous	<i>Clarified that some patients may enter the study having never failed a prior third-line agent wean. These patients will enter the study in Refractory Status Epilepticus (RSE)</i>



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		intravenous infusions of one or more third-line agent and in an EEG burst suppression pattern;	infusions of one or more third-line agent and in an EEG burst <b>or seizure</b> suppression pattern;  <i>Note: revision also appears in Section 8.1.</i>	<i>and the outcome of the protocol-specific QW will determine whether or not they are in Super-Refractory Status Epilepticus (SRSE).</i>
2. Study Synopsis/Exclusion Criteria	2. Study Synopsis/Exclusion Criteria	Exclusion criterion # 3:  Subjects with SRSE due to anoxic/hypoxic encephalopathy	Exclusion criterion # 3:  Subjects with SRSE due to anoxic/hypoxic encephalopathy <b>with highly malignant/malignant EEG features (Westhall, Rosetti et al. 2016)</b>  <i>Note: revision also appears in Section 8.2.</i>	<i>Clarified EEG features indicative of patients with anoxic/hypoxic encephalopathy to aid Investigator/Sponsor determination to exclude patients meeting this criterion.</i>
2. Study Synopsis/Exclusion Criteria	2. Study Synopsis/Exclusion Criteria	Exclusion 4a:  a GFR low enough to warrant dialysis for whatever reason, but	Exclusion 4a:  a GFR low enough to warrant dialysis <b>but</b> for whatever reason,	<i>Revised to clarify the intent of Ex.#5a (also revised in</i>

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		dialysis is not planned or non-continuous dialysis is planned (that would not adequately remove Captisol®)	dialysis <b>that would adequately remove Captisol® is not planned.</b>	<i>Sec. 8.2 - Exclusion Criteria)</i>
2. Study Synopsis/Exclusion Criteria	2. Study Synopsis/Exclusion Criteria	Exclusion criterion # 4, sub-bullet 'e':  a do not resuscitate (DNR) order.	Exclusion criterion # 4, sub-bullet 'e':  <del>a do not resuscitate (DNR) order.</del>  <i>Note: revision also appears in Section 8.2 and DNR removed from List of Abbreviations and Definitions of Terms.</i>	<i>Removed DNR as exclusion criterion due to variations of interpretations of DNR across sites.</i>
2. Study Synopsis/Exclusion Criteria	2. Study Synopsis/Exclusion Criteria	Exclusion 8:  Subjects who have been enrolled in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not withdraw or complete and then re-enroll).	Exclusion 8:  Subjects who have been <b>treated or randomized</b> in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not <b>have received study drug/placebo</b> and then re-enroll).  <i>Note: also revised in Sec. 8.2 - Exclusion Criteria</i>	<i>Revised to clarify the intent of Ex.#8</i>
2. Study	2. Study	Summary statistics will be	Summary statistics will be	<i>Revised the</i>

Section number and title in Protocol Amendment 2, Adults Only, Germany Specific (05 JUL 16)	Section number and title in Protocol Amendment 4, Adults Only, Germany Specific (12 SEP 16)	Original text:	Changed to:	Rationale
Synopsis/Analysis of Secondary Efficacy Endpoints	Synopsis/Analysis of Secondary Efficacy Endpoints	calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are retreated with SAGE-547.	calculated for primary and secondary response and duration of response for those subjects who <b>are</b> treated with <b>a higher dose</b> of SAGE-547.	<i>nomenclature in statistical methods to reflect change from retreatment to treatment with a higher dose of SAGE-547.</i>
Section 3.4.2 / SAGE-547 Clinical Program in the Treatment of SRSE	Section 3.4.2 / SAGE-547 Clinical Program in the Treatment of SRSE	an ongoing Phase 2 open-label trial, Study 547-SSE-201; a planned open-label, expanded access protocol, Study 547-SSE-302;	<b>a completed</b> Phase 2 open-label trial, Study 547-SSE-201; <b>an ongoing</b> open-label, expanded access protocol, Study 547-SSE-302;	<i>Revised introduction based on current status of clinical program.</i>
Section 7.3 / Blinding and Randomization	Section 7.3 / Blinding and Randomization	The second infusion of SAGE-547 will be administered on an open-label basis to subjects who failed the primary endpoint wean.	The second infusion of SAGE-547 will be administered on an open-label basis to subjects who <b>meet the criteria for open-label treatment</b> .	<i>Revised second infusion criteria.</i>
Figure 2: Details of Treatment Administration and Follow-up	Figure 2: Details of Treatment Administration and Follow-up	N/A	'Failure' arrow, with regards to subjects who are considered failures of the blinded infusion, moved from beneath V6 to V10, as V10 is timepoint when decision for open-label treatment is made.	<i>Previous oversight, the modified figure clarifies the timepoint when open-label treatment is</i>

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				<i>determined, at V10.</i>
Section 10.1 / Dosing Schedule (Blinded Infusions)	Section 10.1 / Dosing Schedule (Blinded Infusions)	The infusion rates to accomplish these $\mu\text{g/kg/h}$ doses will be calculated according to the weight of the subject.	The infusion rates to accomplish these $\mu\text{g/kg/h}$ doses will be calculated according to the weight of the subject <b>obtained within the eight-hour window that follows the declaration of the QW failure at V2 and prior to dosing at V3.</b>	<i>The study drug dose is based on the initial pre-dose weight for each six-day infusion.</i>
Section 10.2 / Dosing Schedule (Open-Label Infusions)	Section 10.2 / Dosing Schedule (Open-Label Infusions)	If a subject fails wean from third-line agent(s) or requires re-instatement of third-line therapy within 24 hours of discontinuing the initial infusion of study drug, SAGE-547 Injection will be re-administered according to the dosing schedule in Table 6. The infusion rates to accomplish these $\mu\text{g/kg/h}$ doses will be calculated according to the weight of the subject. These infusion rates will be applied to SAGE-547 re-treatment for the open-label second infusions of study medication.	<b>Those subjects that qualify for the open-label study drug will be administered SAGE-547 Injection according to the dosing schedule in Table 6. The dose will be administered on a <math>\mu\text{g/kg/h}</math> basis, and the subject's weight measured prior to dosing during V10 will be used to calculate the doses.</b>	<i>The study drug dose is based on the initial pre-dose weight for each six-day infusion.</i>

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10.5 Concomitant Medications, Procedures and Treatments	10.5 Concomitant Medications, Procedures and Treatments	Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. All concomitant medications, procedures, and treatments should be documented throughout the study from Screening through Visit 12/12R and recorded on the eCRF.	Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. <b>For all randomized and the first 50 qualifying wean success (QWS) subjects, detailed information on all concomitant medications (concomitant AEDs, third-line agents, pressors, and other concomitant medications), procedures, and treatments should be documented throughout the study from Screening through Visit 12/12R, as described below, and recorded on the eCRF. For subsequent QWS subjects, after the detailed information on all concomitant AEDs, pressors, third-line</b>	<i>Specified the intent to collect minimal data on QWS subjects, following enrollment of 50 QWS subjects.</i>

Section number and title in Protocol Amendment 2, Adults Only, Germany Specific (05 JUL 16)	Section number and title in Protocol Amendment 4, Adults Only, Germany Specific (12 SEP 16)	Original text:	Changed to:	Rationale
			<p>agents, procedures, and treatments collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant AED or pressor, third-line agent, procedure, and/or treatment, and the start and stop dates and times) from Visit 3 through Visit 12 will be recorded in the eCRF. For subsequent QWS subjects, after the detailed information on all concomitant medications collected during the screening period (Visits 1 and 2) has been recorded, only minimal information, to include the name of the concomitant medications and indication only will be recorded from Visit 3 through Visit 12.</p> <p><i>Note: revision appears in SOA</i></p>	

Section number and title in Protocol Amendment 2, Adults Only, Germany Specific (05 JUL 16)	Section number and title in Protocol Amendment 4, Adults Only, Germany Specific (12 SEP 16)	Original text:	Changed to:	Rationale
			<i>footnotes</i>	
Section 11.1.1.1/Weaning	Section 11.1.1.1/Weaning	The following guidance for weaning applies to all weans of third-line agents undertaken during the study.	The following guidance for weaning applies to all weans of third-line agents undertaken during the study. <b>Continued determined efforts to liberate subjects from sedation must be undertaken for the entire duration of the blinded study drug infusion. Each failed wean from third-line agents should be followed by a 6-24 hour period of suppression and then another wean attempt, with further optimization of the AED regimen.</b>	<i>Additional guidance provided for third-line agent weaning during blinded and open-label treatment courses</i>
11.1.1.2 EEG	11.1.1.2 EEG	A 24-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst suppression for the second path to eligibility, and	A 24-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst <b>or seizure</b> suppression for the second path to eligibility, and a	<i>Extended the QWEEG to match QW Guidance in Sec. 11.1.1.1 for Investigators to allow 24 hours to lapse after the end of QW before declaring QW success.</i>

Section number and title in Protocol Amendment 2, Adults Only, Germany Specific (05 JUL 16)	Section number and title in Protocol Amendment 4, Adults Only, Germany Specific (12 SEP 16)	Original text:	Changed to:	Rationale
		a variable pattern for the third path to eligibility.	variable pattern for the third path to eligibility. <b>This EEG also aims to capture the burst or seizure suppression pattern during the 24 hours that precede the QW. If the CEEG does not capture the 24 hours that precede the QW, additional EEG data collected as standard of care prior to the CEEG and prior to the QW may be collected to assess the depth of burst or seizure suppression in the 24 hour period prior to the QW.</b>	
11.2.4. Weight and Height	11.2.4. Weight and Height	Weight and height will be measured at Visit 1 and weight will also be measured once during each 24 hour period of the first infusion of study drug, and of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547. These daily weights will be used to modify the dose of SAGE-547 if required.	Weight and height will be measured at Visit 1. <b>Weight will also be obtained at V2, within the eight hour window that follows the declaration of the QW failure and prior to the initiation of the blinded infusion loading dose at H0 of V3, and will be used to calculate the infusion rates throughout the entire blinded treatment course. If a subject</b>	<i>Clarification on process for obtaining daily weight for dosing.</i>



Section number and title in Protocol Amendment 2, Adults Only, Germany Specific (05 JUL 16)	Section number and title in Protocol Amendment 4, Adults Only, Germany Specific (12 SEP 16)	Original text:	Changed to:	Rationale
			<p><b>qualifies for open-label study drug, the infusion rates for the open-label infusion will be calculated using the subject's weight measured prior to dosing during V10.</b></p> <p><b>If it is not possible to obtain the actual weight at the above-referenced timepoints, permission from the Clinical Monitor must be obtained to use another method to obtain the subject's weight (such as information from the LAR or estimating using an established local protocol).</b></p> <p><b>In addition, a daily weight will be obtained and recorded if this is easily obtained, such as the use of a scale bed.</b></p>	
11.2.5 ECG	11.2.5 ECG	12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug...	<b>For the first 50 subjects randomized in the study,</b> 12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug...	<i>Clarified the number of ECG timepoints required based on order of randomization,</i>

Section number and title in Protocol Amendment 2, Adults Only, Germany Specific (05 JUL 16)	Section number and title in Protocol Amendment 4, Adults Only, Germany Specific (12 SEP 16)	Original text:	Changed to:	Rationale
			<p><b>For the subsequent subjects randomized in the study, the following timepoints for ECG will be used:</b></p> <ul style="list-style-type: none"> <li>• pre-dose and at +1 +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the blinded (first) study drug infusion</li> <li>• pre-dose and at +1 +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the open-label (second) study drug infusion</li> </ul> <p><b>It is not necessary to collect these ECGs with the PK samples at these timepoints and, apart from the +1h ECG, there is +/- 2 hour time window for these ECGs.</b></p> <p><i>Note: revision also made to SOA footnotes and throughout Sec. 12</i></p>	<i>including the window for ECG collection and relation to PK draws.</i>
Sec. 11.2.8.1	Sec. 11.2.8.1	All samples will also be analyzed	All samples <b>from the first 50</b>	<i>Created an upper</i>

Section number and title in Protocol Amendment 2, Adults Only, Germany Specific (05 JUL 16)	Section number and title in Protocol Amendment 4, Adults Only, Germany Specific (12 SEP 16)	Original text:	Changed to:	Rationale
Pharmacokinetic Data	Pharmacokinetic Data	for plasma concentrations of Captisol®.	<b>subjects randomized</b> will also be analyzed for plasma concentrations of Captisol®.	<i>limit on Captisol® samples that will be analyzed by PK vendor.</i>
12.3.1. Visit 3/3R	12.3.1. Visit 3/3R	<ul style="list-style-type: none"> <li>Completion of the FOUR Score</li> <li>– +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the end of the QW)</li> </ul>	<ul style="list-style-type: none"> <li>Completion of the FOUR Score               <ul style="list-style-type: none"> <li>– +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following <b>the final declaration of QW success</b>)</li> </ul> </li> </ul>	<i>Clarification on FOUR Score assessment timeframe for Qualifying Wean Successes (QWS)</i>
12.5.2. Visit 10/10R	12.5.2. Visit 10/10R	<ul style="list-style-type: none"> <li>At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine retreatment with higher dose of study drug. All patients for retreatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.</li> </ul>	<ul style="list-style-type: none"> <li>At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine eligibility for <b>the open-label treatment</b> with the higher dose of study drug. <b>This determination may occur at any point during Visit 10: the higher dose open-label infusion must begin within the Visit 10</b></li> </ul>	<i>Clarification on Visit 10 retreatment eligibility and retreatment infusion window.</i>

Section number and title in Protocol Amendment 2, Adults Only, Germany Specific (05 JUL 16)	Section number and title in Protocol Amendment 4, Adults Only, Germany Specific (12 SEP 16)	Original text:	Changed to:	Rationale
			<b>window.</b> All patients receiving the higher dose open-label treatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.	
14.1.4 Medical Monitor and Emergency Contact Information	14.1.4 Medical Monitor and Emergency Contact Information	[REDACTED], MD [REDACTED]	[REDACTED], MD [REDACTED]  <b>In a study related medical emergency situation, when the assigned Medical Monitor cannot be reached by a caller, an on-call Physician can be reached 24 hours per day, 7 days per week via an [REDACTED] Call-Center:</b>  • Telephone: [REDACTED]	<i>Updated [REDACTED] global 24/7 Medical Monitor and on-call physician contact information.</i>

Section number and title in Protocol Amendment 2, Adults Only, Germany Specific (05 JUL 16)	Section number and title in Protocol Amendment 4, Adults Only, Germany Specific (12 SEP 16)	Original text:	Changed to:	Rationale
			<p>(this is a chargeable telephone number allowing a global reach from both landlines and mobile phones)</p> <ul style="list-style-type: none"> <li>• [REDACTED]</li> </ul> <p>On this internet page a list of country-specific toll-free telephone numbers is provided. It should be noted that not all countries globally have access to toll-free numbers as indicated on the “24/7 Medical Help desk” index. Countries without toll-free numbers need to dial the chargeable number as indicated above. Furthermore, toll-free numbers are not available from mobile phones.</p>	

**Summary of Changes****Protocol-547-SSE-301 (Adults Only, Sweden)****Dated 18 AUG 2016**

The following changes were made to the attached protocol in this amendment. Minor typographical/editorial errors throughout the document were also corrected.

<b>Section number and title in Protocol Amendment 2, Adults Only, Sweden (29 FEB 16)</b>	<b>Section number and title in Protocol Amendment 4, Adults Only, Sweden (18 AUG 16)</b>	<b>Original text:</b>	<b>Changed to:</b>	<b>Rationale</b>
2. Study Synopsis/Study Sites/Number of Subjects	2. Study Synopsis/Study Sites/Number of Subjects	Up to 180 sites in the USA, Europe, and Canada.	Up to 180 sites in the USA, <b>Israel</b> , Europe, and Canada.	<i>Addition of Israel to country list</i>
2. Synopsis: Study Design	2. Synopsis: Study Design	The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst suppression with a third-line agent.	The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst <b>or seizure</b> suppression with a third-line agent.  <i>Note: 'seizure suppression' revised throughout document with regards to EEG suppression goals for managing RSE and SRSE patients, as well as permitting 'seizure suppression' during screening</i>	<i>Allowing burst or seizure suppression during screening period, prior to initiation of QW, allows sites to use a less restrictive approach achieving EEG suppression and one more typical to sites' standard of care when</i>

Section number and title in Protocol Amendment 2, Adults Only, Sweden (29 FEB 16)	Section number and title in Protocol Amendment 4, Adults Only, Sweden (18 AUG 16)	Original text:	Changed to:	Rationale
			<i>period, prior to initiation of qualifying wean (QW).</i>	<i>screening patients.</i>
2. Study Synopsis/Study Design	2. Study Synopsis/Study Design	These subjects will be consented for the study after admission to the intensive care unit, but before any third-line agents are administered for burst suppression.	These subjects will be consented for the study after admission to the intensive care unit, before <b>or after</b> any third-line agents are administered for burst <b>or seizure</b> suppression.  <i><u>Note:</u> revision also appears in Sec. 7.1.</i>	<i>Clarification that subjects may be administered third-line anesthetic agents for EEG burst or seizure suppression prior to or following the consent procedure.</i>
2. Study Synopsis/Study Design	2. Study Synopsis/Study Design	Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within six hours of the investigator's determination that they failed the QW.	Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within <b>eight</b> hours of the investigator's determination that they failed the QW.  <i><u>Note:</u> revision also appears in Sections 7.1, 10.1, 11.2.4, and 12.2.</i>	<i>Extending time frame from failure of QW to when blinded infusion begins will provide greater flexibility for study teams to mobilize and coordinate pre-treatment activities.</i>

Section number and title in Protocol Amendment 2, Adults Only, Sweden (29 FEB 16)	Section number and title in Protocol Amendment 4, Adults Only, Sweden (18 AUG 16)	Original text:	Changed to:	Rationale
2. Study Synopsis/Study Objectives	2. Study Synopsis/Study Objectives	To evaluate the impact of retreatment with a higher dose SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;	To evaluate the impact of <del>retreatment</del> with a higher dose SAGE-547 infusion <del>in subjects who initially fail to respond to double blind study medication;</del>	<i>Revised the nomenclature in other objectives from retreatment to open-label treatment.</i>
2. Study Synopsis/Endpoints	2. Study Synopsis/Endpoints	The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who fail to respond to their randomized double blind treatment and are retreated with a higher dose of SAGE-547.	The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects <del>who fail to respond to their randomized double blind treatment and</del> are retreated with a higher dose of SAGE-547.	<i>Revised the nomenclature in other endpoints to reflect change from retreatment to treatment.</i>
2. Study Synopsis/Inclusion Criteria	2. Study Synopsis/Inclusion Criteria	Inclusion criterion # 2, sub-bullet # 3:  Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed one or more wean attempts from third-line agents and are now on continuous	Inclusion criterion # 2, sub-bullet # 3:  Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed <b>zero</b> , one or more wean attempts from third-line agents and are now on continuous intravenous	<i>Clarified that some patients may enter the study having never failed a prior third-line agent wean. These patients will enter the study in Refractory Status Epilepticus (RSE)</i>



Section number and title in Protocol Amendment 2, Adults Only, Sweden (29 FEB 16)	Section number and title in Protocol Amendment 4, Adults Only, Sweden (18 AUG 16)	Original text:	Changed to:	Rationale
		intravenous infusions of one or more third-line agent and in an EEG burst suppression pattern;	infusions of one or more third-line agent and in an EEG burst <b>or seizure</b> suppression pattern;  <i>Note: revision also appears in Section 8.1.</i>	<i>and the outcome of the protocol-specific QW will determine whether or not they are in Super-Refractory Status Epilepticus (SRSE).</i>
2. Study Synopsis/Exclusion Criteria	2. Study Synopsis/Exclusion Criteria	Exclusion criterion # 3:  Subjects with SRSE due to anoxic/hypoxic encephalopathy	Exclusion criterion # 3:  Subjects with SRSE due to anoxic/hypoxic encephalopathy <b>with highly malignant/malignant EEG features (Westhall, Rosetti et al. 2016)</b>  <i>Note: revision also appears in Section 8.2.</i>	<i>Clarified EEG features indicative of patients with anoxic/hypoxic encephalopathy to aid Investigator/Sponsor determination to exclude patients meeting this criterion.</i>
2. Study Synopsis/Exclusion Criteria	2. Study Synopsis/Exclusion Criteria	Exclusion 5a:  a GFR low enough to warrant dialysis for whatever reason, but	Exclusion 5a:  a GFR low enough to warrant dialysis <b>but</b> for whatever reason,	<i>Revised to clarify the intent of Ex.#5a (also revised in</i>

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		dialysis is not planned or non-continuous dialysis is planned (that would not adequately remove Captisol®)	dialysis <b>that would adequately remove Captisol® is not planned.</b>	<i>Sec. 8.2 - Exclusion Criteria)</i>
2. Study Synopsis/Exclusion Criteria	2. Study Synopsis/Exclusion Criteria	Exclusion criterion # 5, sub-bullet 'e':  a do not resuscitate (DNR) order.	Exclusion criterion # 5, sub-bullet 'e':  <del>a do not resuscitate (DNR) order.</del>  <i>Note: revision also appears in Section 8.2 and DNR removed from List of Abbreviations and Definitions of Terms.</i>	<i>Removed DNR as exclusion criterion due to variations of interpretations of DNR across sites.</i>
2. Study Synopsis/Exclusion Criteria	2. Study Synopsis/Exclusion Criteria	Exclusion 8:  Subjects who have been enrolled in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not withdraw or complete and then re-enroll).	Exclusion 8:  Subjects who have been <b>treated or randomized</b> in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not <b>have received study drug/placebo</b> and then re-enroll).  <i>Note: also revised in Sec. 8.2 - Exclusion Criteria</i>	<i>Revised to clarify the intent of Ex.#8</i>
2. Study	2. Study	Summary statistics will be	Summary statistics will be	<i>Revised the</i>

Section number and title in Protocol Amendment 2, Adults Only, Sweden (29 FEB 16)	Section number and title in Protocol Amendment 4, Adults Only, Sweden (18 AUG 16)	Original text:	Changed to:	Rationale
Synopsis/Analysis of Secondary Efficacy Endpoints	Synopsis/Analysis of Secondary Efficacy Endpoints	calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are retreated with SAGE-547.	calculated for primary and secondary response and duration of response for those subjects who <b>are</b> treated with <b>a higher dose</b> of SAGE-547.	<i>nomenclature in statistical methods to reflect change from retreatment to treatment with a higher dose of SAGE-547.</i>
Section 3.4.2 / SAGE-547 Clinical Program in the Treatment of SRSE	Section 3.4.2 / SAGE-547 Clinical Program in the Treatment of SRSE	an ongoing Phase 2 open-label trial, Study 547-SSE-201; a planned open-label, expanded access protocol, Study 547-SSE-302;	<b>a completed</b> Phase 2 open-label trial, Study 547-SSE-201; <b>an ongoing</b> open-label, expanded access protocol, Study 547-SSE-302;	<i>Revised introduction based on current status of clinical program.</i>
Section 7.3 / Blinding and Randomization	Section 7.3 / Blinding and Randomization	The second infusion of SAGE-547 will be administered on an open-label basis to subjects who failed the primary endpoint wean.	The second infusion of SAGE-547 will be administered on an open-label basis to subjects who <b>meet the criteria for open-label treatment</b> .	<i>Revised second infusion criteria.</i>
Figure 2: Details of Treatment Administration and Follow-up	Figure 2: Details of Treatment Administration and Follow-up	N/A	'Failure' arrow, with regards to subjects who are considered failures of the blinded infusion, moved from beneath V6 to V10, as V10 is timepoint when decision for open-label treatment is made.	<i>Previous oversight, the modified figure clarifies the timepoint when open-label treatment is</i>

Section number and title in Protocol Amendment 2, Adults Only, Sweden (29 FEB 16)	Section number and title in Protocol Amendment 4, Adults Only, Sweden (18 AUG 16)	Original text:	Changed to:	Rationale
				<i>determined, at V10.</i>
Section 10.1 / Dosing Schedule (Blinded Infusions)	Section 10.1 / Dosing Schedule (Blinded Infusions)	The infusion rates to accomplish these $\mu\text{g/kg/h}$ doses will be calculated according to the weight of the subject.	The infusion rates to accomplish these $\mu\text{g/kg/h}$ doses will be calculated according to the weight of the subject <b>obtained within the eight-hour window that follows the declaration of the QW failure at V2 and prior to dosing at V3.</b>	<i>The study drug dose is based on the initial pre-dose weight for each six-day infusion.</i>
Section 10.2 / Dosing Schedule (Open-Label Infusions)	Section 10.2 / Dosing Schedule (Open-Label Infusions)	If a subject fails wean from third-line agent(s) or requires re-instatement of third-line therapy within 24 hours of discontinuing the initial infusion of study drug, SAGE-547 Injection will be re-administered according to the dosing schedule in Table 6. The infusion rates to accomplish these $\mu\text{g/kg/h}$ doses will be calculated according to the weight of the subject. These infusion rates will be applied to SAGE-547 re-treatment for the open-label second infusions of study medication.	<b>Those subjects that qualify for the open-label study drug will be administered SAGE-547 Injection according to the dosing schedule in Table 6. The dose will be administered on a <math>\mu\text{g/kg/h}</math> basis, and the subject's weight measured prior to dosing during V10 will be used to calculate the doses.</b>	<i>The study drug dose is based on the initial pre-dose weight for each six-day infusion.</i>

Section number and title in Protocol Amendment 2, Adults Only, Sweden (29 FEB 16)	Section number and title in Protocol Amendment 4, Adults Only, Sweden (18 AUG 16)	Original text:	Changed to:	Rationale
10.5 Concomitant Medications, Procedures and Treatments	10.5 Concomitant Medications, Procedures and Treatments	Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. All concomitant medications, procedures, and treatments should be documented throughout the study from Screening through Visit 12/12R and recorded on the eCRF.	Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. <b>For all randomized and the first 50 qualifying wean success (QWS) subjects, detailed information on all concomitant medications (concomitant AEDs, third-line agents, pressors, and other concomitant medications), procedures, and treatments should be documented throughout the study from Screening through Visit 12/12R, as described below, and recorded on the eCRF. For subsequent QWS subjects, after the detailed information on all concomitant AEDs, pressors, third-line</b>	<i>Specified the intent to collect minimal data on QWS subjects, following enrollment of 50 QWS subjects.</i>

Section number and title in Protocol Amendment 2, Adults Only, Sweden (29 FEB 16)	Section number and title in Protocol Amendment 4, Adults Only, Sweden (18 AUG 16)	Original text:	Changed to:	Rationale
			<p>agents, procedures, and treatments collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant AED or pressor, third-line agent, procedure, and/or treatment, and the start and stop dates and times) from Visit 3 through Visit 12 will be recorded in the eCRF. For subsequent QWS subjects, after the detailed information on all concomitant medications collected during the screening period (Visits 1 and 2) has been recorded, only minimal information, to include the name of the concomitant medications and indication only will be recorded from Visit 3 through Visit 12.</p> <p><i>Note: revision appears in SOA</i></p>	

Section number and title in Protocol Amendment 2, Adults Only, Sweden (29 FEB 16)	Section number and title in Protocol Amendment 4, Adults Only, Sweden (18 AUG 16)	Original text:	Changed to:	Rationale
			<i>footnotes</i>	
Section 11.1.1.1/Weaning	Section 11.1.1.1/Weaning	The following guidance for weaning applies to all weans of third-line agents undertaken during the study.	The following guidance for weaning applies to all weans of third-line agents undertaken during the study. <b>Continued determined efforts to liberate subjects from sedation must be undertaken for the entire duration of the blinded study drug infusion. Each failed wean from third-line agents should be followed by a 6-24 hour period of suppression and then another wean attempt, with further optimization of the AED regimen.</b>	<i>Additional guidance provided for third-line agent weaning during blinded and open-label treatment courses</i>
11.1.1.2 EEG	11.1.1.2 EEG	A 24-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst suppression for the second path to eligibility, and	A 24-hour duration EEG will be performed from the time of consent (CEEG). The intent is to demonstrate the EEG pattern that corresponds to the path to eligibility for the study for that patient; patterns would be seizure activity for the first path to eligibility, burst <b>or seizure</b> suppression for the second path to eligibility, and a	<i>Extended the QWEEG to match QW Guidance in Sec. 11.1.1.1 for Investigators to allow 24 hours to lapse after the end of QW before declaring QW success.</i>

Section number and title in Protocol Amendment 2, Adults Only, Sweden (29 FEB 16)	Section number and title in Protocol Amendment 4, Adults Only, Sweden (18 AUG 16)	Original text:	Changed to:	Rationale
		a variable pattern for the third path to eligibility.	variable pattern for the third path to eligibility. <b>This EEG also aims to capture the burst or seizure suppression pattern during the 24 hours that precede the QW. If the CEEG does not capture the 24 hours that precede the QW, additional EEG data collected as standard of care prior to the CEEG and prior to the QW may be collected to assess the depth of burst or seizure suppression in the 24 hour period prior to the QW.</b>	
11.2.4. Weight and Height	11.2.4. Weight and Height	Weight and height will be measured at Visit 1 and weight will also be measured once during each 24 hour period of the first infusion of study drug, and of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547. These daily weights will be used	Weight and height will be measured at Visit 1. <b>Weight will also be obtained at V2, within the eight hour window that follows the declaration of the QW failure and prior to the initiation of the blinded infusion loading dose at H0 of V3, and will be used to calculate the infusion rates</b>	<i>Clarification on process for obtaining daily weight for dosing.</i>



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		to modify the dose of SAGE-547 if required.	<p><b>throughout the entire blinded treatment course. If a subject qualifies for open-label study drug, the infusion rates for the open-label infusion will be calculated using the subject's weight measured prior to dosing during V10.</b></p> <p><b>If it is not possible to obtain the actual weight at the above-referenced timepoints, permission from the Clinical Monitor must be obtained to use another method to obtain the subject's weight (such as information from the LAR or estimating using an established local protocol).</b></p> <p><b>In addition, a daily weight will be obtained and recorded if this is easily obtained, such as the use of a scale bed.</b></p>	
11.2.5 ECG	11.2.5 ECG	12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study	<b>For the first 50 subjects randomized in the study,</b> 12-lead ECGs should be performed at Visit 1 and then at the following times	<i>Clarified the number of ECG timepoints required based on</i>

Section number and title in Protocol Amendment 2, Adults Only, Sweden (29 FEB 16)	Section number and title in Protocol Amendment 4, Adults Only, Sweden (18 AUG 16)	Original text:	Changed to:	Rationale
		drug...	<p>relative to the start of each infusion of study drug...</p> <p><b>For the subsequent subjects randomized in the study, the following timepoints for ECG will be used:</b></p> <ul style="list-style-type: none"> <li>• pre-dose and at +1 +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the blinded (first) study drug infusion</li> <li>• pre-dose and at +1 +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the open-label (second) study drug infusion</li> </ul> <p><b>It is not necessary to collect these ECGs with the PK samples at these timepoints and, apart from the +1h ECG, there is +/- 2 hour time window for these ECGs.</b></p> <p><i>Note: revision also made to SOA</i></p>	<p><i>order of randomization, including the window for ECG collection and relation to PK draws.</i></p>

Section number and title in Protocol Amendment 2, Adults Only, Sweden (29 FEB 16)	Section number and title in Protocol Amendment 4, Adults Only, Sweden (18 AUG 16)	Original text:	Changed to:	Rationale
			<i>footnotes and throughout Sec. 12</i>	
Sec. 11.2.8.1 Pharmacokinetic Data	Sec. 11.2.8.1 Pharmacokinetic Data	All samples will also be analyzed for plasma concentrations of Captisol®.	All samples <b>from the first 50 subjects randomized</b> will also be analyzed for plasma concentrations of Captisol®.	<i>Created an upper limit on Captisol® samples that will be analyzed by PK vendor.</i>
12.3.1. Visit 3/3R	12.3.1. Visit 3/3R	<ul style="list-style-type: none"> <li>Completion of the FOUR Score</li> <li>– +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following the end of the QW)</li> </ul>	<ul style="list-style-type: none"> <li>Completion of the FOUR Score <ul style="list-style-type: none"> <li>– +24 hours (+/- 2 hours) after the start of the infusion (QWS subjects complete FOUR Score at some time in the 24 hours following <b>the final declaration of QW success</b>)</li> </ul> </li> </ul>	<i>Clarification on FOUR Score assessment timeframe for Qualifying Wean Successes (QWS)</i>
12.5.2. Visit 10/10R	12.5.2. Visit 10/10R	<ul style="list-style-type: none"> <li>At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine retreatment with higher dose of study drug. All patients for retreatment must have an eligibility form agreed and signed by the medical monitor before the open-label</li> </ul>	<ul style="list-style-type: none"> <li>At Visit 10 only (not Visit 10R), if subject failed the terminal wean, determine eligibility for <b>the open-label treatment</b> with the higher dose of study drug. <b>This determination may occur at any point during Visit 10: the higher dose</b></li> </ul>	<i>Clarification on Visit 10 retreatment eligibility and retreatment infusion window.</i>

Section number and title in Protocol Amendment 2, Adults Only, Sweden (29 FEB 16)	Section number and title in Protocol Amendment 4, Adults Only, Sweden (18 AUG 16)	Original text:	Changed to:	Rationale
		infusion begins.	<b>open-label infusion must begin within the Visit 10 window.</b> All patients receiving the higher dose open-label treatment must have an eligibility form agreed and signed by the medical monitor before the open-label infusion begins.	
14.1.4 Medical Monitor and Emergency Contact Information	14.1.4 Medical Monitor and Emergency Contact Information	[REDACTED], MD [REDACTED]	[REDACTED], MD [REDACTED]  <b>In a study related medical emergency situation, when the assigned Medical Monitor cannot be reached by a caller, an on-call Physician can be reached 24 hours per day, 7 days per week via an [REDACTED] Call-Center:</b>	<i>Updated [REDACTED] global 24/7 Medical Monitor and on-call physician contact information.</i>

Section number and title in Protocol Amendment 2, Adults Only, Sweden (29 FEB 16)	Section number and title in Protocol Amendment 4, Adults Only, Sweden (18 AUG 16)	Original text:	Changed to:	Rationale
			<ul style="list-style-type: none"> <li>Telephone: [REDACTED] (this is a chargeable telephone number allowing a global reach from both landlines and mobile phones)</li> <li>[REDACTED]</li> </ul> <p>On this internet page a list of country-specific toll-free telephone numbers is provided. It should be noted that not all countries globally have access to toll-free numbers as indicated on the “24/7 Medical Help desk” index. Countries without toll-free numbers need to dial the chargeable number as indicated above. Furthermore, toll-free numbers are not available from mobile phones.</p>	
N/A	14.2.4 Reporting to European Regulatory Authorities	N/A	<b>14.2.4. Reporting to European Regulatory Authorities</b>	<i>Section on EU Regulatory Reporting was</i>

Section number and title in Protocol Amendment 2, Adults Only, Sweden (29 FEB 16)	Section number and title in Protocol Amendment 4, Adults Only, Sweden (18 AUG 16)	Original text:	Changed to:	Rationale
			<p><b>The Sponsor or its designee is responsible for SUSAR notification to the relevant regulatory authorities as outlined in the ICH Guidelines. All investigators participating in the study will also be informed as required by regulations.</b></p> <p><b>Any SUSAR is subject to expedited reporting in the EU. The Sponsor or its designee, will report any single SUSAR to the appropriate National CAs and IECs within 7 days if the SUSAR is life-threatening or fatal (with the relevant follow-up information subsequently communicated within an additional eight days), and within 15 days if the SUSAR is neither life-threatening nor fatal. SUSARs reported will be those that have arisen in the present clinical trial and SUSARs that</b></p>	<p><i>omitted from previous amendment and added due to trial occurring throughout EU.</i></p>

<b>Section number and title in Protocol Amendment 2, Adults Only, Sweden (29 FEB 16)</b>	<b>Section number and title in Protocol Amendment 4, Adults Only, Sweden (18 AUG 16)</b>	<b>Original text:</b>	<b>Changed to:</b>	<b>Rationale</b>
			<p><b>have arisen in other clinical trials conducted by the Sponsor with the same medicinal product.</b></p> <p><b>In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to competent authorities of the concerned Member States and to IEC(s)/IRBs as required by national laws.</b></p>	

**Summary of Changes**  
**Protocol-547-SSE-301**  
**Dated 20 September 2016**

The following changes were made to the attached protocol in this amendment. Minor typographical/editorial errors were corrected and administrative revisions were addressed within the document.

Section number and title in Amendment 2 (04 February 2016, Italy Specific)	Section number and title in Amendment 4 (20 September 2016, Italy Specific)	Original text:	Changed to:	Rationale
Synopsis: Study Sites	Synopsis: Study Sites	Up to 180 sites in the USA, Europe, and Canada.	Up to 180 sites in the USA, <b>Israel</b> , Europe, and Canada.	<i>Adding Israel to list of countries, previous omission</i>
Synopsis: Study Design	Synopsis: Study Design	The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst suppression with a third-line agent.	The first path is for subjects who are admitted to the intensive care unit at the study site in status epilepticus, having failed first- and second-line therapies, with a view to initiating burst <b>or seizure</b> suppression with a third-line agent.  <i>Note: 'seizure suppression' revised throughout document with regards to EEG suppression goals for managing RSE and SRSE patients, as well as permitting 'seizure suppression' during screening period, prior to initiation of qualifying wean (QW).</i>	<i>Allowing burst or seizure suppression during screening period, prior to initiation of QW, allows sites to use a less restrictive approach achieving EEG suppression and one more typical to sites' standard of care when screening patients.</i>



Section number and title in Amendment 2 (04 February 2016, Italy Specific)	Section number and title in Amendment 4 (20 September 2016, Italy Specific)	Original text:	Changed to:	Rationale
Synopsis: Study Design	Synopsis: Study Design	These subjects will be consented for the study after admission to the intensive care unit, but before any third-line agents are administered for burst suppression.	These subjects will be consented for the study after admission to the intensive care unit, before <b>or after</b> any third-line agents are administered for burst <b>or seizure</b> suppression.  <i>Note: revision also appears in Sec. 7.1.</i>	<i>Clarification that subjects may be administered third-line anesthetic agents for EEG burst or seizure suppression prior to or following the consent procedure.</i>
Synopsis: Study Design	Synopsis: Study Design	Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within six hours of the investigator's determination that they failed the QW.	Once subjects are deemed to be failures of the QW, they must be randomized and the blinded study drug infusion commenced within <b>eight</b> hours of the investigator's determination that they failed the QW.  <i>Note: revision also appears in Sections 7.1, 10.1, 11.2.4, and 12.2.</i>	<i>Extending time frame from failure of QW to when blinded infusion begins will provide greater flexibility for study teams to mobilize and coordinate pre-treatment activities.</i>

Section number and title in Amendment 2 (04 February 2016, Italy Specific)	Section number and title in Amendment 4 (20 September 2016, Italy Specific)	Original text:	Changed to:	Rationale
Synopsis: Other Objectives	Synopsis: Other Objectives	To evaluate the impact of retreatment with a higher dose SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;	To evaluate the impact of retreatment with a higher dose SAGE-547 infusion in subjects who initially fail to respond to double blind study medication;	<i>Revised the nomenclature in other objectives from retreatment to open-label treatment.</i>
Synopsis: Other Endpoints	Synopsis: Other Endpoints	The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who fail to respond to their randomized double blind treatment and are retreated with a higher dose of SAGE-547.	The same endpoints as described for the primary and secondary endpoints will be calculated for those subjects who are treated with a higher dose of SAGE-547.	<i>Revised the nomenclature in other endpoints to reflect change from retreatment to treatment.</i>

Section number and title in Amendment 2 (04 February 2016, Italy Specific)	Section number and title in Amendment 4 (20 September 2016, Italy Specific)	Original text:	Changed to:	Rationale
Synopsis: Inclusion Criteria	Synopsis: Inclusion Criteria	<p>Inclusion criterion # 2, sub-bullet # 3:</p> <p>Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst suppression pattern;</p>	<p>Inclusion criterion # 2, sub-bullet # 3:</p> <p>Not previously been administered a third-line agent but have been admitted to an intensive care unit with the intent of administering at least one third-line agent for at least 24 hours; or who have previously failed <b>zero</b>, one or more wean attempts from third-line agents and are now on continuous intravenous infusions of one or more third-line agent and in an EEG burst <b>or seizure</b> suppression pattern;</p> <p><i>Note: revision also appears in Section 8.1.</i></p>	<p><i>Clarified that some patients may enter the study having never failed a prior third-line agent wean. These patients will enter the study in Refractory Status Epilepticus (RSE) and the outcome of the protocol-specific QW will determine whether or not they are in Super-Refractory Status Epilepticus (SRSE).</i></p>

Section number and title in Amendment 2 (04 February 2016, Italy Specific)	Section number and title in Amendment 4 (20 September 2016, Italy Specific)	Original text:	Changed to:	Rationale
Synopsis: Exclusion Criteria	Synopsis: Exclusion Criteria	Exclusion criterion # 3:  Subjects with SRSE due to anoxic/hypoxic encephalopathy	Exclusion criterion # 3:  Subjects with SRSE due to anoxic/hypoxic encephalopathy <b>with highly malignant/malignant EEG features (Westhall, Rosetti et al. 2016)</b>  <i>Note: revision also appears in Section 8.2.</i>	<i>Clarified EEG features indicative of patients with anoxic/hypoxic encephalopathy to aid Investigator/Sponsor determination to exclude patients meeting this criterion.</i>
Synopsis: Exclusion Criteria	Synopsis: Exclusion Criteria	Exclusion 5a:  a GFR low enough to warrant dialysis for whatever reason, but dialysis is not planned or non-continuous dialysis is planned (that would not adequately remove Captisol®)	Exclusion 5a:  a GFR low enough to warrant dialysis <b>but</b> for whatever reason, dialysis <b>that would adequately remove Captisol® is not planned.</b>	<i>Revised to clarify the intent of Ex.#5a (also revised in Sec. 8.2 - Exclusion Criteria)</i>

Section number and title in Amendment 2 (04 February 2016, Italy Specific)	Section number and title in Amendment 4 (20 September 2016, Italy Specific)	Original text:	Changed to:	Rationale
Synopsis: Exclusion Criteria	Synopsis: Exclusion Criteria	Exclusion criterion # 5, sub-bullet 'e':  a do not resuscitate (DNR) order.	Removed Exclusion criterion # 5, sub-bullet 'e':  <del>a do not resuscitate (DNR) order.</del>  <i>Note: revision also appears in Section 8.2 and DNR removed from List of Abbreviations and Definitions of Terms.</i>	<i>Removed DNR as exclusion criterion due to variations of interpretations of DNR across sites.</i>
Synopsis: Exclusion Criteria	Synopsis: Exclusion Criteria	Exclusion 9:  Subjects who have been enrolled in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not withdraw or complete and then re-enroll).	Exclusion 9:  Subjects who have been <b>treated or randomized</b> in this trial or any other trial employing SAGE-547 previously (i.e., subjects may not <b>have received study drug/placebo</b> and then re-enroll).	<i>Revised to clarify the intent of Ex.#9 (also revised in Sec. 8.2 - Exclusion Criteria)</i>
Synopsis: Analysis of Secondary Efficacy Endpoints	Synopsis: Analysis of Secondary Efficacy Endpoints	Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who fail initial treatment and are retreated with SAGE-547.	Summary statistics will be calculated for primary and secondary response and duration of response for those subjects who <b>are</b> treated with a <b>higher dose</b> of SAGE-547.	<i>Revised the nomenclature in statistical methods to reflect change from retreatment to treatment with a higher dose of SAGE-547.</i>

Section number and title in Amendment 2 (04 February 2016, Italy Specific)	Section number and title in Amendment 4 (20 September 2016, Italy Specific)	Original text:	Changed to:	Rationale
Section 3.4.2 / SAGE-547 Clinical Program in the Treatment of SRSE	Section 3.4.2 / SAGE-547 Clinical Program in the Treatment of SRSE	an ongoing Phase 2 open-label trial, Study 547-SSE-201; a planned open-label, expanded access protocol, Study 547-SSE-302;	<b>a completed</b> Phase 2 open-label trial, Study 547-SSE-201; <b>an ongoing</b> open-label, expanded access protocol, Study 547-SSE-302;	<i>Revised introduction based on current status of clinical program.</i>
Figure 2: Details of Treatment Administration and Follow-up	Figure 2: Details of Treatment Administration and Follow-up	N/A	'Failure' arrow, with regards to subjects who are considered failures of the blinded infusion, moved from beneath V6 to V10, as V10 is timepoint when decision for open-label treatment is made.	<i>Previous oversight, the modified figure clarifies the timepoint when open-label treatment is determined, at V10.</i>
Section 10.1 / Dosing Schedule (Blinded Infusions)	Section 10.1 / Dosing Schedule (Blinded Infusions)	The infusion rates to accomplish these µg/kg/h doses will be calculated according to the weight of the subject.	The infusion rates to accomplish these µg/kg/h doses will be calculated according to the weight of the subject <b>obtained within the eight-hour window that follows the declaration of the QW failure at V2 and prior to dosing at V3.</b>	<i>The study drug dose is based on the initial pre-dose weight for each six-day infusion.</i>

Section number and title in Amendment 2 (04 February 2016, Italy Specific)	Section number and title in Amendment 4 (20 September 2016, Italy Specific)	Original text:	Changed to:	Rationale
Section 10.2 / Dosing Schedule (Open-Label Infusions)	Section 10.2 / Dosing Schedule (Open-Label Infusions)	If a subject fails wean from third-line agent(s) or requires re-instatement of third-line therapy within 24 hours of discontinuing the initial infusion of study drug, SAGE-547 Injection will be re-administered according to the dosing schedule in Table 6. The infusion rates to accomplish these $\mu\text{g/kg/h}$ doses will be calculated according to the weight of the subject. These infusion rates will be applied to SAGE-547 re-treatment for the open-label second infusions of study medication.	<b>Those subjects that qualify for the open-label study drug will be administered SAGE-547 Injection according to the dosing schedule in Table 6. The dose will be administered on a <math>\mu\text{g/kg/h}</math> basis, and the subject's weight measured prior to dosing during V10 will be used to calculate the doses.</b>	<i>The study drug dose is based on the initial pre-dose weight for each six-day infusion.</i>
10.5 Concomitant Medications, Procedures and Treatments	10.5 Concomitant Medications, Procedures and Treatments	Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. All concomitant	Subjects will receive the standard of care for SRSE. Any concomitant medication, procedure, and treatment determined necessary for the welfare of the subject may be given at the discretion of the Investigator at any time during the study. <b>For all randomized and the first 50 qualifying wean success (QWS)</b>	<i>Specified the intent to collect minimal data on QWS subjects, following enrollment of 50 QWS subjects.</i>

Section number and title in Amendment 2 (04 February 2016, Italy Specific)	Section number and title in Amendment 4 (20 September 2016, Italy Specific)	Original text:	Changed to:	Rationale
		medications, procedures, and treatments should be documented throughout the study from Screening through Visit 12/12R and recorded on the eCRF.	<b>subjects, detailed information on all concomitant medications (concomitant AEDs, third-line agents, pressors, and other concomitant medications), procedures, and treatments should be documented throughout the study from Screening through Visit 12/12R, as described below, and recorded on the eCRF. For subsequent QWS subjects, after the detailed information on all concomitant AEDs, pressors, third-line agents, procedures, and treatments collected during the screening period (Visits 1 and 2) has been recorded, only minimal information (to include the name of the concomitant AED or pressor, third-line agent, procedure, and/or treatment, and the start and stop dates and times) from Visit 3 through Visit 12 will be recorded in the eCRF. For subsequent QWS subjects, after the detailed</b>	



Section number and title in Amendment 2 (04 February 2016, Italy Specific)	Section number and title in Amendment 4 (20 September 2016, Italy Specific)	Original text:	Changed to:	Rationale
			<p>information on all concomitant medications collected during the screening period (Visits 1 and 2) has been recorded, only minimal information, to include the name of the concomitant medications and indication only will be recorded from Visit 3 through Visit 12.</p> <p><i>Note: revision appears in SOA footnotes</i></p>	

Section number and title in Amendment 2 (04 February 2016, Italy Specific)	Section number and title in Amendment 4 (20 September 2016, Italy Specific)	Original text:	Changed to:	Rationale
Sec. 11.1.1.1 Weaning	Sec. 11.1.1.1 Weaning	The following are considered to be minimum maintenance doses of these agents that may be expected alone or in combination to achieve EEG burst suppression. If subjects are on lower doses than these and are not in EEG burst suppression for <b>the 24 hours prior to the QW</b> or the first 12 hours of the blinded study drug infusion, they will be considered to be <b>screen failures</b> /protocol violators and will exit the study.	The following are considered to be minimum maintenance doses of these agents that may be expected alone or in combination to achieve EEG burst suppression. If subjects are on lower doses than these and are not in EEG burst suppression for the first 12 hours of the blinded study drug infusion, they will be considered to be protocol violators and will exit the study.	<i>Removed requirement for patients to be in EEG burst suppression in the 24 hours prior to the QW. Clarified that burst suppression is required only during the first 12 hours of the blinded study drug infusion. Patients in seizure suppression for 24 hours pre-QW will not be considered screen failures.</i>

Section number and title in Amendment 2 (04 February 2016, Italy Specific)	Section number and title in Amendment 4 (20 September 2016, Italy Specific)	Original text:	Changed to:	Rationale
Sec. 11.1.1.1 Weaning	Sec. 11.1.1.1 Weaning	The Clinical Standardization Team will be able to discuss EEGs related to key study timepoints ( <b>qualifying wean</b> , terminal wean, and the period after the end of the blinded study drug infusion if the terminal wean was successful) in a timely manner in order to provide advice about compliance with the Clinical Standardization Guidelines.	The Clinical Standardization Team will be able to discuss EEGs related to key study timepoints (terminal wean and the period after the end of the blinded study drug infusion if the terminal wean was successful) in a timely manner in order to provide advice about compliance with the Clinical Standardization Guidelines.	<i>Removed guidelines for CST review of QWEEG, providing clarification on guidelines for sites to contact CST during TW and the Primary Endpoint Assessment period.</i>

Section number and title in Amendment 2 (04 February 2016, Italy Specific)	Section number and title in Amendment 4 (20 September 2016, Italy Specific)	Original text:	Changed to:	Rationale
Section 11.1.1.1/Weaning	Section 11.1.1.1/Weaning	The following guidance for weaning applies to all weans of third-line agents undertaken during the study. These weans include the qualifying wean (QW); ...	The following guidance for weaning applies to all weans of third-line agents undertaken during the study. <b>Continued determined efforts to liberate subjects from sedation must be undertaken for the entire duration of the blinded study drug infusion. Each failed wean from third-line agents should be followed by a 6-24 hour period of suppression and then another wean attempt, with further optimization of the AED regimen. Weans include the qualifying wean (QW); ...</b>	<i>Additional guidance provided for third-line agent weaning during blinded and open-label treatment courses.</i>

Section number and title in Amendment 2 (04 February 2016, Italy Specific)	Section number and title in Amendment 4 (20 September 2016, Italy Specific)	Original text:	Changed to:	Rationale
Sec. 11.1.1.2 EEG	Sec. 11.1.1.2 EEG	<p>First bullet point:</p> <p>This EEG will capture the burst suppression pattern during the 24 hours that precede the QW.</p>	<p>First bullet point:</p> <p>This EEG <b>also aims to</b> capture the burst <b>or seizure</b> suppression pattern during the 24 hours that precede the QW. <b>If the CEEG does not capture the 24 hours that precede the QW, additional EEG data collected as standard of care prior to the CEEG and prior to the QW may be collected to assess the depth of burst or seizure suppression in the 24 hour period prior to the QW.</b></p>	<p><i>Previous editorial oversight, intention is to permit collection of SOC EEG data that may precede CEEG, in order to collect EEG data on the depth of EEG suppression in the 24 hrs prior to QW.</i></p>
Section 11.2.4 / Weight and Height	Section 11.2.4 / Weight and Height	<p>Weight and height will be measured at Visit 1 and weight will also be measured once during each 24 hour period of the first infusion of study drug, and of the second infusion of SAGE-547 should the subject qualify for the second infusion of SAGE-547. These daily weights will be used to modify the dose of SAGE-547 if required. If it is not possible to weigh the subject daily, an actual weight must be obtained prior to</p>	<p>Weight and height will be measured at Visit 1. Weight will also be obtained at <b>V2, within the eight hour window that follows the declaration of the QW failure and prior to the initiation of the blinded infusion loading dose at H0 of V3, and will be used to calculate the infusion rates throughout the entire blinded treatment course. If a subject qualifies for open-label study drug, the infusion rates for</b></p>	<p><i>Revised the recording of weight to align with availability of scale beds and to define the weight collection used to calculate the infusion rates for each treatment course.</i></p>

Section number and title in Amendment 2 (04 February 2016, Italy Specific)	Section number and title in Amendment 4 (20 September 2016, Italy Specific)	Original text:	Changed to:	Rationale
		starting the blinded study drug, and that weight used to calculate the dose of study drug to be administered. If this is not possible, permission from the Monitor must be obtained to use another method to obtain the subject's weight (such as information from the LAR or estimating using an established local protocol).	<b>the open-label infusion will be calculated using the subject's weight measured prior to dosing during V10.</b> <b>If it is not possible to obtain an actual weight at the above-referenced time points,</b> permission from the <b>Clinical</b> Monitor must be obtained to use another method to obtain the subject's weight (such as information from the LAR or estimating using an established local protocol). <b>In addition, a daily weight will be obtained and recorded if this is easily obtained, such as the use of a scale bed.</b>	

Section number and title in Amendment 2 (04 February 2016, Italy Specific)	Section number and title in Amendment 4 (20 September 2016, Italy Specific)	Original text:	Changed to:	Rationale
Sec. 11.2.5 ECG	Sec. 11.2.5 ECG	12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug...	<p><b>For the first 50 subjects randomized in the study</b>, 12-lead ECGs should be performed at Visit 1 and then at the following times relative to the start of each infusion of study drug...</p> <p><b>For the subsequent subjects randomized in the study, the following timepoints for ECG will be used:</b></p> <p><b>pre-dose and at +1 +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the blinded (first) study drug infusion</b></p> <p><b>pre-dose and at +1 +12, +24, +48, +72, +96, +120, +144, and +192 hours after the start of the open-label (second) study drug infusion</b></p> <p><b>It is not necessary to collect these ECGs with the PK samples at these timepoints and, apart from the +1h ECG, there is +/- 2 hour time window for these ECGs.</b></p> <p><i>Note: revision also made to SOA footnotes and throughout Sec. 12</i></p>	<i>Clarified the number of ECG timepoints required based on order of randomization, including the window for ECG collection and relation to PK draws.</i>

Section number and title in Amendment 2 (04 February 2016, Italy Specific)	Section number and title in Amendment 4 (20 September 2016, Italy Specific)	Original text:	Changed to:	Rationale
Sec. 11.2.8.1 Pharmacokinetic Data	Sec. 11.2.8.1 Pharmacokinetic Data	Plasma Analysis section, bullet # 4:  All samples will also be analyzed for plasma concentrations of Captisol®.	Plasma Analysis section, bullet # 4:  All samples <b>from the first 50 subjects randomized</b> will also be analyzed for plasma concentrations of Captisol®.	<i>Created an upper limit on Captisol® samples that will be analyzed by PK vendor.</i>
Sec. 14.1.4 Medical Monitor and Emergency Contact Information	Sec. 14.1.4 Medical Monitor and Emergency Contact Information	[REDACTED], MD	[REDACTED], MD  In a study related medical emergency situation, when the assigned Medical Monitor cannot be reached by a caller, an on-call Physician can be reached 24 hours per day, 7 days per week via an [REDACTED] Call-Center:  • Telephone: [REDACTED] (this is a chargeable telephone	<i>Updated [REDACTED] global 24/7 Medical Monitor and on-call physician contact information.</i>



Section number and title in Amendment 2 (04 February 2016, Italy Specific)	Section number and title in Amendment 4 (20 September 2016, Italy Specific)	Original text:	Changed to:	Rationale
			<p>number allowing a global reach from both landlines and mobile phones)</p> <ul style="list-style-type: none"> <li>• [REDACTED]</li> </ul> <p>On this internet page a list of country-specific toll-free telephone numbers is provided. It should be noted that not all countries globally have access to toll-free numbers as indicated on the “24/7 Medical Help desk” index. Countries without toll-free numbers need to dial the chargeable number as indicated above. Furthermore, toll-free numbers are not available from mobile phones.</p>	
N/A	Sec. 14.2.4 Reporting to European Regulatory Authorities	N/A	<p><b>14.2.4 Reporting to European Regulatory Authorities</b></p> <p><b>The Sponsor or its designee is responsible for SUSAR notification to the relevant regulatory authorities as outlined in the ICH</b></p>	<p><i>Section on EU Regulatory Reporting was omitted from previous amendment and added due to trial</i></p>

Section number and title in Amendment 2 (04 February 2016, Italy Specific)	Section number and title in Amendment 4 (20 September 2016, Italy Specific)	Original text:	Changed to:	Rationale
			<p><b>Guidelines. All investigators participating in the study will also be informed as required by regulations.</b></p> <p><b>Any SUSAR is subject to expedited reporting in the EU. The Sponsor or its designee, will report any single SUSAR to the appropriate National CAs and IECs within 7 days if the SUSAR is life-threatening or fatal (with the relevant follow-up information subsequently communicated within an additional eight days), and within 15 days if the SUSAR is neither life-threatening nor fatal. SUSARs reported will be those that have arisen in the present clinical trial and SUSARs that have arisen in other clinical trials conducted by the Sponsor with the same medicinal product.</b></p> <p><b>In addition to the expedited</b></p>	<p><i>occurring throughout EU.</i></p>

<b>Section number and title in Amendment 2 (04 February 2016, Italy Specific)</b>	<b>Section number and title in Amendment 4 (20 September 2016, Italy Specific)</b>	<b>Original text:</b>	<b>Changed to:</b>	<b>Rationale</b>
			<b>reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to competent authorities of the concerned Member States and to IEC(s)/IRBs as required by national laws.</b>	

**Summary of Changes**  
**Protocol-547-SSE-301**  
**Dated 14 FEB 2017**

The following changes were made to the attached protocol in this amendment. Minor typographical/editorial errors throughout the document were also corrected.

Section number and title in Protocol Amendment 4, Adults Only (18 AUG 16)	Section number and title in Protocol Amendment 5, (14 FEB 17)	Original text:	Changed to:	Rationale
Title Page	Title Page	<b>PROTOCOL NUMBER: 547-SSE-301 ADULT ONLY VERSION IND NUMBER: 117901</b>	<b>PROTOCOL NUMBER: 547-SSE-301 IND NUMBER: 117901</b>	<i>Reference to 'Adult Only Version' removed to reflect protocol inclusion of pediatric subjects</i>
2. Study Synopsis/Study Sites/Number of Subjects	2. Study Synopsis/Study Sites/Number of Subjects	Subjects will be aged 18 years or more, in SRSE	Subjects will be aged <b>two</b> years or more, in SRSE	<i>To reflect inclusion of pediatric subjects down to the age of 2 years</i>
2. Study Synopsis/Study Objectives/Primary Objective	2. Study Synopsis/Study Objectives/Primary Objective	To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult subjects with SRSE, and for	To determine the response to a 144-hour (6 day) continuous intravenous infusion of SAGE-547 compared to placebo administered to support the weaning of all third-line agents in adult <b>and pediatric</b> subjects with SRSE, and for the response to	<i>To reflect inclusion of pediatric subjects</i>

Section number and title in Protocol Amendment 4, Adults Only (18 AUG 16)	Section number and title in Protocol Amendment 5, (14 FEB 17)	Original text:	Changed to:	Rationale
		the response to endure at least 24 hours after the end of the SAGE-547 or placebo infusion (primary response)	endure at least 24 hours after the end of the SAGE-547 or placebo infusion (primary response)  <i>Note: change is also present in Section 5.1 Primary Objectives,</i>	
2. Study Synopsis/Study Objectives/Other Objectives	2. Study Synopsis/Study Objectives/Other Objectives	To evaluate the Modified Rankin Score (mRS)	To evaluate the Modified Rankin Score (mRS) ( <b>age ≥ 17 years</b> )  <i>Note: change is also present in Study Synopsis/Study Endpoints/Other Endpoints, Schedule of Assessments, Section 5.4 Other Objectives, Section 6.4 Other Endpoints, and 11.2.8.8. Modified Rankin Scale-9Q (mRS-9Q)</i>	<i>Clarification that the mRS is only applicable to adult patients over the age of 17</i>
2. Study Synopsis/Inclusion Criteria	2. Study Synopsis/Inclusion Criteria	1. Subjects 18 years of age and older	1. Subjects <b>two (2)</b> years of age and older  <i>Note: change is also present in Section 8.1 Inclusion Criteria</i>	<i>To reflect inclusion of pediatric subjects</i>
2. Study Synopsis/Exclusion Criteria	2. Study Synopsis/Exclusion Criteria	NA	4. Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing underlying neurological	<i>Additional exclusion criteria relevant to pediatric</i>

Section number and title in Protocol Amendment 4, Adults Only (18 AUG 16)	Section number and title in Protocol Amendment 5, (14 FEB 17)	Original text:	Changed to:	Rationale
			disorder.  <i>Note: change is also present in Section 8.2 Exclusion Criteria</i>	<i>population</i>
Section 11.1.1.2. EEG	Section 11.1.1.2. EEG	However, this protocol does not mandate continuous EEG monitoring and breaks from EEG monitoring to provide relief to the scalp from the irritating effects of the electrodes are advised, according to local practice.	However, this protocol does not mandate continuous EEG monitoring and breaks from EEG monitoring to provide relief to the scalp from the irritating effects of the electrodes are advised, <b>particularly in children</b> , according to local practice.	<i>To provide additional procedural guidance for pediatric subjects</i>
Section 11.2.2. Clinical Laboratory Tests	Section 11.2.2. Clinical Laboratory Tests	These samples will be analyzed at a central laboratory; hour-to-hour medical decisions will be based on sampling for laboratory testing done outside the protocol as part of normal standard of care. GFR will be calculated by the central laboratory.	<b>For adults and children <math>\geq 30</math> kg</b> , these samples will be analyzed at a central laboratory; hour-to-hour medical decisions will be based on sampling for laboratory testing done outside the protocol as part of normal standard of care. GFR will be calculated by the central laboratory. <b>For children under 30 kg, results of local laboratory testing undertaken at the protocolled timepoints may be sent to the central laboratory for inclusion in the central study</b>	<i>To provide additional procedural guidance for pediatric subjects</i>

Section number and title in Protocol Amendment 4, Adults Only (18 AUG 16)	Section number and title in Protocol Amendment 5, (14 FEB 17)	Original text:	Changed to:	Rationale
			<b>laboratory database; this obviates the need for additional blood sampling for central laboratory testing.</b>	
Section 11.2.2.2. Pregnancy Test	Section 11.2.2.2. Pregnancy Test	Females of child-bearing potential will be tested for pregnancy by serum pregnancy test at Visit 1. In this study, since an accurate history of menstruation in girls and menopause in older women may not be available at Visit 1, “child-bearing potential” is taken to mean any female aged 18 years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy.	Females of child-bearing potential will be tested for pregnancy by serum pregnancy test at Visit 1. In this study, since an accurate history of menstruation in girls and menopause in older women may not be available at Visit 1, “child-bearing potential” is taken to mean any female aged <b>10</b> years to 55 years, unless there is certainty that they are pre-menstrual or post-menopausal or that they have had a hysterectomy.  <i>Note: change is also present in Schedule of Assessments, and 12.1 Visit 1</i>	<i>To provide additional procedural guidance for pediatric subjects</i>
Section 11.2.8.1. Pharmacokinetic Data	Section 11.2.8.1. Pharmacokinetic Data	Each blood sample will be 3 ml in volume for subjects weighing 30 kg or more, and 1 ml in volume for subjects weighing less than 30 kg. Separate aliquots will be	Each blood sample will be 3 ml in volume for <b>adults and children</b> weighing 30 kg or more, and 1 ml in volume for <b>children</b> weighing less than 30 kg. Separate aliquots	<i>To provide additional procedural guidance for pediatric subjects</i>

Section number and title in Protocol Amendment 4, Adults Only (18 AUG 16)	Section number and title in Protocol Amendment 5, (14 FEB 17)	Original text:	Changed to:	Rationale
		obtained from each sample to service the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum blood draw for PK analysis for a subject having two infusions of study drug will be 99 ml (33 ml for subjects weighing less than 30 kg).	will be obtained from each sample to service the different analytical laboratories and provide a back-up sample at each timepoint for each subject. The maximum blood draw for PK analysis for a subject having two infusions of study drug will be 99 ml (33 ml for <b>children</b> weighing less than 30 kg).	



**Summary of Changes to  
Protocol 547-SSE-301, Amendment #5  
Date of Amendment: 03 May 2017**

The following substantive changes are made in Protocol 547-SSE-301, Amendment #5. In general, these include a change in assumptions for the sample size estimate yielding a lower overall target enrollment and a change reflecting that the Sponsor may elect not to conduct the Interim Analysis. In addition, minor editorial revisions (eg, formatting, punctuation, spelling), not listed below may have been made throughout the protocol.

<b>Section Number and Title</b>	<b>Original Text:</b>	<b>Changed To:</b>	<b>Rationale:</b>
Document Footer	12 August 2016	<del>12 August 2016</del> 03 May 2017	Administrative update to reflect date of current amendment
Title Page and Signature Page	[REDACTED], MD [REDACTED]	[REDACTED], MD [REDACTED]	Administrative update to reflect current title
Title Page		<b>Date of Amendment Five: 03 May 2017</b>	Administrative update to reflect date of current amendment
Signature Page	[REDACTED]	[REDACTED]	Administrative update to reflect appropriate signatory
Synopsis, Number of Subjects and Section 8 Selection and Withdrawal of Subjects	The study will randomize 140 subjects at up to 180 sites.	The study will randomize <del>140</del> -126 subjects at up to 180 sites.	Amended sample size estimate to reflect change in assumption of the placebo success rate. See below.

Section Number and Title	Original Text:	Changed To:	Rationale:
Synopsis, Study Design, Paragraph 6 and Section 7.1 Overview of Study Design, paragraph 5	Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo.	Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with <del>70-63</del> subjects to be randomized to SAGE-547 and <del>70-63</del> subjects to be randomized to placebo.	Amended sample size estimate to reflect change in assumption of the placebo success rate. See below.
Synopsis, Statistical Analysis, Interim Analysis and Section 13.1.1 Interim Analysis	When approximately 50% of the subjects have completed the study, an interim analysis will be conducted by the independent DSMB for sample size re-estimation purposes.	When approximately 50% of the subjects have completed the study, an interim analysis <del>will</del> <b>may</b> be conducted by the independent DSMB for sample size re-estimation purposes.	Wording revised to reflect that the interim analysis may not be performed.
Synopsis, Statistical Analysis, Sample Size and Section 13.2 Determination of Sample Size	The sample size of this study is based on the assumption of a 65% response rate to SAGE-547 treatment and a 35% response rate to placebo treatment and a 1:1 randomization schedule. Under these assumptions, with 70 subjects randomized to SAGE-547 and 70 subjects randomized to placebo, there would be >90% power for detecting a significant difference between groups at a 5% level of significance.	The sample size of this study is based on the assumption of a <del>65% response rate to SAGE-547 treatment and a 35%</del> <b>25%</b> response rate to placebo treatment, <b>a 30% treatment difference between SAGE-547 and placebo</b> , and a 1:1 randomization schedule. Under these assumptions, with <del>70-63</del> subjects randomized to SAGE-547 and <del>70-63</del> subjects randomized to placebo, there would be >90% power for detecting a significant difference between groups <b>with a 2-sided Chi-squared test</b> at a 5% level of significance.	It has been noted that > 50% of subjects successfully wean off third-line anesthetics during the qualifying wean prior to randomization. This high wean rate is likely to result in a very low placebo response rate in the randomized portion of the study. Thus, the assumed placebo response rate has been modified from 35% to 25%, with no change in the assumed difference between the rates of response to SAGE-547 and placebo,

Section Number and Title	Original Text:	Changed To:	Rationale:
			yielding a sample size estimate of 120 subjects, while maintaining adequate power in the study.
7.1 Overview of Study Design, Figure 1	<p><i>[removed Figure 1]</i></p>	<p>Replaced Figure 1 (new figure)</p>	Original figure could not be edited. Figure redrawn to remove the specification of the number of subjects per arm.
Section 7.3 Blinding and Randomization	Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with 70 subjects to be randomized to SAGE-547 and 70 subjects to be randomized to placebo.	Subjects will be randomized to SAGE-547 or placebo in a 1:1 ratio with <del>70-63</del> subjects to be randomized to SAGE-547 and <del>70-63</del> subjects to be randomized to placebo.	Amended sample size estimate to reflect change in assumption of the placebo success rate. See above.
Section 14.2.2 Data Safety Monitoring Board	An independent DSMB will monitor the clinical, PK and PD data for safety signals throughout the study and will be asked to assess the placebo response rate at the time of the interim analysis to determine final sample size.	An independent DSMB will monitor the clinical, PK and PD data for safety signals throughout the study and will be asked to assess the placebo response rate at the time of the interim analysis ( <b>if conducted</b> ) to determine final sample size.	Wording revised to reflect that the interim analysis may not be performed.