9. DOCUMENTATION OF STATISTICAL METHODS

Statistical Analysis Plan

STATISTICAL ANALYSIS PLAN

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VERSION FINAL 1.0

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
AE	Adverse event
AED	Anti-epileptic drug
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
AUC_{last}	Area under the plasma concentration-time curve from time 0 extrapolated to infinity
AUC_{∞}	Area under the plasma concentration-time curve from time 0 up to the time of last quantifiable plasma concentration
BMI	Body mass index
BUN	Blood urea nitrogen
CBC	Complete blood count
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression – Severity
CLs	Systemic clearance
C_{max}	Maximum observed plasma concentration
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
CSR	Clinical study report
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EEG	Electroencephalogram
eGFR	Estimated glomerular filtration rate
EOS	End of study
ESETT	Established Status Epilepticus Treatment Trial
FOUR	Full Outline of UnResponsiveness
GOS	Glasgow Outcome Scale
HPBCD	Hydroxypropyl beta-cyclodextrin
HR	Heart rate

Abbreviation or Specialist Term	Explanation
ICU	Intensive Care Unit
ITT	Intent to Treat
IV	Intravenous
LAR	Legally authorized representative
LOCF	Last observation carried forward
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
mRS	Modified Rankin Scale
PK	Pharmacokinetic
PP	Per-protocol
PR	Interval between the P and R waves on the electrocardiogram tracing
PT	Preferred term
QRS	QRS waves complex on the electrocardiogram tracing
QT	Interval between the Q and T waves on the electrocardiogram tracing
QTc	Corrected QT interval
QTcF	QTc using the Fridericia correction
QW	Qualifying wean
QWS	Qualifying wean success
RBC	Red blood cell
RSE	Refractory status epilepticus
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SE	Status epilepticus
SOC	System organ class
SRS	Severity Rating Scale
SRSE	Super-refractory status epilepticus
STESS	Status Epilepticus Severity Score

Abbreviation or Specialist Term	**Explanation**
TLA	Third-line agent
t_{max}	Time to maximum plasma concentration

1. PURPOSE OF THE ANALYSES

This statistical analysis plan (SAP) has been developed to provide detailed descriptions of pre-specified methods to be used for the analyses of study data for Sage Therapeutics Protocol Number 547-SSE-301, Amendment 5: 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 dated 03 May 2017.

Analysis datasets for data analyses, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will form the basis for the results sections of the clinical study report (CSR) for this trial.

This SAP will be finalized and signed-off before database lock and study treatment unblinding. After database lock, any additional analyses required to supplement the pre-planned statistical analyses described in this SAP will be described in the CSR.

ICON is responsible for the statistical analysis and reporting of the study data.

2. PROTOCOL SUMMARY

2.1. 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 super refractory status epilepticus (SRSE), and for the response to endure at least 24 hours after cessation of the SAGE-547 or placebo infusion (primary response).

Secondary Objectives:

- 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;
- To compare between SAGE-547 and placebo Clinical Global Impression – Improvement (CGI-I) response rates;
- 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;
- To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;
- To compare between SAGE-547 and placebo 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;
- To compare between SAGE-547 and placebo 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;
- To compare between SAGE-547 and placebo the number of separate episodes of status epilepticus occurring up to Visit 12;
- To compare between SAGE-547 and placebo 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 as compared to placebo via:

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

e. Mortality.

Other Objectives:

- To evaluate the impact of treatment with a higher dose of SAGE-547 infusion;
- To evaluate the pharmacokinetics of SAGE-547, and present Captisol® and identified SAGE-547 metabolite plasma concentrations;
- To correlate changes in QT/QTc interval with plasma concentrations of SAGE-547.
- To determine the number of days in the Intensive Care Unit (ICU), number of days in hospital, discharge destination from the ICU, discharge destination from the hospital, discharge ability criteria, resource use for subjects discharged from hospital before Visit 12/12R;
- To evaluate Clinical Global Impression (CGI) Scale;
- To evaluate the Full Outline of UnResponsiveness (FOUR) Score;
- To evaluate the Glasgow Outcome Score (GOS);
- To evaluate the Supervision Rating Scale (SRS);
- To evaluate the Modified Rankin Scale (mRS) (age ≥17 years);
- To evaluate the below data in subjects with a qualifying wean success:
  - Adverse events and medications;
  - Laboratory testing (hematology, serum chemistry, and urinalysis);
  - Vital signs (blood pressure, heart rate, temperature, weight);
  - ECG parameters;
  - Mortality;
  - Epilepsy status;
  - Outcome data.

2.2. Overall Study Design and Plan

Figure 1 provides an overview of the study design.

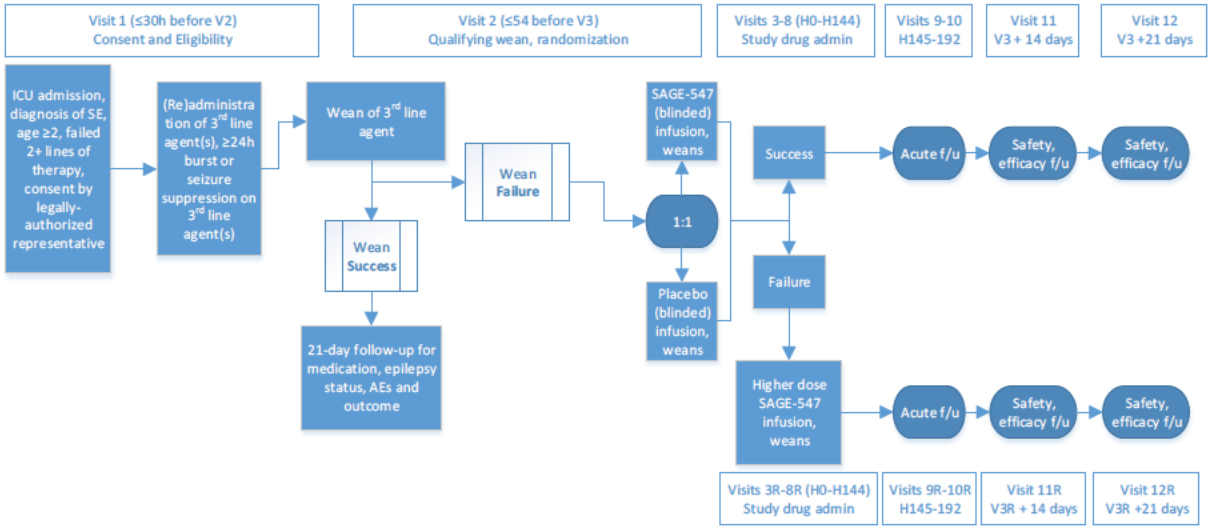
This is a randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy and safety of SAGE-547 administered as a continuous intravenous infusion as compared to placebo in subjects with SRSE. Prior to randomization, subjects with status epilepticus will be administered one or more third-line agents at a dose sufficient to maintain a burst or seizure suppression pattern on the electroencephalogram (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). Subjects who are successfully weaned during the QW (ie, wean off third-line agents with no need to restart any 3rd line agent during the 24 hours post wean) 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 in a 1:1 ratio. 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). Subjects must commence the blinded study treatment infusion within eight hours of the investigators determination of QW failure. Burst suppression must be maintained for the first 12 hours of the infusion of study drug.

For all randomized subjects, 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 response criteria, with a response defined as the ability to wean the subject off all third-line agents before the end of the infusion of blinded study treatment without the need to re-institute a third-line agent for at least 24 hours following cessation of the blinded study treatment. 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 response.

Those subjects who fail to meet the primary endpoint and require re-institution of a third-line agent regimen before the end of the blinded study treatment infusion or within 24 hours of completing the blinded study treatment 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 initiation of the open-label infusion.

Figure 1: Study Design



2.3. Study Population

Subjects will be aged two years or more, in SRSE, and managed in an intensive care setting.

2.4. Treatment Regimen

Dosing Schedule (Blinded Infusions)

SAGE-547 Injection or placebo will be administered according to the dosing schedule in Table 1. 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 1: 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 H129 – H136 H137 – H144	8 hour taper 8 hour taper 8 hour taper	65 µg/kg/h 45 µg/kg/h 25 µg/kg/h

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 2. 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 2: 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 H127 – H132 H133 – H138 H139 – H144	6 hour taper 6 hour taper 6 hour taper 6 hour taper	125 µg/kg/h 95 µg/kg/h 65 µg/kg/h 35 µg/kg/h

2.5. Selection of Subjects and Treatment Assignment

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

2.6. Sample Size Determination

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 use (yes or no) and number of previous third-line agent wean attempts prior to randomization (one vs. two or more). A modification of the Pocock and Simon (1975) "range method" minimization algorithm will be used to allocate treatments and ensure an approximate balance across treatment groups while minimizing imbalance within each stratum.

3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

The following are general conventions for the analysis of study data. If alternative methods are present in the specific evaluation sections of this SAP, those conventions will take precedence over these general conventions.

- Continuous study measurements will be summarized by treatment group (SAGE-547 or Placebo) and timepoint (as applicable) using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Means and medians will be presented with one more decimal place than the precision of the data. Standard deviations will be presented with two more decimal places than the precision of the data. Minimums and maximums will be presented with the same precision as the original data.
- Categorical study assessments will be summarized by treatment group (SAGE-547 or Placebo) and timepoint (as applicable) using frequency counts and percentages. Unless stated otherwise, percentages are based on the number of subjects in the analysis set. Percentages will be presented with one decimal place (xx.x), with the exception of 100%, which will be displayed without any decimal places.
- Descriptive summaries based on the Intent to Treat (ITT) analysis set, modified ITT (mITT) analysis set, per-protocol (PP) analysis set, pharmacokinetics (PK) analysis set (as described in Section 4) will be displayed by randomized treatment.
- Descriptive summaries based on the safety analysis set (described in Section 4) will be displayed by actual treatment received (SAGE-547 or Placebo). Summaries based on the Safety analysis set (open-label subset) will be displayed by actual treatment received and overall. Summaries based on the ITT analysis set (open-label subset) will be displayed by randomized treatment and overall.
- Summaries based on the qualifying wean success (QWS) analysis set (as described in Section 4.6) will be displayed overall.
- All listings will be listed by randomized treatment group, if applicable.
- Scheduled assessments will be included in summaries. Unscheduled assessments will only be included in the display sections that report abnormal laboratory, vitals, or ECG values. Data from all assessments (scheduled and unscheduled), will be included in listings. For the purpose of reporting abnormal laboratory, vitals, or ECG values for the open-label subset, the below rules will be used to classify the measurements into either the double-blind or open-label period:
  - Measurements that started on or after the initiation of open-label treatment will be assigned to open-label period.
  - Measurement that started before the initiation of open-label treatment will be assigned to double-blind period.
- All statistical tests will be performed at a significance level of 0.05 (two-tailed). Where applicable, two-sided 95% confidence intervals will be reported. For tables

based on open-label subset and QWS analysis sets, no statistical tests will be performed.

- P-values will be reported to 3 decimal places, with values less than 0.001 displayed as '<0.001'. Unless otherwise noted, no adjustments for multiple comparisons will be made.
- No preliminary rounding will be performed; rounding should only occur after analysis. To round, consider the digit to the right of last significant digit: if <5 then round down, if ≥5 then round up.

Table 3: Overview of Summary/Analyses by Analysis Sets

Variables (described in Sections 5 to 9)	**Analysis Sets**	**Data used in Analysis/Summary**
Primary and secondary efficacy variables	ITT, mITT (selected secondary efficacy variables), PP (selected secondary efficacy variables)	Variables derived or assessed during double-blind period
	ITT (Open-label subset)	Variables derived or assessed during open-label period
Outcome variables (except FOUR) and pharmacoeconomic variables	ITT	Variables assessed during double-blind and open-label period (Visit 1, Visit 12, Visit 12R, if applicable)
	QWS	Variables assessed for this group of subjects
Study drug injection, Continuous IV Infusion of Third-Line Agent	Safety	Include timepoints assessed during the double-blind period
	Safety (Open-label subset)	Include timepoints assessed during the open-label period
	QWS	Not applicable
Safety data by timepoint (laboratory testing, vital signs, ECG); outcome variable FOUR	Safety (for safety variables) ITT (for FOUR)	Include timepoints assessed during the double-blind period
	Safety (Open-label subset) for safety variables ITT (Open-label subset) for FOUR	Include timepoints assessed during the double-blind period and open-label period
	QWS	Data collected for this group of subjects

Table 3: Overview of Summary/Analyses by Analysis Sets (Continued)

Variables (described in Sections 5 to 9)	Analysis Sets	Data used in Analysis/Summary
PK concentration and PK parameters	PK	Data collected or derived during the double-blind period
	PK (Open-label subset)	Data collected or derived during the double-blind period and open-label period
Safety data (TEAEs, concomitant medications/procedures)	Safety	Include events occurred during the double-blind period (described on next page how to group TEAEs and concomitant medications/procedures into double-blind period or open-label period for the open-label subset)
	Safety (Open-label subset)	Include events occurred during the open-label period
	QWS	Described on next page on how TEAE and concomitant medication is defined for this group of subjects
Disposition, demographic data, medical history, prior medication, mortality	Safety	Data collected for safety analysis set
	Safety (Open-label subset)	Data collected for open-label subset
	QWS	Data collected for QWS analysis set

ECG = electrocardiogram, FOUR = Full Outline of UnResponsiveness, mITT = Modified Intent to Treat, ITT = Intent to Treat, IV = Intravenous, PK = pharmacokinetic, QWS = qualifying wean success, TEAE = treatment-emergent adverse events.

- Unless stated otherwise, the baseline will be calculated as the last observed assessment (including scheduled and unscheduled assessments) before the initiation of the infusion of blinded treatment. For summaries based on the QWS analysis set, the baseline is defined as the last observed assessment collected before the end date/time of the infusion of continuous intravenous (IV) third-line agent with successful qualifying wean + 24 hours. Change from baseline values will be calculated as the post-baseline value minus the respective baseline value.
- For the safety analysis set, prior medications are those that started and ended before the initiation of the infusion of blinded treatment. Concomitant medications are those that started before initiation of blinded treatment and continued into blinded treatment or those that started after the initiation of the infusion of blinded treatment. For open-label subset, concomitant medications that started before the initiation of open-label treatment will be assigned to the double-blind period. The concomitant medications that started before the initiation of open-label treatment and continued into open-label treatment or those that started on or after the initiation of the open-label treatment will be assigned to the open-label period.

- For the QWS analysis set, prior medications are those that started and ended before the end date/time of the infusion of continuous IV third-line agent with successful qualifying wean + 24 hours. Concomitant medications are those that started before and continued into the (end date/time of the infusion of continuous IV third-line agent with successful qualifying wean + 24 hours) or those that started on or after the (end date/time of the infusion of continuous IV third-line agent with successful qualifying wean + 24 hours).
- For the safety analysis set, Treatment-Emergent Adverse Events (TEAEs) are defined as those that begin on or after initiation of the infusion of blinded treatment. For open-label subset, TEAEs that started on or after the initiation of blinded treatment and before the initiation of open-label treatment will be assigned to the double-blind period. TEAEs that started on or after the initiation of open-label treatment will be assigned to open-label period. Please refer to Table 3 for the further classification of TEAEs by the following treatment periods:
  - Double-blind treatment period
  - Double-blind extended follow-up period
  - Open-label treatment period
  - Open-label extended follow-up period

For the TEAEs that occurred during the treatment period, please refer to Table 4 for the classification of TEAEs by the following dose phases:

- Loading phase (ie, the initial 24 hours following the start of infusion)
- Maintenance phase (ie, from 24 hours following the start of infusion to the end of the maintenance dose)
- Taper phase (ie, from the end of maintenance dose to the end of infusion)
- Acute follow-up phase (ie, the initial 24 hours following end of infusion)

All adverse event (AE) tables will be summarized by treatment period. Selected AE tables will be summarized by dose phase.

Table 4: Classification of TEAEs by Treatment Period

Subjects not entering open-label period:

TEAE Start Date/time	TEAE Classification by Treatment Period
Blinded infusion start date/time ≤ AE start date/time ≤ (Blinded infusion end date/time + 24 hours)	Double-blind Treatment Period
(Blinded infusion end date/time + 24 hours) < AE start date/time	Double-blind Extended Follow-up Period

AE = adverse event.

Subjects entering open-label period:

	TEAE Start Date/time	TEAE Classification by Treatment Period
For TEAEs during double-blind period (ie, the TEAEs started on or after the initiation of double-blind treatment and before the initiation of open-label treatment)	Blinded infusion start date/time ≤ AE start date/time ≤ (Blinded infusion end date/time + 24 hours)	Double-blind Treatment Period
	(Blinded infusion end date/time + 24 hours) < AE start date/time < Open-label infusion start date/time	Double-blind Extended Follow-up Period
For TEAEs during open-label period (ie, the TEAEs started on or after the initiation of open-label treatment)	Open-label infusion start date/time ≤ AE start date/time ≤ (Open-label infusion end date/time + 24 hours)	Open-label Treatment Period
	(Open-label infusion end date/time + 24 hours) < AE start date/time	Open-label Extended Follow-up Period

AE = adverse event, TEAE = treatment-emergent adverse events.

Table 5: Classification of TEAEs by Dose Phase

Subjects not entering open-label period:

	TEAE Start Date/time	TEAE Classification by Dose Phase
For TEAEs in Double-blind Treatment Period from Table 3-2	Blinded infusion start date/time ≤ AE start date/time ≤ (Blinded infusion start date/time + 24 hours)	Double-blind Treatment Period: Loading Phase
	(Blinded infusion start date/time + 24 hours) < AE start date/time ≤ (Blinded maintenance dose end date/time)	Double-blind Treatment Period: Maintenance Phase
	(Blinded maintenance dose end date/time) < AE start date/time ≤ (Blinded infusion end date/time)	Double-blind Treatment Period: Taper Phase
	(Blinded infusion end date/time) < AE start date/time ≤ (Blinded infusion end date/time + 24 hours)	Double-blind Treatment Period: Acute Follow-up Phase

Note: if subject did not receive a certain dose level, then no TEAE will be associated with that dose phase
AE = adverse event, TEAE = treatment-emergent adverse events.

Subjects entering open-label period:

	TEAE Start Date/time	TEAE Classification by Dose Phase
For TEAEs in Double-blind Treatment Period from Table 3-2	Blinded infusion start date/time ≤ AE start date/time ≤ (Blinded infusion start date/time + 24 hours)	Double-blind Treatment Period: Loading Phase
	(Blinded infusion start date/time + 24 hours) < AE start date/time ≤ (Blinded maintenance dose end date/time)	Double-blind Treatment Period: Maintenance Phase
	(Blinded maintenance dose end date/time) < AE start date/time ≤ (Blinded infusion end date/time)	Double-blind Treatment Period: Taper Phase
	(Blinded infusion end date/time) < AE start date/time ≤ (Blinded infusion end date/time + 24 hours)	Double-blind Treatment Period: Acute Follow-up Phase

For TEAEs in Open-label Treatment Period from Table 3-2	Open-label infusion start date/time ≤ AE start date/time ≤ (Open-label infusion start date/time + 24 hours)	Open-label Treatment Period: Loading Phase
	(Open-label infusion start date/time + 24 hours) < AE start date/time ≤ (Open-label maintenance dose end date/time)	Open-label Treatment Period: Maintenance Phase
	(Open-label maintenance dose end date/time) < AE start date/time ≤ (Open-label infusion end date/time)	Open-label Treatment Period: Taper Phase
	(Open-label infusion end date/time) < AE start date/time ≤ (Open-label infusion end date/time + 24 hours)	Open-label Treatment Period: Acute Follow-up Phase

Note: if subject did not receive a certain dose level, then no TEAE will be associated with that dose phase
AE = adverse event, TEAE = treatment-emergent adverse events.

- For the QWS analysis set, emergent AEs are defined as those AEs that started on or after the end date/time of the infusion of continuous IV third-line agent with successful qualifying wean + 24 hours (ie, end date/time of infusion + 24 hours ≤ AE start date).
- For all data, the visit or start date (and time when available) will be used to calculate study day. The study day for double-blind period is calculated as: visit date/time-initiation of the blinded treatment + 1; Study day for open-label period is calculated as: visit date/time - initiation of the infusion of open-label treatment + 1.
- All subject data, including unscheduled assessments, will be displayed in listings.
- End of study values are calculated using the last observation carried forward (LOCF) methodology (including scheduled and unscheduled assessments)
- Unless stated otherwise, available data from screen failures will be excluded from all tables and figures, but will be presented in any applicable data listings where data was collected for screen failure subjects.
- SAS statistical software, version 9.1.3 or later, will be used for all analyses.

The following conventions will be used for missing adverse event dates and prior and concomitant dates.

Adverse Event Onset Date

If an AE onset date is completely missing (ie, in which the day, month, and year are all unknown), then the AE onset date will be set to the date of initiation of the treatment.

For a partial AE onset date and time,

- When the year is present and the month and day are missing:
  - If the year of AE onset = the year of initiation of the treatment, then the month and day will be set to the month and day of initiation of the treatment.
  - If the year of AE onset < the year of initiation of the treatment, then the month and day will be set to December 31st.

  - If the year of AE onset > the year of initiation of the treatment, then month and day will be set to January 1st.

- When the year and day are present and the month is missing:
  - If the year of AE onset = the year of initiation of the treatment, then the month will be set to the month of initiation of the treatment.
  - If the year of AE onset < the year of initiation of the treatment, then the month will be set to December.
  - If the year of AE onset > the year of initiation of the treatment, then the month will be set to January.
- When the month and year are present and the day is missing:
  - If the year of AE onset = the year of initiation of the treatment and:
    - the month of AE onset = the month of initiation of the treatment, then the day will be set to the day of initiation of the treatment.
    - the month of AE onset < the month of initiation of the treatment, then the day will be set to the last day of the month.
    - the month of AE onset > the month of initiation of the treatment, then the day will be set to the 1st day of month.
  - If the year of AE onset < the year of initiation of the treatment, then the day will be set to the last day of the month.
  - If the year of AE onset > the year of initiation of the treatment, then the day will be set to the 1st day of the month.
- If the imputed AE onset date is after the AE stop date, then the onset date will be set to the AE stop date.

Prior and Concomitant Medication Date

If the start date (or end date) of a medication is completely missing (ie, in which the day, month, and year are all unknown) or only the day is known, then the start date (or end date) will not be imputed. Unless the end date is before the start date of blinded infusion, the medication will be considered concomitant.

For a partial start date of medication,

- If the year is present and the month and day are missing, then the month and day will be set to January 1.
- If the year and day are present and the month is missing, then the month will be set to January.
- If the year and month are present and the day is missing, then the day will be set to the 1st day of month.

- If the imputed start date of medication is after the non-imputed end date of medication, then the start date will be set to the end date of medication.

For a partial end date of medication,

- If the year is present and the month and day are missing, then the month and day will be set to December 31.
- If the year and day are present and the month is missing, then the month will be set to December.
- If the year and month are present and the day is missing, then the day will be set to the last day of the month.

4. ANALYSIS SETS

4.1. Safety Analysis Set

The safety analysis set will include all subjects who had an infusion of blinded study medication initiated.

Subjects will be classified according to actual treatment received. If a subject receives SAGE-547 at any time during the double-blind treatment period, that subject will be summarized in the SAGE-547 group. This analysis set will be used for all safety analyses.

Safety analysis set (open-label subset) will include subjects in the safety analysis set who also had an initiation of open-label SAGE-547 treatment.

4.2. Intent to Treat Analysis Set

The Intent to Treat (ITT) analysis set will include all subjects who had an infusion of blinded study medication initiated.

Subjects will be classified according to randomized treatment. This analysis set will be used for all efficacy analyses.

The ITT analysis set (open-label subset) will include subjects in ITT analysis set who also had an initiation of open-label SAGE-547 treatment.

4.3. Modified Intent to Treat Analysis Set

The modified Intent to Treat (mITT) analysis set will include all subjects in the ITT set who:

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

For subjects on multiple third-line agents, only one wean attempt is required from any of the third-line agents to qualify for this analysis set.

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

4.4. Per-Protocol Analysis Set

The Per–Protocol (PP) analysis set is defined as a subset of the ITT analysis set but will exclude data from all subjects with major protocol violations or deviations that could potentially confound the efficacy evaluation.

Subjects will be classified according to randomized treatment received. This analysis set will be used for sensitivity/supportive analyses to examine the robustness of results for the primary and key secondary efficacy endpoints.

4.5. Pharmacokinetics Analysis Set

The pharmacokinetics (PK) analysis set will include all subjects who at least had an infusion of blinded or open-label SAGE-547 initiated and have at least one pharmacokinetic sample collected.

This analysis set will be used for all PK analyses.

4.6. Qualifying Wean Success Analysis Set

The qualifying wean success (QWS) analysis set will include all subjects who wean off third-line agents with no need to restart any third line agent during the 24 hours post wean. This analysis set will be used for summaries of all data collected for these subjects.

4.7. Pharmacogenetic Analysis Set

The pharmacogenetic analysis set will include all subjects who consented to being included in the pharmacogenetic assessment and provided a pharmacogenetic sample. No analyses of this analysis set are included in this SAP. Any analyses conducted for this analysis set will be described in a separate document.

5. STUDY SUBJECTS

5.1. Disposition of Subjects

Subjects or their legally authorized representatives (LARs) may withdraw consent to participate in the study at any time for any reason without compromising the subject's medical care. The Investigator will also withdraw subjects if clinically indicated, upon the request of Sage Therapeutics, or upon termination of the study.

Study completion and withdrawal from the study will be summarized by treatment group for all randomized subjects. The summary table will include the numbers of subjects included in each analysis set and those who completed or did not complete the study, along with any reasons for non-completion. Reasons will include the subject or LAR is unwilling or unable to adhere to the protocol-specified visits, AEs, lack of efficacy, subject died, withdrew consent, development of ineligibility criteria, lost to follow-up, sponsor discretion, investigator discretion, study closed/terminated, and an 'other' category for reasons different than those previously listed. Separate summaries will be created for the QWS analysis set.

For subjects that terminate the study early, study day of termination will be calculated as (date of termination – date of initiation of the randomized treatment infusion + 1).

A data listing for all subjects will display disposition characteristics, including date of initiation of the infusion of study treatment, study completion status, last study day/date completed, reason(s) for non-completion, date of early termination assessment/study day of termination, and any specific comments related to non-completion.

5.2. Protocol Deviations

Protocol deviations will be evaluated for all subjects in the safety analysis set. A data listing by treatment group (including QWS if applicable), subject, and visit/timepoint will present details of each deviation. A by-subject listing will display date/time of informed consent, whether all eligibility criteria were met, any criteria that were not met, and whether an entry waiver was granted. A list of study inclusion and exclusion criteria is given in Table 6. All protocol deviations will be classified by the Sponsor as major or minor prior to database lock to facilitate the defining of the PP analysis set (see Section 4.4). Subjects with major deviations that could potentially confound treatment effect will be excluded from the PP analysis set.

Examples of major deviations are the following:

- Subject received the incorrect blinded study drug
- Subject was not receiving any third-line agent at start of study drug infusion
- Subject received <80% of the total dose expected during the loading and maintenance infusions
- Subject received >120% of the total dose expected during the loading and maintenance infusions
- Subject received >148 hour total infusion (ie, >4 hours longer than expected)

- Subject received <116 hour loading + maintenance infusion (ie, >4 hours shorter than expected)
- Subject received >123 hour maintenance infusion (ie, >4 hours longer than expected)
- Subject had a >4 hour gap in the maintenance infusion

Table 6: Protocol Inclusion and Exclusion Criteria

Inclusion Criteria:	
	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 (eg, benzodiazepine or other emergent initial anti-epileptic [AED] treatment), according to institution standard of care, and; • Failed to respond to at least one second-line agent (eg, 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:	
	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. 4. Children (subjects aged less than 17 years) with an encephalopathy due to a rapidly progressing 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 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.

Inclusion Criteria:	
	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 (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 (ie, subjects may not have received study drug/placebo and then re-enroll).

6. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographics and baseline characteristics will be summarized by treatment group for the safety analysis set. Separate summaries will be created for the safety analysis set (open-label subset) and QWS analysis set.

Demographic data will include:

- Age (calculated as the number of years from date of birth to the date of informed consent)
- Age group (<18, 18 to <65, ≥65 years)
- Pediatric age group (2 to <6, 6 to <12, 12 to <18 years)
- Gender (male, female)
- Race (White, Black, Asian, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Country
- Region (North America, Rest of World)
- Height (cm)
- Weight (kg)
- Weight group (≤30, >30 kg)
- Body Mass Index (BMI; kg/m^2) calculated as weight/$[height]^2$
- BMI group (<25, 25 to <30, 30 to <40, ≥40 kg/m^2)

Baseline characteristics will include Status Epilepticus (SE) and wean history:

- Previous diagnosis of epilepsy (yes, no)
- Etiology of index case of status epilepticus (epilepsy with antiepileptic drug noncompliance, epilepsy with/without known trigger, autoimmune/infectious, medication/substance related, genetic/malformations of the cortical development, metabolic, neoplastic, traumatic, vascular, unknown/cryptogenic)
- Structural cause of status epilepticus (structural, non-structural)
- Pre-dose duration of SE
- Pre-dose duration of SE Category (0 to 1, 2 to 5, 6 to 10, >10 days)
- Number of previous wean attempts (0, 1, 2 to 3, >3)
- Number of AEDs at baseline
- Number of AEDs at baseline category (1 to 3, >3)
- Number of third-line agents (TLAs) at baseline (not needed for QWS)

- Number of TLAs at baseline category (1, 2, 3, >3) (not needed for QWS)
- Type of TLA at baseline (ketamine, midazolam, pentobarbital, thiopental, propofol) (not needed for QWS)
- Concomitant pentobarbital/thiopental use (yes, no) (not needed for QWS)

Baseline characteristics will also include the following functional assessment information collected during the baseline period (Visit 1):

- Status Epilepticus Severity Score (STESS)
- Full Outline of UnResponsiveness (FOUR)
- Supervision Rating Scale (SRS)
- Modified Rankin Scale (mRS)
- Clinical Global Impression-Severity (CGI-S)

The pre-dose duration of each diagnosis of SE, refractory SE (RSE), and SRSE will be calculated as the minimum value of (the difference between the diagnosis end date and the diagnosis start date + 1) and (the difference between the date of initiation of blinded treatment and the diagnosis start date +1). Durations of diagnosis will be summarized by treatment group for the safety analysis set and the safety analysis set (open-label subset). Separate summaries will be created for the QWS analysis set. For the QWS analysis set, durations of diagnosis will be calculated as the minimum value of (the difference between the diagnosis end date and the diagnosis start date + 1) and (the difference between the end date/time of the infusion of continuous IV third-line agent with successful qualifying wean + 24 hours and the diagnosis start date +1).

Demographic and baseline characteristics data will be listed by treatment group (including QWS group if applicable) and subject. Details related to SE disease progression, including diagnosis, start and stop dates, duration before initiation of the infusion of SAGE-547 or placebo will be listed by treatment group (including QWS group if applicable) and subject.

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.1. Summaries of medical history will be presented for the safety analysis set, safety analysis set (open-label subset), and QWS analysis set. These frequency tables will be sorted by system organ class (SOC) in alphabetical order and then by preferred term in descending order of frequency based on the Total column (where present), then the SAGE-547 column, then the Placebo column within SOC. Preferred terms with the same frequency within SOC will be sorted alphabetically. Medical history details, including medical condition, start and end dates, and ongoing status will be listed by treatment group (including QWS if applicable) and subject.

7. EFFICACY EVALUATION

7.1. Overview of Efficacy Analyses

Change from baseline (described in Section 3) will be calculated at each timepoint and for the end of study observation where applicable. Continuous endpoints will be summarized with n, mean, standard deviation, median, minimum and maximum. Categorical endpoints will be summarized by counts and percentages.

7.2. Analysis Methods

7.2.1. Primary Efficacy Variable

7.2.1.1. Derivation of Variable

Treatment response will be derived, with response defined as weaning the subject off all third-line agents for seizure or burst suppression before the completion of the randomized treatment infusion without having to re-institute any third-line agent for seizure or burst suppression during the 24 hours after the end of the randomized treatment infusion. 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 a responder. As such, the primary variable of treatment response is a composite endpoint of three variables: absence of third-line agents at Hour 144, no re-institution of third-line agents for *at least* 24 hours after the end of the randomized treatment infusion, and evidence of physiologic brain activity.

Absence of third-line agents at Hour 144

An indicator of absence of third-line agents for seizure or burst suppression will be calculated as:

- IF the third-line agent stop date/time is less than the randomized treatment stop date/time, THEN set the absence indicator equal to 1.
- IF there is no third-line agent stop date/time or if the third-line agent stop date/time is greater than or equal to the randomized treatment stop date/time, THEN set the absence indicator equal to 0.

For subjects on more than one third-line agent, the third-line agent stop date/time will be the latest stop date/time of all third-line agents. Only third-line agents with an indication of seizure or burst suppression will be included in this calculation.

No re-institution of third-line agents for at least 24 hours after the end of the randomized treatment infusion

An indicator of no re-institution of third-line agents for *at least* 24 hours after the end of the randomized treatment infusion will be calculated as:

- IF the difference between the third-line agent re-institution date/time and the randomized treatment stop date/time is greater than or equal to 24 hours, THEN set the no re-institution indicator equal to 1.

- IF there is no third-line agent stop date/time or if the difference between the third-line agent re-institution date/time and the randomized treatment stop date/time is less than 24 hours, THEN set the no re-institution indicator equal to 0.

Only third-line agents with an indication of seizure or burst suppression will be included in determination of re-institution of third-line agents.

Evidence of physiologic brain activity

Investigators will assess for physiologic brain activity using the EEG performed at Visit 9. An indicator of physiologic brain activity will be calculated as:

- IF the investigator assessment of physiologic brain activity is equal to "Yes", THEN set the physiologic brain activity indicator equal to 1.
- IF the investigator assessment of physiologic brain activity is equal to "No", THEN set the physiologic brain activity indicator equal to 0.

Treatment response

Using the three previous variables, an indicator of treatment response will be calculated as:

- IF the sum of the three previous variables is equal to 3, then set the treatment response indicator equal to 1.
- IF the sum of the three previous variables is less than 3, then set the treatment response indicator equal to 0.

A separate treatment response variable will be calculated for those subjects receiving SAGE-547 during the open-label period. Similar to the above derivation for the randomized treatment period, treatment response during the open-label period is a composite endpoint of three variables: absence of third-line agents before completion of the open-label SAGE-547 infusion, no re-institution of third-line agents for *at least* 24 hours after the end of the open-label infusion, and evidence of physiologic brain activity post completion of the open-label infusion (Visit 9R).

7.2.1.2. Analysis of Variable

The analysis of treatment response between SAGE-547 treated subjects and placebo treated subjects will be performed on the ITT analysis set using logistic regression methods. The model will include terms for treatment group, concomitant pentobarbital/thiopental use (yes or no), and number of previous third-line agent wean attempts prior to randomization (one vs. two or more). Model based point estimates (ie, odds ratios), 95% confidence intervals, and p-values will be reported.

As a supportive analysis, the Cochran-Mantel-Haenszel (CMH) test will be performed for the ITT analysis set with covariates 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 chi-square statistic and its associated p-value will be reported. In case of convergence issues with the primary logistic regression model, the CMH test will be used as the primary analysis.

Additional supportive analyses of the primary endpoint will be performed on the mITT and PP analysis sets. In addition, subgroup analyses of the primary endpoint will be performed using the ITT analysis set by the following variables:

- Concomitant pentobarbital/thiopental use (yes, no)
- The number of third-line agents (one, two, or three) administered post-randomization during the double-blind period
- The third line agent that was the subject of the terminal wean
- Region (North America, Rest of World)
- Gender (male, female)
- Age group (<18, 18 to <65, ≥65 years)
- Pediatric age group (2 to <6, 6 to <12, 12 to <18 years)
- Race (White, Black, Asian, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Weight group (≤30, >30 kg)
- BMI group (<25, 25 to <30, 30 to <40, ≥40 kg/m^2)
- Etiology of index case of status epilepticus category (epilepsy with antiepileptic drug noncompliance, epilepsy with/without known trigger, autoimmune/infectious, medication/substance related, genetic/malformations of the cortical development, metabolic, neoplastic, traumatic, vascular, unknown/cryptogenic)
- Structural cause of SE category (structural, non-structural)
- Previous epilepsy diagnosis (yes, no)
- Number of AEDs at baseline category (1 to 3, >3)
- Number of TLAs at baseline category (1, 2, 3, >3)
- Type of TLA at baseline (ketamine, midazolam, pentobarbital, thiopental, propofol)
- Number of previous wean attempts (0, 1, 2 to 3, >3)
- Pre-dose duration of SE category (0 to 1, 2 to 5, 6 to 10, >10 days)

Subgroup analyses for the primary endpoint will be conducted both descriptively and using previously described logistic regression methods where sufficient numbers of subjects are available in a given subgroup. Forest plots will be presented for those subgroups with sufficient numbers of subjects.

Treatment response during the open-label period will be summarized by randomized treatment group and overall. No statistical tests will be performed for summaries of treatment response during the open-label period.

Response rates will be presented by treatment group.

7.2.2. Secondary Efficacy Analyses

7.2.2.1. Derivation of Variables

Absence of third-line agents

The calculation of absence of third-line agents was described in Section 7.2.1.1 .

Clinical Global Impression – Improvement (CGI–I) response

An indicator of CGI-I response will be calculated as:

- IF the CGI-I score is equal to 1 ("very much improved") or 2 ("much improved"), THEN set the CGI-I response indicator equal to 1.
- IF the CGI-I score is greater than 2, THEN set the CGI-I response indicator equal to 0.

At Visit 12 and Visit 12R (if applicable), if the CGI-I score is missing, assume CGI-I response = 0.

Time from treatment response to re-institution of any third-line agent

The time from treatment response to re-institution of any third-line agent will be calculated as the difference between the start date/time of any re-institution of a third-line agent and the date/time of meeting the treatment response definition (ie, the randomized treatment stop date/time + 24 hours). The time from treatment response to re-institution of any third-line agent will only be calculated for subjects meeting the treatment response definition. For subjects meeting the treatment response definition, if no re-institution of any third-line agent is required, the time from treatment response to re-institution will be censored at the day of study completion or early termination.

Time from absence of third-line agents to re-institution of any third-line agent

The time from absence of third-line agents to re-institution of any third-line agent will be calculated as the difference between the start date/time of any re-institution of a third-line agent and date/time of meeting the absence of third-line agents definition (ie, the third-line agent stop date/time). The time from absence of third-line agents to re-institution of any third-line agent will only be calculated for subjects meeting the absence of third-line agents definition. For subjects meeting the absence of third-line agents definition, if no re-institution of any third-line agent is required, the time from absence of third-line agents to re-institution will be censored at the day of study completion or early termination.

Number of days post treatment without status epilepticus

The number of days post randomized treatment without status epilepticus will be calculated as the difference between the stop date of infusion of SAGE-547 or placebo and the date of first SE after H144 reported in the case report form (CRF). A higher number of days without status epilepticus indicates a better outcome. If no episodes of status epilepticus have occurred post treatment, the number of days post treatment without status epilepticus will be censored at the day of study completion or early termination.

Number of days post treatment without seizures

The number of days post randomized treatment without seizures (convulsive or non-convulsive) will be calculated as the difference between the stop date of infusion of blinded treatment and the date of first seizure after H144 reported in the CRF. A higher number of days without seizures indicates a better outcome. If no seizures have occurred post treatment, the number of days post treatment without seizures will be censored at the day of study completion or early termination.

Number of post treatment status epilepticus episodes

The number of post randomized treatment status epilepticus episodes will be reported in the CRF.

New diagnosis of epilepsy

The presence of a new diagnosis of epilepsy after Visit 11/11R will be reported in the CRF.

Absence of third-line agents at Hour 168

An additional indicator of absence of third-line agents for seizure or burst suppression will be calculated as:

- IF the third-line agent stop date/time is less than the randomized treatment stop date/time + 24 hours, THEN set the absence indicator equal to 1.
- IF there is no third-line agent stop date/time or if the third-line agent stop date/time is greater than or equal to the randomized treatment stop date/time + 24 hours, THEN set the absence indicator equal to 0.

For subjects on more than one third-line agent, the third-line agent stop date/time will be the latest stop date/time of all third-line agents. Only third-line agents with an indication of seizure or burst suppression will be included in this calculation.

All secondary efficacy variables will be derived separately for those subjects receiving open-label SAGE-547 during the open-label period.

7.2.2.2. Analysis of Variables

Secondary endpoints will be compared between SAGE-547 and placebo treated subjects on the ITT analysis set using a hierarchical testing process at the 5% level of significance. The comparison for statistical significance of secondary efficacy endpoints will use the order of endpoints as listed in Section 7.2.2.1. 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.

Categorical endpoints (ie, absence of third-line agents, CGI-I response, a new diagnosis of epilepsy, absence of third-line agents at Hour 168) will be evaluated using logistic regression methods similar to those described in Section 7.2.1.2.

The below continuous variable will be analyzed using Analysis of Covariance (ANCOVA) methods:

- Number of post randomized treatment status epilepticus episodes

The ANCOVA models will include covariates for treatment, concomitant pentobarbital/thiopental use, and number of previous wean attempts. The comparison of interest will be the difference between the SAGE-547 and placebo groups. Model based point estimates (ie, LS means), 95% confidence intervals, and p-values will be reported. If the continuous data contains many tied observations, a non-parametric analysis may also be performed.

The below variables will be analyzed using Cox Proportional Hazard model:

- Time from treatment response to re-institution of any third-line agent
- Time from absence of third-line agents to re-institution of any third-line agent
- Number of days post randomized treatment without status epilepticus
- Number of days post randomized treatment without seizures

The Cox Proportional Hazards model will include the baseline stratification factors (concomitant pentobarbital/thiopental use and number of previous wean attempts). Model based point estimates (ie, hazard ratios), 95% confidence intervals, and p-values will be reported.

Similar analyses for secondary endpoints will be performed using the mITT analysis set. Selected variables will also be analyzed using the PP analysis set. No hierarchical testing process will be used for either of these analysis sets.

Descriptive statistics will be presented by treatment group and study assessment (if applicable). An additional descriptive summary will be presented for the ITT analysis set (open-label subset) based on data from the open-label period only. No statistical tests will be performed for the ITT analysis set (open-label subset).

7.2.3. Other Analyses

An additional sensitivity analysis using a permutation test will be conducted for the primary endpoint. For this sensitivity analysis, at least 1000 dummy randomization schedules will be produced. The treatment assignments for each dummy schedule will be merged with treatment response values for each subject by randomization number. Odds ratio estimates will be calculated for each of these randomizations. The distribution of odd ratios will be plotted via a histogram with the observed odds ratio from the actual randomization displayed. The probability of the permutation results showing an estimate as extreme as that from the actual randomization schedule will be estimated.

7.2.4. Pharmacoeconomic Variables

7.2.4.1. Derivation of Variables

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 >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 >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)?

In addition, intubation and extubation dates and times will be collected and entered into the medical history and/or concomitant procedures CRF pages. The time to extubation will be calculated as: end date of extubation or tracheostomy – start date of double-blind treatment.

All other pharmacoeconomic variables will be collected on the CRF, no derivation will be performed.

7.2.4.2. Analysis of Variables

Selected pharmacoeconomic variables will be summarized by randomized treatment group using appropriate descriptive statistics for the ITT analysis set. Separate summaries will be created for the QWS analysis set (where applicable).

All pharmacoeconomic data will be listed by treatment group (including QWS group if applicable) and subject.

7.2.5. Outcome Variables

7.2.5.1. Derivation of Variables

Clinical Global Impression (CGI)

Any CGI value of "0" will be considered missing as this score denotes "Not assessed".

CGI Severity of Illness (CGI-S) score

Baseline CGI-S values are calculated as the last recorded value prior to the initiation of blind treatment. Change from baseline values are calculated as the assessment scores minus the baseline score. The rule for QWS baseline derivation is stated in Section 3.

CGI Improvement (CGI-I) score

CGI-I score will be collected at Visit 12 or Visit 12R.

Full Outline of UnResponsiveness (FOUR)

FOUR score will be collected at Visit 1, 24, 48, 72, 96, 120, 144, 168, and 192 hours (all ±2 hours) relative to the start of each infusion of study drug, and at V11 or V11R, and at V12 or V12R. The total score is derived as the sum of the 4 scores (eye responses, motor responses, brainstem reflexes, and breathing pattern).

Glasgow Outcome Score (GOS)

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

Supervision Rating Scale (SRS)

SRS scores will be collected at Visit 1, Visit 12 or Visit 12R.

Modified Rankin Scale (mRS)

For subjects aged 17 years or more, modified Ranking Scale will be evaluated at Visit 1, Visit 12 or Visit 12R.

7.2.5.2. Analysis of Variables

Except for the FOUR, both reported values and changes from baseline (if applicable) will be summarized for Visit 12, Visit 12R, and Visit12/12R by randomized treatment groups based on ITT analysis set. Separate summaries will be created for the QWS analysis set.

For the FOUR, reported values and changes from baseline will be summarized for each timepoint and end of study (EOS) by treatment groups based on the ITT analysis set for the assessment during the double-blind period. Similar summary will be based on ITT analysis set (open-label subset) including the timepoints during the entire study and EOS. In addition, reported values and changes from baseline at each timepoint will be summarized based on QWS analysis set.

All data will be listed by randomized treatment group (including QWS group if applicable) and subject.

7.2.6. Exploratory Variables

Epilepsy and SRSE Status

Diagnosis of RSE and SRSE will be summarized using number and percentage of subjects by treatment group, by timepoint and overall.

QTc interval changes and plasma concentrations of SAGE-547

The relationship between plasma concentrations of SAGE-547 and QTc interval changes may be explored using scatter plot of individual SAGE-547 concentrations versus QTcF change from baseline values. In addition, correlation coefficient may be estimated from these data.

The analysis will be done based on PK Analysis Set for the assessment during the double-blind period. An additional scatter plot may be produced for the open label treatment period.

Pharmacogenetic Data Analyses

The analysis of pharmacogenetic data is not described in this SAP. Should the pharmacogenetic data be analyzed, a separate analysis plan will be generated.

EEG analysis

The analysis of EEG data is not described in this SAP. All EEG analyses will be conducted by Biomedical Systems and will be described in a separate document.

8. SAFETY EVALUATION

8.1. Overview of Safety Analysis Methods

Safety assessments, including adverse events, vital signs, clinical laboratory measures, ECGs, mortality and concomitant medication use, are part of safety endpoints for this study.

All safety assessments will be collected periodically throughout the study according to the Schedule of Events (Section 12.1).

For all safety endpoints, descriptive statistics will be presented by treatment group and study assessment (if applicable) based on the safety analysis set. In addition, some safety endpoints will be summarized overall and by treatment group for the safety analysis set (open-label subset). Summaries based on safety analysis set will only include those timepoints assessed during the double-blind period. Summaries based on the safety analysis set (open-label subset) will include those timepoints assessed during the open-label period for TEAEs and concomitant medications and procedures and will include all timepoints assessed during both the double-blind and open-label periods for vital signs, laboratory assessments, etc.

8.2. Extent of Exposure

8.2.1. Historical Use of First-Line, Second-Line agents and Continuous IV Third-Line Agents

Historical IV first and second line agent use will be presented in a data listing with the following details: name of agent, start date/time, end date/time, dose, unit, frequency, route of administration, date of failure.

Historical IV Third-Line agent use will be presented in a data listing with the following details: name of agent, start date/time, end date/time, total days in use, number of wean attempts, wean outcome.

Descriptive statistics for the total hours in use and total number of wean attempts for each unique IV Third-Line agent will be provided in a summary table. This summary will be based on safety analysis set. Separate summaries will be created for the safety analysis set (open-label subset) and QWS analysis set.

8.2.2. Concomitant Use of Third-line Agents

Concomitant use of IV Third-Line Agents will be presented in a data listing with the following details: name of agent, start date/time, end date/time, dose, unit, wean type, wean outcome, and indication.

Please refer to Section 3 regarding the assignment of study period of concomitant third-line agents for safety analysis set.

Duration of exposure for burst suppression or seizure suppression in hours and total dose will be summarized in a table with descriptive statistics for each third-line agent by treatment group.

This summary will be based on safety analysis set for those third-line agents assigned to double-blind period and safety analysis set (open-label subset) for those third-line agents assigned to open-label period. Separate summaries will be created for the QWS analysis set.

8.2.3. Study Drug Injection

Details pertaining to the administration of study drug will be listed, including type of infusion (loading/maintenance/taper), dose, infusion rate and unit, start date/time of dose, and end date/time of dose, infusion stopped after this dose.

Treatment exposure will be defined as the number of hours that the subject was exposed to study treatment. It will be calculated by treatment group and in the following categories: loading dose, maintenance dose, and tapering dose. Treatment exposure will be summarized by treatment group with descriptive statistics. This summary will be based on safety analysis set for the treatment exposure in the double-blind period, and based on safety analysis set (open-label subset) for the treatment exposure in open-label period.

8.3. Adverse Events

Treatment-Emergent Adverse Events (TEAEs) are defined as those that begin on or after initiation of the infusion of SAGE-547 or placebo.

Adverse events will be classified by type, incidence, severity, and causality. The overall incidence of AEs will be summarized using the MedDRA™ coding system and classified by System Organ Class (SOC), preferred term (PT), and by treatment group.

Please refer to Section 3 regarding the assignment of study treatment period of TEAEs and dose phase of TEAEs for safety analysis set.

An overall summary table will be developed to report the number of adverse events and the incidence of subjects having at least one adverse event in the following categories:

- TEAEs
- TEAEs indicated as serious (SAEs)
- TEAEs leading to death
- TEAEs leading to study drug discontinuation
- TEAEs by maximum severity as assessed by Investigator (mild, moderate, severe)

Tabulation (using counts and percentages) of TEAEs and serious TEAEs will be presented by SOC and PT. In addition, tabulation of TEAEs will be presented by PT for each of the following:

- TEAEs by maximum severity
  - Subjects with multiple TEAEs with the same PT will be summarized at the maximum severity and counted one time for that PT.
- TEAEs related to study drug

  - Subjects with multiple TEAEs with the same PT will be summarized at the highest relationship and counted one time for that PT.
- TEAEs leading to study drug discontinuation
- TEAEs leading to death

All the summaries will be based on safety analysis set for those TEAEs assigned to double-blind period and safety analysis set (open-label subset) for those TEAEs assigned to open-label period. When reporting the number of TEAEs, if the same TEAE occurs for a subject on multiple occasions the event will be counted once for each occurrence. Separate summaries will be created for the QWS analysis set.

All adverse events and related details will be listed by treatment group (including QWS group if applicable) and subject. Adverse events that are not considered treatment-emergent will be included and identified in all listings, but not included in summaries.

Treatment-emergent AEs will be analyzed by following categorical subgroups:

- Gender (male, female)
- Age group (<18, 18 to <65, ≥65 years)
- Pediatric age group (2 to <6, 6 to <12, 12 to <18 years)
- Race (White, Black, Asian, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Weight group (≤30, >30 kg)
- BMI group (<25, 25 to <30, 30 to <40, ≥40 kg/m^2)
- Region (North America, Rest of World)
- Number of AEDs at baseline category (1 to 3, >3)
- Number of TLAs at baseline category (1, 2, 3, >3)
- Type of TLA at baseline (ketamine, midazolam, pentobarbital, thiopental, propofol)
- Number of previous wean attempts (0, 1, 2 to 3, >3)
- Previous epilepsy diagnosis (yes, no)
- Etiology of index case of status epilepticus category (epilepsy with antiepileptic drug noncompliance, epilepsy with/without known trigger, autoimmune/infectious, medication/substance related, genetic/malformations of the cortical development, metabolic, neoplastic, traumatic, vascular, unknown/cryptogenic)
- Structural cause of SE category (structural, non-structural)
- Pre-dose duration of SE Category (0 to 1 day, 2 to 5 days, 6 to 10 days, >10 days)
- Concomitant pentobarbital/thiopental use (yes, no)

For each subgroup, the number and percentage of subjects who experienced at least one TEAE will be tabulated by treatment group, in addition to the incidences of individual adverse events by MedDRA SOC and preferred term. Subgroup summaries will only be produced for the double-blind treatment period.

8.4. Serious Adverse Events and Other Significant Adverse Events

The number and percent of subjects with serious adverse events will be tabulated by MedDRA SOC and preferred term. In addition, a listing of subjects with serious adverse events will be generated. Similar displays will be produced for adverse events leading to study drug discontinuation. A by-treatment group (including QWS group if applicable), by-subject data listing will provide details of any subject deaths that occur in the study.

8.5. Concomitant and Prior Medications

Subjects will be receiving standard of care for SRSE and other concomitant medications as deemed necessary by the investigator.

Prior and concomitant medications will be summarized separately. Please refer to Section 3 for the classification of prior medications and concomitant medication, and the study period assignment (double-blind or open-label) for the concomitant medication for the open-label subset.

For AEDs and pressors, all dose changes and related details (start/stop date and time, frequency, route) for each medication will be recorded. Medications apart from pressors and AEDs will be classified as 'Other'.

Four data listings will be provided: one for prior AEDs and pressors, one for 'Other' prior medications, one for concomitant AEDs and pressors, and one for 'Other' concomitant medications. Details including medication name, drug class, indication, dose and units, frequency, route of administration, start and stop date/times, and whether or not the medication is ongoing will be provided in a data listing sorted by treatment group (including QWS group if applicable), subject and start time.

Summary for prior AEDs and pressors and 'Other' prior medications will be based on safety analysis set. Summary for concomitant AEDs and pressors and 'Other' concomitant medications will be based on safety analysis set for those concomitant medications assigned to double-blind period and safety analysis set (open-label subset) for those concomitant medications assigned to open-label period. Frequency counts and percentages for each drug category will be presented.

Separate summaries will be created for the QWS analysis set.

8.6. Clinical Laboratory Evaluation

Blood samples will be collected for hematology, serum chemistry, and determination of pregnancy (in female subjects). Urine samples for urinalysis will be collected.

All clinical laboratory test results outside the reference range will be flagged. In addition, lab test results considered potentially clinically significant will be flagged.

8.6.1. 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).

Table 7: Hematology Potentially Clinically Significant Values

Hematology variable	Potentially clinically significant values
Hemoglobin	<125 g/L or >185 g/L (males) <110 g/L or >165 g/L (females)
Hematocrit	<0.415 or >0.504 (males) <0.359 or >0.446 (females)
Platelet count	<125 10^9/L or >600 10^9/L
White Blood Cells	<2.5 10^9/L or >15 10^9/L
Basophils	>0.5 10^9/L
Eosinophils	>1.5 10^9/L
Lymphocytes	<0.5 10^9/L or >6.0 10^9/L
Monocytes	>1.4 10^9/L
Neutrophils	<1.5 10^9/L

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.

Table 8: Serum Chemistry Potentially Clinically Significant Values

Chemistry variable	Potentially clinically significant values
Alanine aminotransferase (ALT)	>3 x ULN
Albumin	<28 g/L or >70 g/L
Aspartate aminotransferase (AST)	>3 x ULN
Bicarbonate	<18 mmol/L or >30 mmol/L
Bilirubin	>2 x ULN
Blood urea nitrogen (BUN)	>10.71 mmol/L
Calcium	<2.0 mmol/L or >2.75 mmol/L
Chloride	<90 mmol/L or >120 mmol/L
Creatine kinase	>3 x ULN
Creatinine	>140 umol/L
Potassium	<3.5 mmol/L or >5.2 mmol/L
Sodium	<132 mmol/L or >145 mmol/L
Protein	<45 g/L
Glucose	<2.8 mmol/L or >13.9 mmol/L

Estimated glomerular filtration rate (eGFR) will be calculated by the central laboratory and the below values will be listed and summarized:

- For subjects ≥18, using eGFR by Modification of Diet in Renal Disease (MDRD)
- For subjects <18, using eGFR by Schwartz.

Chemistry and hematology laboratory results, including any noted abnormalities, will be summarized and listed separately by category. Reported values and changes from baseline will be summarized for each timepoint by treatment groups based on safety analysis set for the assessment during the double-blind period and safety analysis set (open-label subset) for the assessment during the entire study. Separate summaries will be created for the QWS analysis set.

The number and percent of subjects who met the above criteria at any time during the double-blind treatment period will be tabulated. A separate tabulation will be presented for the open-label period.

A summary of subjects with abnormal liver enzymes and liver function tests post-baseline will be presented, including abnormalities that worsened for subjects with baseline abnormal levels and ALT and AST shifts from baseline. This summary of abnormal liver enzymes will only be performed for the double-blind treatment period.

8.6.2. Pregnancy Test

Female subjects of child-bearing potential will be tested for pregnancy by serum pregnancy test at Visit 1. Female subjects with a positive pregnancy test will be ineligible for study participation.

Pregnancy test results will not be listed separately; they will be included in the inclusion/exclusion criteria results.

8.6.3. Urinalysis

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

Urinalysis results, including any noted abnormalities, will be listed by subject and timepoint. Reported values and changes from baseline will be summarized for each timepoint by treatment group based on safety analysis set for the assessment during the double-blind period and safety analysis set (open-label subset) for the assessment during the entire study. Categorical urinalysis results will also be summarized. Separate summaries will be presented for the QWS analysis set.

8.6.4. ECG

ECG parameters, including heart rate (HR), PR interval, QRS interval, QT interval, and QTc interval as well as overall interpretation as Normal or Abnormal will be listed by treatment group and subject. Date and time of assessments, along with any abnormalities will be included in the listing.

In addition, the below parameter will be calculated, listed and summarized:

- QTc by Fridericia's correction (QTcF), calculated as:

  QTcF = QT/cube root(60/HR)

Reported values and changes from baseline will be summarized for each timepoint by treatment groups based on safety analysis set for the assessment during the double-blind period and safety analysis set (open-label subset) for the assessment during the entire study. Separate summaries will be created for the QWS analysis set.

QT and QTcF will be flagged according to the following criteria:

- >450 msec
- >480 msec
- >500 msec

The change from baseline in QTcF and QT will be flagged according to the following criteria:

- >30 msec increase
- >60 msec increase

The number and percent of subjects who met the above criteria at any time during the double-blind treatment period will be tabulated. A separate tabulation will be presented for the open-label period. Subjects will only be counted once under the maximum criteria met.

8.6.5. Mortality

In the event the subject has died, the date of death, cause of death, and category of cause will be listed by study period (including QWS if applicable) and subject. The category of cause will be captured on the eCRF as one of the following: 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; or Other (specify).

The number and percentage of subjects will be presented for cause of death category by treatment groups.

8.6.6. Vital Signs

Collected vital signs will include heart rate, blood pressure, and temperature. Weight will also be included as part of the vital signs analysis.

Results for each vital sign parameter will be listed by treatment group (including QWS group if applicable) and subject for each study timepoint.

Reported values and changes from baseline will be summarized for each timepoint by treatment groups based on safety analysis set for the assessment during the double-blind period and safety analysis set (open-label subset) analysis set for the assessment during the entire study. Separate summaries will be created for the QWS analysis set.

Blood pressure and heart rate will be flagged according to the following criteria:

- Systolic blood pressure:
  - <90 mmHg
  - >180 mmHg
- Diastolic blood pressure:
  - <50 mmHg
  - >110 mmHg
- Heart rate:
  - <40 bpm
  - >120 bpm

Change from baseline in blood pressure will be flagged according to the following criteria:

- Systolic blood pressure:
  - ≥30 mmHg increase
  - ≥30 mmHg decrease
- Diastolic blood pressure:
  - ≥20 mmHg increase
  - ≥20 mmHg decrease

The number and percent of subjects who met the above criteria at any time during the double-blind treatment period will be tabulated. A separate tabulation will be presented for the open-label period.

9. PHARMACOKINETIC EVALUATION

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]).

9.1. Formal PK Analysis

9.1.1. Plasma Analysis

Plasma will be collected to assay for SAGE-547 concentrations at the following timepoints 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.

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).

To maintain the blind, all subjects will have samples taken as outlined above. Subjects receiving SAGE-547 will have all samples analyzed for SAGE-547, SAGE-547 metabolites (if and when these are identified), and hydroxypropyl beta-cyclodextrin (HPBCD) concentrations. Subjects on placebo may have samples analyzed to investigate endogenous allopregnanolone and metabolite concentrations, as well as HPBCD concentrations; experience with the plasma concentration data will determine if placebo samples are analyzed.

Plasma PK parameters for SAGE-547 will be calculated where appropriate (eg, C_{max}, t_{max}, AUC_{last}, AUC_{∞}, CL_s). In addition, similar PK parameters will be calculated for HPBCD. 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.

PK concentration data will be summarized for each timepoint for the SAGE-547 group during the double-blind period based on the PK analysis set. PK concentration data will also be summarized for each timepoint during the open-label period by randomized treatment group (SAGE-547 and placebo) and overall based on PK analysis set (open-label subset). Similar summaries will be presented for PK parameters.

9.1.2. Other Analysis

For subjects undergoing a spinal or ventricular tap during infusion of study drug, the subject or his/her LAR will be asked for consent for a sample to be retained frozen for subsequent analysis of SAGE-547 concentrations.

The analysis of cerebral spinal fluid concentration data is not described in this SAP. Any summaries of this data will be reported outside of the CSR.

10. CHANGES TO PLANNED ANALYSES

10.1. Changes from Protocol

Table 9: Changes from Protocol

Protocol Section	Protocol Text	Change from Protocol	Rationale
Section 5.2 – Secondary Objectives	4. To compare the change in Clinical Global Impression Scale between SAGE-547 and placebo up to Visit 12;	4. To compare between SAGE-547 and placebo the time between meeting the secondary response endpoint, defined above, and the re-institution of any third-line agent for seizure or burst suppression up to Visit 12;	This objective was re-worded to specify the actual CGI endpoint to be compared between treatment groups (ie, CGI-I response).
Section 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).	To determine the safety and tolerability of a 144-hour infusion of SAGE-547 as compared to placebo.	The language of this objective was clarified to specify that comparisons will be performed for the two treatment groups used in this study (ie, SAGE-547 and Placebo). The reference to the four subject groups was removed.
Section 5.4 – Other Objectives		To evaluate Clinical Global Impression (CGI) Scale;	Objective added to examine other CGI endpoints not specified in Secondary Objectives.
Section 5.4 – Other Objectives		To evaluate the below data in subjects with a qualifying wean success: Adverse events and medications; Laboratory testing (hematology, serum chemistry, and urinalysis); Vital signs (blood pressure, heart rate, temperature, weight); ECG parameters; Mortality; Epilepsy status; Outcome data.	Objective added to examine various endpoints in qualifying wean success subjects.

Protocol Section	Protocol Text	Change from Protocol	Rationale
Section 7.1 – Overview of Study Design	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 63 subjects to be randomized to SAGE-547 and 63 subjects to be randomized to placebo.	Amended sample size estimate to reflect change in assumption of the placebo success rate. This text was also updated in Amendment 5 dated 03 May 2017.
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 63 subjects to be randomized to SAGE-547 and 63 subjects to be randomized to placebo.	Amended sample size estimate to reflect change in assumption of the placebo response rate. This text was also updated in Amendment 5 dated 03 May 2017.
Section 8 – Selection and Withdrawal of Subjects	The study will randomize 140 subjects at up to 180 sites.	The study will randomize 126 subjects at up to 180 sites.	Amended sample size estimate to reflect change in assumption of the placebo success rate. This figure was also updated in Amendment 5 dated 03 May 2017.
Section 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.		Sponsor made the decision that the interim sample size re-estimation analysis would not be performed. Therefore, text regarding the planned interim analysis was removed from the SAP.
Section 13.1.2 – Study Populations	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.	The Per–Protocol (PP) analysis set is defined as a subset of the ITT analysis set but will exclude data from all subjects with major protocol violations or deviations that could potentially confound the efficacy evaluation. Subjects will be classified according to randomized treatment received.	The definition of the PP analysis set was updated to be a subset of the MITT analysis set, to further define what is considered a major violation or deviation, and to classify subjects according to randomized treatment.

Protocol Section	Protocol Text	Change from Protocol	Rationale
Section 13.1.2 – Study Populations	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 pharmacokinetics (PK) analysis set will include all subjects who at least had an infusion of blinded or open-label SAGE-547 initiated and have at least one pharmacokinetic sample collected.	The definition of the PK analysis set was updated to include subjects exposed to SAGE-547 during open-label period.
Section 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.	The analysis of treatment response between SAGE-547 treated subjects and placebo treated subjects will be performed on the ITT analysis set using logistic regression methods. The model will include terms for treatment group, concomitant pentobarbital/thiopental use (yes or no), and number of previous third-line agent wean attempts prior to randomization (one vs. two or more). Model based point estimates (ie, odds ratios), 95% confidence intervals, and p-values will be reported. As a supportive analysis, the Cochran-Mantel-Haenszel (CMH) test will be performed for the ITT analysis set with covariates 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 chi-square statistic and its associated p-value will be reported. In case of convergence issues with the primary logistic regression model, the CMH test will be used as the primary analysis.	The primary analysis was updated to be conducted using logistic regression. The CMH test as specified in the protocol will now be supportive (unless convergence issues are encountered with logistic regression model).
Section 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 (Protocol Section 6).	Secondary endpoints will be compared between SAGE-547 and placebo treated subjects on the ITT analysis set using a hierarchical testing process at the 5% level of significance. The comparison for statistical significance of secondary efficacy endpoints will use the order of endpoints as listed in Section 7.2.2.1.	The hierarchical testing of secondary endpoints was updated.

Protocol Section	Protocol Text	Change from Protocol	Rationale
Section 13.1.5 – Analysis of Secondary Efficacy 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.	Categorical endpoints (ie, absence of third-line agents, CGI-I response, a new diagnosis of epilepsy) will be evaluated using logistic regression methods similar to those described in Section 7.2.1.2.	The analysis of secondary dichotomous endpoints was updated to use logistic regression methods similar to those used for the primary endpoint.

Protocol Section	Protocol Text	Change from Protocol	Rationale
Section 13.1.5 – Analysis of Secondary Efficacy Endpoints	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.	The below continuous variable will be analyzed using Analysis of Covariance (ANCOVA) methods: Number of post randomized treatment status epilepticus episodes The ANCOVA models will include covariates for treatment, concomitant pentobarbital use, and number of previous wean attempts. The comparison of interest will be the difference between the SAGE-547 and placebo groups. Model based point estimates (ie, LS means), 95% confidence intervals, and p-values will be reported. If the continuous data contains many tied observations, a non-parametric analysis may also be performed. The below variables will be analyzed using Cox Proportional Hazard model: Time from treatment response to re-institution of any third-line agent Time from absence of third-line agents to re-institution of any third-line agent Number of days post randomized treatment without status epilepticus Number of days post randomized treatment without seizures The Cox Proportional Hazards model will include the baseline stratification factors (concomitant pentobarbital use and number of previous wean attempts). Model based point estimates (ie, hazard ratios), 95% confidence intervals, and p-values will be reported.	The analysis of secondary continuous endpoints was updated to use either ANCOVA or Cox proportional hazards models (depending on the type of endpoint).

Protocol Section	Protocol Text	Change from Protocol	Rationale
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 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.	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, yielding a sample size estimate of 120 subjects, while maintaining adequate power in the study. This text was also updated in Amendment 5 dated 03 May 2017.

ATTACHMENT 1. HANDLING RE-ENROLLED SUBJECTS

In Listings

Subject number will be consolidated under the initial subject number. All subjects will have a multi-part subject number with the format as: Initial Subject Number/Subject Number. For example, one subject could have subject numbers of [redacted], where [redacted] was assigned prior to the first qualifying wean success, [redacted] was assigned prior to the second qualifying wean success, and [redacted] was assigned prior to randomization, respectively. In the listings, data collected for subject [redacted] will be displayed with combined subject number of [redacted]; data collected for subject [redacted] will be displayed with combined subject number of [redacted]; data collected for subject [redacted] will be displayed with combined subject number of [redacted].

In Tables

For the summaries based on safety analysis set or ITT analysis set, data collected on the randomized subject will be used (in the example mentioned above, data collected for [redacted] will be used).

For the summaries based on the qualifying wean success analysis set, data collected on the last qualifying wean success will be used (in the example mentioned above, data collected for [redacted] will be used).

ATTACHMENT 2. UNIT CONVERSION FOR CONTINUOUS IV THIRD-LINE AGENTS

For each record of the Continuous IV third-line agent data, the dose administered during that dosing time period will be converted to a standard unit of mg/kg/h (as specified in the below table).

Unit as captured on CRF[1]	**Derivation of Standard Dose (mg/kg/h)**
ug/kg/min	ADOSE = CMDOSTXT*0.001*60
ug/kg/h	ADOSE = CMDOSTXT*0.001
mg/kg	ADOSE = CMDOSTXT/CMDUR
mg/kg/h	ADOSE = CMDOSTXT
mg/h	ADOSE = CMDOSTXT/WEIGHT
mg	ADOSE = CMDOSTXT/WEIGHT/CMDUR
ug	ADOSE = CMDOSTXT*0.001/WEIGHT/CMDUR
mg/kg/day	ADOSE = CMDOSTXT/24
ug/min	ADOSE = CMDOSTXT*0.001*60/WEIGHT

[1]CMDOSU in SDTM dataset
[2]ADOSE in ADaM dataset
CMDOSTXT = the dose in original CRF units
CMDUR = the number of hours between start and stop date/times (derived as end date/time – start date/time)
WEIGHT = baseline weight in kg

11. REFERENCES

1. SJ Pocock and R Simon. Sequential treatment assignment with balancing for prognostic factors for the controlled clinical trial. *Biometrics*, 31:103–115, 1975.

12. APPENDICES

12.1. Schedule of Events

Table 10: Schedule of Assessments for Protocol 547-SSE-301: One Infusion of Study Drug (blinded)

	V1 V2-≤30h	V2 V3-≤54h	V3 0-24h	V4 25h-48h	V5 49h-72h	V6 73h-96h	V7 97h-120h	V8 121h-144h	V9 145h-168h	V10 169h-192h	V11 V3+14d (±2d)	V12 V3+21d (±2d)
Eligibility Checklist	X											
Informed Consent [a]	X											
Inclusion/Exclusion Criteria	X											
Demography [b]	X											
Medical/SE/Wean History [c]	X											
Height	X											
Weight [d]	X	X	X	X	X	X	X	X		X		
Serum Pregnancy Test [e]	X											
Hematology [f]	X		X	X		X		X		X		
Serum Chemistry and GFR [f]	X		X	X		X		X		X	X[g]	
Urinalysis [h]	X		X	X		X		X		X		
Pharmacogenetic sample	X											
Vital Signs [i]	X		X	X	X	X	X	X	X	X		
ECG [j]	X		X	X	X	X	X	X	X	X		
Plasma Sampling (PK)[k]			X	X	X	X	X	X	X			
STESS	X											
FOUR Score [m]	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X[o]											X
Modified Rankin Score (mRS) [n]	X[o]											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[p]				
EEG	X	X				X		X	X			
Randomization		X										
Study Drug Administration [q]			X	X	X	X	X	X				
TW Outcome & Open-label Treatment Decision										X[r]		
Physiologic Brain Activity									X			
Adverse Events [s]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant AEDs[t]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents [u]	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 11: 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 [a]	X										E
Inclusion/Exclusion Criteria	X										E
Demography [b]	X										
Medical and SE and Wean History [c]	X										T
Height	X										A
Weight [d]	X	X	X	X	X	X	X	X		X	B
Serum Pregnancy Test [e]	X										L
Hematology [f]	X		X	X		X		X		X	E
Serum Chemistry and GFR[f]	X		X	X		X		X		X	
Urinalysis [h]	X		X	X		X		X		X	E
Pharmacogenetic sample	X										X
Vital Signs [i]	X		X	X	X	X	X	X	X	X	T
ECG [j]	X		X	X	X	X	X	X	X	X	E
Plasma Sampling (PK)[k]			X	X	X	X	X	X	X		N
STESS	X										I
FOUR Score [m]	X		X	X	X	X	X	X	X	X	O
Glasgow Outcome Score (GOS)											N
Supervision Rating Scale (SRS)	X[o]										
Modified Rankin Score (mRS) [n]	X[o]										
Epilepsy Status	X										N
Clinical Global Impression (CGI)	X										E
Continuous IV Third-Line Agent(s)	X	Wean	X	X	Wean	Wean	Wean	Wean [p]			X
EEG	X	X				X		X	X		T
Randomization		X									
Study Drug Administration [q]			X	X	X	X	X	X			
TW Outcome and Open-label Treatment Decision										X[r]	P
Physiologic Brain Activity									X		
Adverse Events [s]	X	X	X	X	X	X	X	X	X	X	A
Concomitant Anti-Epileptic Drugs [t]	X	X	X	X	X	X	X	X	X	X	G
Concomitant Third-Line Agents [u]	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 12: Schedule of Assessments for Protocol 547-SSE-301: Two Infusions of Study Drug (one blinded, one open-label) (Continued)

	V3R 0-24h	V4R 25h-48h	V5R 49h-72h	V6R 73h-96h	V7R 97h-120h	V8R 121h-144h	V9R 145h-168h	V10R 169h-192h	V11R V3R+14d (±2d)	V12R V3R+21d (±2d)
Weight [d]	X	X	X	X	X	X				
Serum Pregnancy Test [e]										
Hematology [f]	X	X		X		X		X		
Serum Chemistry and GFR[f]	X	X		X		X		X	X[g]	
Urinalysis [h]	X	X		X		X		X		
Vital Signs [i]	X	X	X	X	X	X	X	X		
ECG [j]	X	X	X	X	X	X	X	X		
Plasma Sampling (PK)[k]	X	X	X	X	X	X	X			
STESS										
FOUR Score [m]	X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)										X
Supervision Rating Scale (SRS)										X
Modified Rankin Score (mRS) [n]										X
Epilepsy Status										X
Clinical Global Impression Scale (CGI)										X
Continuous IV Third-Line Agent(s)	X	X	Wean	Wean	Wean	Wean [p]				
EEG				X		X	X			
Randomization										
Study Drug Administration [q]	X	X	X	X	X	X				
TW Success and Physiologic Brain Activity							X			
Adverse Events [s]	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs [t]	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents [u]	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 12: 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 [a]	X											
Inclusion/Exclusion Criteria	X											
Demography [b]	X											
Medical and SE and Wean History [c]	X											
Height	X											
Weight [d]	X											
Serum Pregnancy Test [e]	X											
Hematology [f]	X											
Serum Chemistry and GFR [f]	X											
Urinalysis [h]	X											
Pharmacogenetic sample	X											
Vital Signs [i]	X											
ECG [j]	X											
STESS	X											
FOUR Score [m]	X		X	X	X	X	X	X	X	X	X	X
Glasgow Outcome Score (GOS)												X
Supervision Rating Scale (SRS)	X[o]											X
Modified Rankin Score (mRS) [n]	X[o]											X
Epilepsy Status	X											X
Clinical Global Impression (CGI)	X											X
Continuous IV Third-Line Agent(s)	X	Wean										
EEG	X	X										
Adverse Events [s]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Anti-Epileptic Drugs [t]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Third-Line Agents [u]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Pressors [t]	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

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

[b] Demographic information will be obtained by proxy and confirmed by the subject when possible.

[c] 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.

[d] 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).

[e] 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.

[f] 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.

[g] Blood samples will be taken at V11 or V11R for serum chemistry (renal panel only).

[h] Urine samples will be taken for urinalysis and NAG 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.

[i] 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).

[j] 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 (± 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. 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 +/- 2 hour time window for these ECGs.

[k] 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 +/- 5 minutes; all other timepoints will have a window of +/- 15 minutes.

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

[n] Modified Rankin Score (mRS) applicable for subjects ≥17 years old only.

[o] 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.

[p] 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.

[q] Study drug infusion is intended for IV administration only with a dedicated peripheral IV line using Sage-approved IV administration bags and lines.

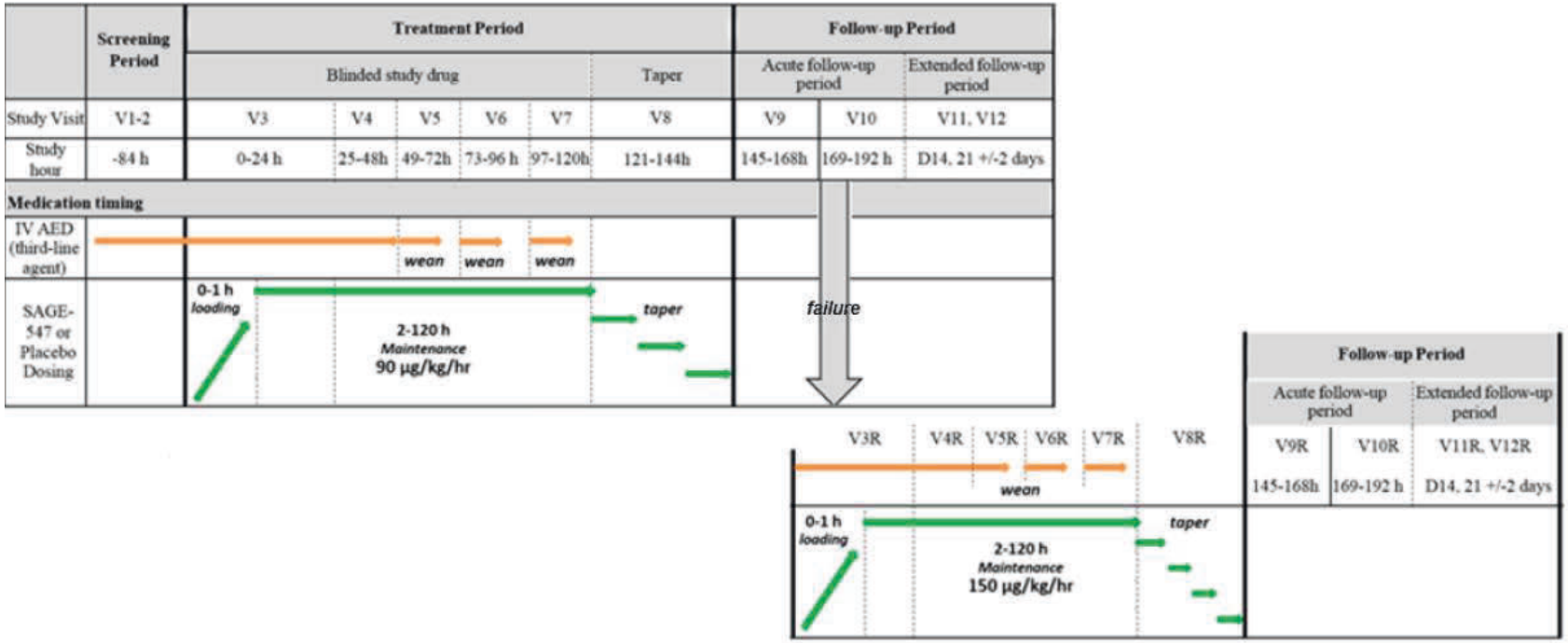
[r] At V10 only a decision to re-treat at a higher dose of SAGE-547 will be made by the Investigator if the continuous IV third-line agent wean has failed or the third-line agent requires re-introduction during V9. Subjects who become eligible for open-label study drug at a higher dose of SAGE-547 will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

[s] 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.

[t] 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.

[u] 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.

12.2. Timeline for Dosing and Study-Specific Assessments



13. LISTING AND TABLE SPECIFICATIONS

The structure and contents of all listings, tables and figures listed will be defined in a group of separate documents.