PROTOCOL: 1042-SE-3003

TITLE:	A double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of intravenous ganaxolone in status epilepticus
DRUG:	Ganaxolone
IND:	129433
EUDRACT NO.:	TBD

SPONSOR: Marinus Pharmaceuticals, Inc.
5 Radnor Corporate Center
100 Matsonford Road, Suite 500
Radnor, PA 19087 USA

PROTOCOL HISTORY:
Amendment 5: 06May2024, Version 6.0
Amendment 4: 13Oct2023, Version 5.0
Amendment 3: 10June2022, Version 4.0
Amendment 2: 19November2021, Version 3.0
Amendment 1: 14July2020, Version 2.0
Original Protocol: 13April2020, Version 1.0

PROTOCOL SIGNATURE PAGE

Sponsor's (Marinus) Approval

Signature:	**Date:**
[redacted], **MD, PhD,** | [redacted], **Clinical Development**	

Investigator's Acknowledgement

I have read this protocol for Marinus Study 1042-SE-3003.

Title: A double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of intravenous ganaxolone in status epilepticus.

I have fully discussed the objective(s) of this study and the contents of this protocol with the Sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide the information contained herein to a participant in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, participant to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the Sponsor.

Investigator Name and Address: (handprint or type)	

Signature: _____ **Date:** _____

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **5**	**Amendment Date** **06 May 2024**	**Global/Country/Site Specific** **Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Updated Interim Analysis subsection to note that the interim analysis was performed and that the Data Monitoring Committee recommended that the study continue without modification.		Section 10.7
Added language to clarify that randomization stopped at 100 participants for business reasons.		Section 3.1.1
Made minor copyediting and formatting changes.		Throughout document.

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the Marinus Serious Adverse Event form within 24 hours to the Marinus Drug Safety vendor. A copy of this form must also be sent to the contract research organization (CRO)/Medical Monitor by e-mail using the details below.

Email: [redacted]
Fax: [redacted]

In addition, for protocol or safety related issues the investigator must contact the Medical Monitor:

Medical Monitor:

[redacted]**, MD, PhD**

[redacted], Clinical Development

Marinus Pharmaceuticals, Inc.

Email: [redacted]

Mobile Telephone Number: [redacted] (primary contact method via text or call to this number and followed by e-mail)

If unavailable:

[redacted]**, MD**

[redacted], Clinical Development

Marinus Pharmaceuticals, Inc.

Email: [redacted]

Mobile Telephone Number: [redacted] (primary contact method via text or call to this number followed by e-mail)

ADDITIONAL CONTACT INFORMATION

In case of any other issues including non-safety related issues or if the Medical Monitor is unable to be reached, the Investigator must contact the Marinus Program or Clinical Trial Manager:

Marinus Trial Manager:

[redacted]

[redacted]

Marinus Pharmaceuticals, Inc.

Email: [redacted]

Mobile Telephone Number: [redacted](primary contact method via text or call)

Marinus Program Manager:

[redacted]**, PharmD**

[redacted], Clinical Development Operations

Marinus Pharmaceuticals, Inc.

Email: [redacted]

Mobile Telephone Number: [redacted](primary contact method via text or call)

TABLE OF CONTENTS

PROTOCOL SIGNATURE PAGE 2
SUMMARY OF CHANGES FROM PREVIOUS VERSION 3
EMERGENCY CONTACT INFORMATION 4
ADDITIONAL CONTACT INFORMATION 5
LIST OF TABLES 11
LIST OF FIGURES 11
ABBREVIATIONS 12
STUDY SYNOPSIS 14
STUDY SCHEDULE(S) 27
1 BACKGROUND INFORMATION 33
1.1 Indication and Current Treatment Options 33
1.2 Product Background and Clinical Information 34
2 STUDY OBJECTIVES AND PURPOSE 37
2.1 Rationale for the study 37
2.2 Study Objectives 39
2.2.1 Primary Objective 39
2.2.2 Secondary Objectives 39
2.2.3 Exploratory Objectives 39
3 STUDY DESIGN 39
3.1 Study Design and Flow Chart 39
3.1.1 Double-blind Phase 39
3.1.2 Open-label Phase 40
3.2 Interim Analysis 41
3.3 Duration and Study Completion Definition 41
3.4 Sites and Regions 41
4 STUDY POPULATION 41
4.1 Inclusion Criteria 41
4.2 Exclusion Criteria 42
4.3 Restrictions 43
4.4 Reproductive Potential 43
4.4.1 Female Contraception 43
4.4.2 Male Contraception 44
4.5 Discontinuation of Participants 44
4.5.1 Investigational product discontinuation 44
4.5.1.1 Reasons for IP discontinuation include, but are not limited to, the following: 45
4.5.1.2 Study Withdrawal 45
4.5.2 Participant Withdrawal Criteria 45
4.5.3 Reasons for Study Discontinuation 46
4.5.4 Participants Lost to Follow-up Prior to Last Scheduled Visit 46

5 PRIOR AND CONCOMITANT TREATMENT 46
5.1 Prior Treatment 46
5.2 Concomitant Treatment 47
5.2.1 Permitted Treatment....48
5.2.2 Prohibited Treatment 48
6 INVESTIGATIONAL PRODUCT 48
6.1 Identity of Investigational Product....48
6.1.1 Blinding the Treatment Assignment 49
6.1.2 Double-Blind Phase 49
6.1.3 Open-Label Phase 49
6.2 Administration of Investigational Product(s)....49
6.2.1 Interactive Response Technology for Investigational Product Management 49
6.2.2 Allocation of Participants to Treatment....49
6.2.2.1 Double-Blind Phase 49
6.2.2.2 Open-Label Phase 49
6.2.3 Dosing....50
6.2.3.1 Participants weighing at least 40 kg: 51
6.2.3.2 Participants weighing <40 kg will be dosed on a per kilogram basis:....52
6.2.4 Investigational Product Infusion Precautions 53
6.2.5 Medical Oversight....54
6.2.6 Investigational Product Tapering (One or More May Apply) 54
6.2.7 Dose Adjustments and Interruptions....54
6.2.8 Unblinding the Treatment Assignment....55
6.2.8.1 Double-Blind Phase 55
6.3 Labeling, Packaging, Storage, and Handling....55
6.3.1 Labeling 55
6.3.2 Packaging....56
6.3.3 Storage 56
6.4 Investigational Product Accountability....56
6.5 Participant Compliance....57
7 STUDY PROCEDURES....58
7.1 Study Schedule....58
7.1.1 Screening Period 58
7.1.1.1 Screening....58
7.1.1.2 Screen Failures....58
7.1.2 Treatment Period....59
7.1.2.1 Investigational Product Initiation Through Taper (Day 1 to Day 2) 59
7.1.3 Follow-up Period (starting at IP discontinuation through Week 4)....59
7.1.4 Additional Care of Participants After the Study....59
7.2 Study Evaluations and Procedures....60
7.2.1 Demographic and Other Baseline Characteristics 60

7.2.2 Efficacy 60
7.2.2.1 Electroencephalogram (EEG) 60
7.2.2.2 Status Epilepticus Severity Score (STESS) 60
7.2.2.3 Clinical Global Impression of Severity and Improvement (CGI-S and CGI-I, respectively) 61
7.2.2.4 Richmond Agitation and Sedation Scale (RASS) 61
7.2.2.5 The Full Outline of UnResponsiveness (FOUR) Score 61
7.2.2.6 Seizure Description Questionnaire 61
7.2.2.7 Status Epilepticus Cessation Questionnaire 61
7.2.2.8 Super Refractory Status Epilepticus Questionnaire 61
7.2.2.9 Modified Rankin Scale (mRS) 61
7.2.2.10 EuroQol (EQ-5D-5L) 62
7.2.3 Safety 62
7.2.3.1 Medical, Seizure or SE, and Medication History 62
7.2.3.2 Physical Examination 62
7.2.3.3 Adverse Event Collection 63
7.2.3.4 Vital Signs 63
7.2.3.5 Electrocardiography (ECG) 63
7.2.3.6 Cardiodynamic 12-Lead Electrocardiography (ECG) Monitoring 63
7.2.3.7 Clinical Laboratory Evaluations 64
7.2.4 Others 66
7.2.4.1 Clinical Pharmacology Blood Sample Collection and Handling Procedures 66
7.2.4.2 Shipment of Plasma Pharmacokinetic Samples 66
7.2.4.3 Plasma Drug Assay Methodology 66
7.3 Healthcare Utilization Questionnaires 68
8 ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT 69
8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events 69
8.1.1 Severity Categorization 69
8.1.2 Relationship Categorization 70
8.1.3 Outcome Categorization 70
8.1.4 Symptoms of the Disease Under Study 70
8.1.5 Clinical Laboratory and Other Safety Evaluations 71
8.1.6 Pregnancy 71
8.1.7 Medication Errors and Other Reportable Information 72
8.2 Serious Adverse Event Procedures 72
8.2.1 Reference Safety Information 72
8.2.2 Reporting Procedures 72
8.2.3 Serious Adverse Event Definition 73
8.2.4 Serious Adverse Event Collection Time Frame 73
8.2.5 Serious Adverse Event Onset and Resolution Dates 73

8.2.6 Fatal Outcome 74
8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting 74
9 DATA MANAGEMENT 75
9.1 Data Collection 75
9.2 Clinical Data Management 75
9.3 Data Monitoring Committee (DMC) 75
10 STATISTICAL CONSIDERATIONS 75
10.1 Statistical Analysis Process 75
10.2 Sample Size Determination 76
10.3 Analysis Populations 76
10.4 Statistical Analyses 76
10.4.1 Primary Endpoints (Double-Blind Phase) 76
10.4.2 Key Secondary Endpoints (Double-Blind Phase) 77
10.4.3 Other Secondary Endpoints 77
10.4.4 Healthcare Utilization Endpoints 78
10.4.5 Open-Label Endpoints 78
10.5 Safety Analyses 78
10.6 Pharmacokinetic Analyses 79
10.7 Interim Analyses 79
11 SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES 79
11.1 Sponsor's Responsibilities 80
11.1.1 Good Clinical Practice (GCP) Compliance 80
11.1.2 Public Posting of Study Information 80
11.1.3 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees 80
11.1.4 Study Suspension, Termination, and Completion 80
11.2 Investigator's Responsibilities 81
11.2.1 Good Clinical Practice Compliance 81
11.2.2 Protocol Adherence and Investigator Agreement 81
11.2.3 Documentation and Retention of Records 82
11.2.3.1 Case Report Forms 82
11.2.3.2 Recording, Access, and Retention of Source Data and Study Documents 82
11.2.3.3 Audit/Inspection 83
11.2.3.4 Financial Disclosure 83
11.3 Ethical Considerations 83
11.3.1 Informed Consent 83
11.3.2 Institutional Review Board or Ethics Committee 84
11.4 Privacy and Confidentiality 84
11.5 Study Results/Publication Policy 85
12 REFERENCES 87

13 APPENDICES 91

LIST OF TABLES

Table 1. Schedule of Assessments (Double Blind and Open-Label Phases) 27
Table 2. Investigational Product Infusion and Pharmacokinetic Sample Collection (Double Blind and Open-Label Phases) 32
Table 3. Enrollment in Study 1042-SE-2001 Dose Level Cohorts 38
Table 4. Dosing for Participants ≥40 kg (on a mg/hour basis) 52
Table 5. Dosing for Participants <40 kg (on a mg/kg/hour basis) 53
Table 6. Clinical Laboratory Tests 65
Table 7. Volume of Blood to Be Drawn from Each Participant 67
Table 8. Volume of Blood to Be Drawn from Each Participant (Pediatric Institution Sample Volumes) 67

LIST OF FIGURES

Figure 1. Study Design Flow Chart 40

ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice daily
BMI	body mass index
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
CRA	clinical research associate
CRO	contract research organization
CSE	convulsive status epilepticus
DMC	data monitoring committee
EC	Ethics Committee
ECG	electrocardiography
eCRF	electronic case report form
EEG	electroencephalography
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ESE	established status epilepticus
ESETT	Established Status Epilepticus Treatment Trial
EU	European Union
Euro QOL	Euro Quality of Life
FCBP	Females of childbearing potential
FDA	United States Food and Drug Administration
FOUR Score	Full Outline of UnResponsiveness Score
GABA	gamma-aminobutyric acid
GCP	Good Clinical Practice
GCSE	generalized convulsive status epilepticus
GNX	ganaxolone
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	Intensive Care Unit
ILAE	International League Against Epilepsy
IV	intravenous
IM	intramuscular
IP	investigational product
IRB	Institutional Review Board
ITT	Intent to treat
LAR	legal authorized representative
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NCSE	non-convulsive status epilepticus

NLT	not less than
PND	Postnatal Day
RASS	Richmond Agitation and Sedation Scale
PK	pharmacokinetic
RSE	refractory status epilepticus
SAE	serious adverse event
SAP	Statistical Analysis Plan
SE	status epilepticus
SRSE	super refractory status epilepticus
STESS	Status Epilepticus Severity Scale
ULN	upper limit of normal

STUDY SYNOPSIS

Protocol number: 1042-SE-3003	**Drug**: GGGanaxolone
Title of the study: A double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of intravenous ganaxolone in status epilepticus	
Number of participants (total and for each treatment arm): The term "participant" will be used in place of "subject" in accordance with the Food and Drug Administration (FDA) glossary, which states these may be used interchangeably. The double-blind phase of the study plans to screen approximately 160 patients aged 12 years of age and older with status epilepticus (SE) to randomize approximately 124 participants. Participants will be randomized in a 1:1 ratio to receive ganaxolone IV solution or placebo added to SE standard of care. Should the interim analysis result in demonstration of efficacy, the study will transition to an open-label treatment with all participants receiving ganaxolone IV solution added to SE standard of care.	
Investigator(s): Multicenter study	
Site(s) and Region(s): Multicenter study to be conducted in the United States, Canada, and Australia at approximately 100 sites	
Study period (planned): August 2020 to December 2024	**Clinical phase**: 3
Objectives: **Primary:** • To evaluate the efficacy and safety of ganaxolone IV for the treatment of SE after failure of two or more antiseizure medications. **Secondary:** • To assess the time to SE cessation following ganaxolone administration. • To evaluate the sustained efficacy of ganaxolone IV beyond the 48-hour treatment period as assessed by prevention of progression to IV anesthesia for the treatment of SE. **Exploratory:** • To determine the effect of ganaxolone on healthcare resource utilization. • To assess the effect of ganaxolone on doses of other antiseizure treatments and changes in seizure burden. • To evaluate the effect of ganaxolone on quality of life, functional status, and level of responsiveness.	
Rationale: Status epilepticus is defined as a prolonged, self-sustaining seizure or recurrent seizures without intervening recovery of consciousness.[1] The International League Against Epilepsy (ILAE) further defined SE as a condition resulting either from the failure of mechanisms responsible for seizure termination or from the initiation of mechanisms leading to prolonged seizures.[2] SE duration is typically defined as 5 minutes for convulsive (CSE) and 10 minutes for nonconvulsive (NCSE).[3] The ILAE has proposed definitions that encompass the time at which seizures become self-sustaining (t1) and a time when neurologic damage results (t2).[2] For generalized convulsive status epilepticus (GCSE), these are 5 and 30 minutes, respectively; for NCSE, they are 10 and 60 minutes. Status epilepticus is a neurological emergency that requires urgent treatment to stop seizures and avoid neurologic sequelae.[4] Mortality can range from 3% to 40% depending on etiology, age, SE type, and duration.[5,6,7] Convulsive SE is associated with complications that include cardiac arrhythmias, rhabdomyolysis, pulmonary edema, electrolyte and glucose imbalances and body temperature disturbances. Approximately one third of patients with refractory status epilepticus (RSE) and super refractory SE (SRSE) will die and one-third will recover with chronic neurologic sequelae.	

Benzodiazepines are the agents of choice for first-line treatment of SE, but may cause respiratory depression and hypotension, requiring the use of supportive therapies.[8] Approximately 35% to 45% of patients fail first-line treatment with benzodiazepines and are then considered to have established status epilepticus (ESE). The recently published findings from the Established Status Epilepticus Treatment Trial (ESETT), comparing the efficacy and safety of three commonly administered second-line IV antiepileptic drug (AEDs; fosphenytoin, levetiracetam and valproic acid) found that SE was not controlled in over 50% of ESE patients and that none of the medications tested was superior to the others.[9]

When a patient fails to respond to a benzodiazepine and the initial second-line IV AED, they are classified as having refractory SE (RSE). Refractory SE develops in 31% to 50% of patients with SE and has a mortality of 16 to 39%.[1,10,11] Because SE tends to become more refractory as it progresses, patients who fail second-line IV AEDs may require treatment with an IV anesthetic.[12,13] Third-line agents such as pentobarbital, midazolam and propofol are administered at anesthetic doses to induce coma that is maintained for 24 hours or longer, after which the dose of anesthetic agent is reduced to determine whether seizure activity has been aborted. IV anesthesia is an independent risk factor for increased morbidity and mortality in SE, with longer duration of anesthesia associated with a worse prognosis.[14,15,16]

Few drugs are approved for the treatment of SE and there is a need for more evidence-based, efficacious therapies. Treatment resistance in SE has been partially attributed to the internalization of post-synaptic γ-aminobutyric acid $(GABA)_A$ receptors and externalization of glutamate receptors.[10,12] With the down-regulation of $GABA_A$-mediated synaptic inhibition that occurs in SE, antiepileptic treatments relying on enhancement of synaptic $GABA_A$ neurotransmission become less effective.

Ganaxolone is a potent positive allosteric modulator of $GABA_A$ receptors that binds at a site distinct from that responsible for the action of benzodiazepines and barbiturates.[17] Unlike benzodiazepines, neuroactive steroids such as ganaxolone bind to both synaptic and extrasynaptic $GABA_A$ receptors.[18] By enhancing $GABA_A$ receptor function, especially through its action at extrasynaptic $GABA_A$ receptors, ganaxolone provides an alternative mechanism in the treatment of seizures. Thus, ganaxolone may serve as a novel and effective therapy in the management of SE.

The ganaxolone to be used for this study is a proprietary IV formulation solubilized by Captisol® (betadex sulfobutyl ether sodium). Dosing targets plasma concentrations of ganaxolone that mimic those associated with anticonvulsant effects in preclinical animal models of SE and that are expected to demonstrate anticonvulsant properties in humans. The dose of Captisol® will not exceed 50 g/day (1.25 g/kg/day in participants weighing <40 kg) which corresponds to a maximum ganaxolone dose of 833 mg/day (20.825 mg/kg/day in participants weighing <40 kg).

Investigational Product, Dose, and Mode of Administration:

Once consent/assent has been obtained or deferred where allowed by law, ganaxolone IV solution or placebo, referred to as investigational product (IP) throughout this document, will be added to standard of care.

Participants must have received any two or more of the following agents for treatment of the current episode of SE, administered at an adequate dose and for a sufficient duration, in the judgment of the investigator, to demonstrate efficacy:

- Benzodiazepines,
- IV Fosphenytoin/phenytoin,
- IV Valproic acid,
- IV Levetiracetam,
- IV Lacosamide,
- IV Brivaracetam, or
- IV Phenobarbital.

Fosphenytoin and phenytoin will be counted as 1 AED. Levetiracetam and brivaracetam will be counted as 2 AEDs.

Investigational product for administration will be provided to the site as individual 500 mL bottles of 1 mg/mL of ganaxolone, or placebo. Each bottle contains not less than (NLT) 425 mL of IP.

Investigational product should be administered through a dedicated peripheral or central IV line or a dedicated lumen of a multi-lumen catheter. Note: At any time, the infusion rate of IP may be temporarily decreased or permanently stopped for safety reasons.

The total time of IP administration will be 48 hours (36 hours IP administration and 12 hours of IP taper). The investigator will confirm that the participant meets clinical and electroencephalographic (EEG) criteria for SE during the 60-minute period prior to IP initiation and will reconfirm that ongoing ictal activity is present within 30 minutes immediately prior to IP initiation. The dosing of IP will be as follows:

Participants weighing at least 40 kg:

- A 30 mg bolus dose (over ~3 minutes) will be administered with a continuous infusion of 80 mg/hour for 2 hours followed by a continuous infusion rate of 40 mg/hour for 10 hours, and then 20 mg/hour for the remaining 12 hours of Day 1 (time 0 to 24 hours).
- On Day 2, from 24 to 36 hours following IP initiation, the continuous infusion rate of 20 mg/hour can be increased up to a maximum rate of 45 mg/hour until the start of the taper at 36 hours. The infusion rate will be determined by the investigator to best manage seizure relapse and cannot exceed a rate of 45 mg/hour between 24 and 36 hours following IP initiation.
- To taper IP, beginning 36 hours following IP initiation, the infusion rate will be reduced by 33.3% every 4 hours until the infusion is stopped or until the infusion rate becomes too low to sustain the IV line.

  Note: If, according to the investigator's clinical judgment, IP taper needs to start sooner than 36 hours after initiation, the infusion rate will be decreased by 33.3% of the rate at the beginning of the IP taper every 4 hours.
- At the time the IP infusion is discontinued, the participant will progress to the follow-up period assessments/procedures.

Participants weighing <40 kg will be dosed on a per-kilogram basis:

- A 0.75 mg/kg bolus dose (over ~3 minutes) will be administered with a continuous infusion at a dose of 2 mg/kg/hour for 2 hours followed by a continuous infusion dose of 1 mg/kg/hour for 10 hours, and 0.5 mg/kg/hour for the remaining 12 hours of Day 1 (time 0 to 24 hours).
- On Day 2, 24 to 36 hours following IP initiation, the continuous infusion rate of 0.5 mg/kg/hour can be increased up to a maximum of 1.125mg/kg/hour until the start of IP taper at 36 hours. The infusion rate will be determined by the investigator to best manage seizure relapse and cannot exceed a rate of 1.125 mg/kg/hour during hours 24 to 36 of Day 2.
- To taper IP, beginning 36 hours following IP initiation, the infusion rate will be reduced by 33.3% every 4 hours until the infusion is stopped or until the infusion rate becomes too low to sustain the IV line.

  Note: If, according to the investigator's clinical judgment, IP taper needs to start sooner than 36 hours after initiation, the infusion rate will be decreased by 33.3% of the rate at the beginning of the IP taper every 4 hours.
- At the time the IP infusion is discontinued, the participant will progress to the follow-up period assessments/procedures.

Investigational product infusion precautions:

Throughout the study, heart rate and rhythm, blood pressure, and oxygen saturation will be monitored. Investigational product may be temporarily or permanently discontinued, if clinically indicated, for treatment of persistent hypotension (sustained systolic blood pressure 90 mmHg), cardiac arrhythmia or oxygen desaturation.

Investigational product may also be terminated for any serious adverse event during infusion that the treating physician believes is IP related and necessary for participant safety. Investigational product discontinuation does not affect continued participation in the study. All participants should be followed, regardless of early discontinuation of IP, until the final study follow-up visit/contact unless consent is withdrawn.

Medical oversight:

Participants will require close medical monitoring as defined by local institutional practice guidelines for the treatment of patients with the diagnosis of seizures and/or status epilepticus.

Telemedicine:

Telemedicine is an acceptable practice for conducting protocol-driven assessments/procedures as defined by local institutional practice guidelines.

Investigational product discontinuation (one or more may apply):

- Scenarios for stopping IP without a taper may include:
  - Participants who receive IP for less than 2 hours.
  - Investigational product infusion is discontinued or interrupted (e.g., for safety concerns related or not related to IP or due to planned medical procedures), and a decision is made not to restart the infusion.
  - If at any time during IP administration the participant progresses to an anesthetic with the primary intent specifically to treat seizures or achieve burst suppression.
  - For other safety reasons based on the investigator's clinical judgment.

Dose adjustments and interruptions:

Investigational product dose (infusion rate) decreases, and interruptions are discouraged during treatment. However, if there is an urgent medical need (e.g., severe hypotension, severe sedation) or standard of care requires a procedure for which the infusion rate would need to be temporarily decreased or interrupted (e.g., MRI) it should be kept as short as possible and should not exceed 2 hours. If the interruption is >2 hours, the Medical Monitor should be consulted before restarting the infusion.

Note:

- After a dose (infusion rate) decrease or interruption, the investigator's clinical judgment of risk/benefit will determine IP administration or discontinuation.
- Investigational product discontinuation does not affect continued participation in the study. All participants should be followed, regardless of early discontinuation of IP, until they reach the final study follow-up visit/contact unless consent is withdrawn.
- In cases when IP discontinuation is being considered (e.g., severe sedation), when possible, the Medical Monitor should be contacted prior to infusion termination.
- If the decision is made to restart IP, the infusion should be restarted at the rate matching the rate at the corresponding nominal time, counted from the start of the IP infusion on Day 1. Investigational product bolus or "catch-up" dose to deliver the IP that was missed during the interruption should not be administered.

Dose (infusion rate) increases above those specified in the protocol are not allowed at any time during infusion. This is to ensure daily Captisol® and ganaxolone limits are maintained at ≤50 g/day (1.25 g/kg/day in participants weighing <40 kg) and ≤833 mg/day (20.825 mg/kg/day in participants weighing <40 kg), respectively.

Methodology:

This is a double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of ganaxolone IV solution in SE, with the option to transition the study to an open-label phase to obtain additional safety data. Screening, duration of the treatment, and follow-up periods, as well as the study schedule, remain the same for participants enrolled under either the double-blind or open-label phases.

As previously described, IP will be added to standard of care after failure of two or more antiseizure treatments (benzodiazepine and one IV AED or two IV AEDs).

Potential participants may be identified in the emergency department, ICU, or other units in the hospital, and will be consented/assented and then screened for inclusion/exclusion criteria prior to being randomized to start IP treatment. Investigational product will be administered as a 3-minute bolus that will be started with a continuous IV infusion of IP lasting for 36 hours and followed by a 12- hour taper. After the IP has been discontinued, the follow-up period assessments/procedures will be collected every 24 hours through 120 hours (or until hospital discharge) and at the time of hospital discharge followed by weekly follow-up visits/contacts at Week 1, 2, 3 and 4.

Weeks 1, 2, 3, and 4 visits can be conducted as inpatient visits, if the participant is still in the hospital or as a telephone contact if the participant has been discharged. Attempts should be made to have discharged participants return for one of these visits to be in person. In total, each participant will be followed for approximately 4 weeks following IP initiation.

An interim analysis will be conducted when approximately two-thirds of the ITT population have completed 72 hours of efficacy assessments (approximately 41 participants per arm). Enrollment in the double-blind phase will continue until the DMC provides a recommendation regarding study continuation. Based upon the interim analysis results, recommendation from the DMC, and agreement from the Sponsor, the double-blind study will either continue without modification or will transition to enrollment in an open-label phase. All participants enrolled subsequently will receive open--label ganaxolone IV solution added to SE standard of care. Approximately 60 to 100 study participants will receive ganaxolone IV in the double-blind and open-label phases combined.

Screening

Procedures specific to this protocol will not be performed until written informed consent/assent from the prospective participant/participant's parent/guardian/legally authorized representative (LAR) has been appropriately obtained according to institution policy. As many of the participants will not be able to provide consent/assent, a parent/guardian/LAR may provide consent on behalf of the participant. Where allowed by law, if the patient lacks the capacity to make informed decisions regarding his/her medical treatment options, the treating clinician may follow their deferred consenting practices. As soon as the participant is able, according to institution guidelines, consent/assent will be obtained. Consent/assent for participants who are known to be at risk for SE may be obtained prior to the occurrence of SE.

Standard of care assessments conducted prior to obtaining informed consent, that the investigator judges to be clinically relevant to the participant's current condition, can be utilized in the study and do not need to be repeated. For medically unstable participants, screening activities (e.g., labs or vital signs) should be collected as close to IP initiation as possible.

Treatment and Follow-up

Investigational Product Dosing

Approximately 160 participants will be enrolled in the double-blind phase of the study. For the double-blind phase, participants will be randomized (1:1) to receive either ganaxolone IV solution or placebo added to SE standard of care. In the open-label phase, all enrolled participants will receive ganaxolone IV solution added to SE standard of care. Investigational product will be given as a bolus plus continuous infusion. Following IP initiation, the standard duration of treatment is 2 days (48 hours) which includes a 12-hour taper.

Safety and Assessments

Investigational product will be given in addition to standard of care for SE and other medical or surgical interventions deemed appropriate by the investigator. Safety and tolerability will be monitored including but not limited to the following:

1. Physical examination should be completed:
    a. Predose (screening) or, if unable to perform predose, conduct within 2 hours following IP initiation, and at 36 hours, if clinically indicated, following IP initiation,
    b. At the time of IP discontinuation (+/- 1 hour), either at the end of the taper or if the IP administration is stopped without a taper,
    c. 24 hours (+/- 1 hour) following IP discontinuation, and
    d. At the time of hospital discharge.
    e. For participants who terminate early from the study, at the time of early termination (whenever possible).
    f. At any other time based on the clinical judgment of the investigator.
2. Status Epilepticus Severity Score (STESS) should be collected predose (screening).
3. Vital signs should be collected:
    a. Predose (screening), 60 minutes (+/- 15 min), 2 (+/- 15 min), 6, 10, 24, and 36 hours (+/- 2 hour) following IP initiation,
    b. At the time of IP discontinuation (+/- 1 hour), either at the end of the taper or if the IP administration is stopped without a taper,
    c. 24 hours (+/- 2 hour) following IP discontinuation, and
    d. At the time of hospital discharge.

e. For participants who terminate early from the study, at the time of early termination (whenever possible).
f. At any other time based on the clinical judgment of the investigator.

4. Weight and height should be collected predose (screening) for calculation of the BMI inclusion criterion, if feasible. If unable to collect predose, collect prior to the end of the first 24 hours of the follow-up period.
5. Richmond Agitation and Sedation Scale (RASS) and the Full Outline of UnResponsiveness (FOUR) Score Scale should be collected:
   a. Predose (screening),
   b. 60 minutes (+/- 15 min), 2, 6, 10 (+/- 30 min), 24 and 36 hours (+/- 1 hour) following IP initiation,
   c. At the time of IP discontinuation (+/- 1 hour), either at the end of the taper or if the IP administration is stopped without a taper,
   d. 24 (+/- 1 hour), 48, 72, 96, and 120 hours (+/- 2 hours) following IP discontinuation, and
   e. At the time of hospital discharge.
   f. At the weekly follow-up visits (Week 1, 2, 3, or 4) for hospitalized participants and for participants who have been discharged (whenever possible).
   g. For participants who terminate early from the study, at the time of early termination (whenever possible).
6. Electrocardiogram (ECG), the participant should have a safety 12 lead ECG:
   a. Predose (screening), 2 (+/- 30 min) following IP initiation,
   b. At the time of IP discontinuation (+/- 1 hour), either at the end of the taper or if the IP administration is stopped without a taper,
   c. 24 hours (+/- 1 hour) following IP discontinuation, and
   d. At the time of hospital discharge.
   e. For participants who terminate early from the study, at the time of early termination (whenever possible).
   f. At any other time based on the clinical judgment of the investigator.
7. Cardiodynamic 12 lead ECG monitoring: Select sites will participate in a sub study using a continuous 12 lead ECG recorder which should begin approximately 60 minutes prior to the initiation of IP and continue for 36 hours following IP initiation.
8. Clinical laboratory measures, hematology, serum chemistry (including creatinine, blood urea nitrogen [BUN], estimated glomerular filtration rate [eGFR] calculation (if available), creatinine clearance calculation (if available), and concomitant AED levels (fosphenytoin/phenytoin, valproic acid, levetiracetam, lacosamide, phenobarbital, or brivaracetam, if collected per standard of care), and Urinalysis (including urine protein and microscopic, if any abnormal value is observed on the urine dipstick test), should be collected:
   a. Predose (screening), if unable to collect predose, collect within 2 hours following IP initiation,
   b. At the time of IP discontinuation (+/- 1 hour); either at the end of the taper or if the IP administration is stopped without a taper,
   c. 24 hours (+/- 1 hour) following IP discontinuation, and
   d. At the time of hospital discharge.
   e. At the weekly follow-up visits (Week 1, 2, 3, or 4) for hospitalized participants and for participants who have been discharged (whenever possible).
   f. For participants who terminate early from the study, at the time of early termination (whenever possible).
   g. In the event of an SAE.
   h. At any other time based on the clinical judgment of the investigator.

   Urine chemistry samples for N-acetyl-β-D-glucosaminidase [NAG], β2-microglobulin, and creatinine should be collected:

a. Predose (screening), if unable to collect predose, collect within 2 hours following IP initiation,
b. 24 hours (+/- 1 hour) following IP discontinuation, and
c. At the time of hospital discharge.
d. At the weekly follow-up visits (Week 1, 2, 3, or 4) for hospitalized participants and for participants who have been discharged (whenever possible).
e. For participants who terminate early from the study, at the time of early termination (whenever possible).

Urine samples will be stored frozen unless otherwise dictated or revised in the Biospecimen Manual.

Coagulation (including fibrinogen, activated partial prothrombin time [APTT], prothrombin time [PT] and international normalized ratio [INR]) samples should be collected:

a. Predose (screening), if unable to collect predose, collect within 2 hours following IP initiation,
b. 24 hours (+/- 1 hour) following IP discontinuation, and
c. At the time of hospital discharge.
d. For participants who terminate early from the study, at the time of early termination (whenever possible).
e. At any other time based on the clinical judgment of the investigator.

9. Drugs of abuse testing should be collected predose (screening) per institution standard of care. Alcohol testing should be collected if medically indicated. Samples can be urine or serum. If unable to collect predose, collect as soon as possible following IP initiation. Enrollment is not contingent upon results. However, if a participant has a positive test result, it will be at the investigator's discretion to weigh the risks versus benefits for enrollment or continued participation.
10. Pregnancy test for females of childbearing potential, should be collected predose (screening). Samples can be urine or serum. If unable to collect predose, collect as soon as possible following IP initiation. Enrollment is not contingent upon results. However, if a participant has a positive test result, it will be at the investigator's discretion to weigh the risks versus benefits for enrollment or continued participation. If the institution requires the pregnancy test results to be obtained prior to IP initiation, the institution's guidelines will be followed.
11. Electroencephalogram is required for confirmation of CSE and NCSE diagnosis. Ideally, continuous EEG monitoring should start at least 60 minutes before IP initiation and continue through the end of the first 24 hours of the follow-up period.

    Sites will be offered the use of a rapid EEG device to assist with screening of participants with NCSE. It is preferred that a conventional EEG is used for the purposes of confirming inclusion criterion #3 and EEG monitoring during IP administration. In situations when a conventional EEG is not immediately available, the rapid EEG may be used to confirm inclusion criterion #3. Since the rapid EEG has a limited battery life, it should be switched to a conventional EEG within several hours but not earlier than 90 minutes after IP initiation to allow uninterrupted collection of EEG for the 30-minute SE cessation co-primary endpoint. It will be at the investigator's discretion if the use of the rapid EEG will benefit their site. The device should be used according to institution standard practices.
12. Blood sampling (venous or arterial) for pharmacokinetic (PK) analysis of ganaxolone and Captisol® will be collected at the following times:

    Required collections:

    a. After the start of the IP infusion: 60 minutes (+/- 5 min), then 2, 6 (+/- 5 min), 10, 24 and 36 hours (+/- 2 hour) following IP initiation,
    b. At the time of IP discontinuation (+/- 1 hour), either at the end of the taper or if the IP administration is stopped without a taper (e.g., when the participant progresses to IV anesthesia for seizure/SE treatment), and
    c. 24 hours (+/- 1 hour) following IP discontinuation.

    Variable PK collection times based on participant response:

    Between IP initiation and at the end of the first 24 hours of the follow-up period, where possible, collect a PK sample:

    d. At the time of an SAE (related or not related)

Pharmacokinetic samples should be collected from the contralateral peripheral access or the arterial line and avoid collecting samples downstream of the IP infusion. The location of IP access and location of PK sample collection should be documented in the participant's source. If the PK sample cannot be collected due to poor venous or arterial access and the IP infusion site is the only viable option, the sample should not be collected and the reason for non-collection documented in the participant's source. Pharmacokinetic samples will be stored frozen as per the Biospecimen Manual.

13. Blood gas samples, arterial or venous, if collected to manage the participant's care from the time of SE diagnosis through the end of the first 24 hours of the follow-up period, the electronic case report form (eCRF) should be completed. If samples are not collected, a sample is not required.

    If a decision is made to intubate the participant between IP initiation through the end of the first 24 hours of the follow-up period, a blood gas sample should be collected. The sample should be collected immediately prior to or as close as possible to the time of intubation.

14. Clinical Global Impression of Severity and Improvement (CGI-S and CGI-I, respectively)

    CGI-S should be collected:

    a. Predose (screening)

    CGI-I should be collected:

    a. 10 and 24 hours (+/- 1 hour) following IP initiation,
    b. The time of IP discontinuation (+/- 1 hour), either at the end of the taper or if the IP administration is stopped without a taper,
    c. 24 (+/- 1 hour), 48, 72, 96, and 120 hours (+/- 2 hours) following IP discontinuation, and
    d. At the time of hospital discharge.
    e. Week 1, 2, 3, and 4 follow-up visits (in person or via telephone contact).
    f. For participants who terminate early from the study, collect at the time of early termination (whenever possible).

15. EuroQoL (EQ-5D-5L) questionnaire should be collected:

    a. 120 hours (+/- 2 hour) following IP discontinuation and
    b. At the time of hospital discharge.
    c. Week 2, 3, and 4 follow-up visits (in person or via telephone contact).
    d. For participants who terminate early from the study, collect at the time of early termination (whenever possible).

16. Modified Rankin Scale (mRS) should be collected:

    a. 24 (+/- 1 hour), 48, 72, 96, and 120 hours (+/- 2 hours) following IP discontinuation, and
    b. At the time of hospital discharge.
    c. Week 2, 3 and 4 follow-up visits (in person or via telephone contact).
    d. For participants who terminate from the study, collect at the time of early termination (whenever possible).

17. Etiology of Status Epilepticus Questionnaire should be collected predose (screening).
18. Seizure Description Questionnaire should be collected predose (screening) and as close as possible to IP initiation.
19. Status Epilepticus Cessation Questionnaire should be collected as close as possible to 24 and 72 hours following IP initiation.
20. Super Refractory Status Epilepticus Questionnaire should be collected as close as possible to the diagnosis of SRSE and no later than the final study follow-up visit/contact.
21. Adverse events (AEs) and Concomitant medications: AEs will be collected from the time of IP initiation until the final study follow-up visit/contact via non-direct questioning. Concomitant medications will be collected during the same time period.

    a. All adverse events and associated concomitant medications will be collected through the final study follow-up visit/contact.

b. For participants who terminate early from the study, prior to discontinuation, as much information as is available should be recorded for AEs/SAEs and their associated concomitant medications, especially those that may have led to the early termination.

c. AEDs administered within 14 days of IP initiation will be recorded along with the reason for administration.

Instructions for collecting benzodiazepines, AEDs, anesthesia, and vasopressor medications prior to and post IP initiation is referenced in Sections 5.1 and 5.2. Some concomitant medications only require eCRF entries to support the highest dose administered, please reference the eCRF Completion Guidelines for details.

22. Healthcare Utilization Questionnaires include the Hospitalization Questionnaire and the Positive Pressure Ventilation (PPV) and Intubation Questionnaire. The Hospitalization Questionnaire should be collected at hospital discharge or at final study visit/contact.

The need for non-invasive or invasive ventilatory support within 24 hours prior to IP initiation and following IP initiation and within 48 hours following IP discontinuation should be collected as close as possible to the event.

Study follow-up and discontinuation:

Participants who terminate early from the study, e.g., due to withdrawal of consent, should have early termination procedures completed when early termination is being considered, wherever possible.

Participants who discontinue IP with or without a taper (e.g., were administered IP for less than 2 hours, progress to anesthesia for seizure suppression or discontinue IP due to safety or any other reason except due to withdrawal of consent) will continue in the study. The follow-up period assessments/procedures will be collected every 24 hours through 120 hours (or until hospital discharge) and at the time of hospital discharge, followed by weekly follow-up visits/contacts at Week 1, 2, 3, and 4.

All participants who discontinue IP, except those who are terminated early from the study, will have the follow-up period assessments/procedures, and the follow-up visits/contacts at Week 1, 2, 3, and 4. Weeks 1, 2, 3 and 4 visits can be conducted as an inpatient visit, if the participant is still in the hospital or as a telephone contact, if the participant has been discharged. Attempts should be made to have discharged participants return for one of these visits to be in person.

During these visits/contacts, the site will follow-up on all SAEs and AEs, and medications administered. Each participant will be followed for approximately 4 weeks.

During the study, it is expected that the total blood volume drawn from pediatric participants for all safety and pharmacokinetic sampling will be approximately 36 mL and will not exceed 40 mL of blood. The total blood drawn from adult participants will be approximately 140.3 mL and will not exceed 190.4 mL.

Inclusion and Exclusion Criteria:

Inclusion Criteria:

1. Participant, participant's parent, guardian, or LAR must provide signed informed consent/assent, and once capable (per institutional guidelines), there must be documentation of consent/assent by the participant demonstrating they are willing and aware of the investigational nature of the study and related procedures. Where allowed by law, if the patient lacks the capacity to make informed decisions regarding his/her medical treatment options, the treating clinician may follow their deferred consenting practices. The clinician will make the final decision based on the best interests of the patient.
2. Male or females 12 years of age and older at the time of the first dose of IP.
3. SE meeting the following criteria:
   a. A diagnosis of SE with or without prominent motor features based on clinical and EEG findings according to the investigator's judgment, based on the following:
      i. For SE with prominent motor features: Clinical and EEG seizure activity indicative of convulsive, myoclonic or focal motor SE
      ii. For SE without prominent motor features (nonconvulsive SE): Appropriate clinical features and an EEG indicative of NCSE (see modified Salzburg criteria[19] in Appendix 3).
      iii. For any type of SE:

- Approximately 6 minutes of cumulative seizure activity over a 30-minute period within the hour before IP initiation, AND
- Seizure activity during the 30 minutes immediately prior to IP initiation.

b. The treating clinician(s) anticipate that IV anesthesia is likely to be the next treatment for SE that persists following initiation of IP.

4. Participants must have received any two or more of the following agents for treatment of the current episode of SE administered at an adequate dose and for a sufficient duration, in the judgment of the investigator, to demonstrate efficacy (guidelines for adequate doses are provided in Appendix 2):
    - Benzodiazepines,
    - IV Fosphenytoin/phenytoin,
    - IV Valproic acid,
    - IV Levetiracetam,
    - IV Lacosamide,
    - IV Brivaracetam, or
    - IV Phenobarbital
5. BMI <40 or, if BMI is not able to be calculated at screening, participant is assessed by investigator as not morbidly obese.

Exclusion Criteria:

1. Life expectancy of less than 24 hours.
2. Anoxic brain injury or an uncorrected, rapidly reversable metabolic condition as the primary cause of SE (e.g., hypoglycemia <50 mg/dL or hyperglycemia >400 mg/dL).
3. Participants who have received high-dose IV anesthetics (e.g., midazolam, propofol, thiopental, or pentobarbital) during the current episode of SE for more than 18 hours, or who continue to have clinical or electrographic evidence of persistent seizures while receiving high-dose IV anesthetics.
4. Clinical condition or advance directive that would NOT permit use of IV anesthesia.
5. Participants known or suspected to be pregnant.
6. Participants with known allergy or sensitivity to progesterone or allopregnanolone medications/supplements.
7. Receiving a concomitant IV product containing Captisol® (marketed products listed in Appendix 4).
8. Known or suspected hepatic insufficiency or hepatic failure leading to impaired synthetic liver function.
9. Known or suspected stage 3B (moderate to severe; eGFR 44-30 mL/min/1.73m^2), stage 4 (severe; eGFR 29-15 mL/min/1.73m^2), or stage 5 (kidney failure; eGFR <15 mL/min/1.73m^2 or dialysis) kidney disease.
10. Use of an investigational product for which less than 30 days or 5 half-lives have elapsed from the final product administration. Participation in a non-interventional clinical study does not exclude eligibility.
11. Known or suspected history or evidence of a medical condition that, in the investigator's judgment, would expose participant to an undue risk of a significant adverse event or would interfere with assessments of safety or efficacy during the study.

Maximum Duration of Participant Involvement in the Study:

- The screening period is from the time consent/assent is obtained (or deferred, if allowed by law) to immediately prior to IP initiation (excluding pre-consent). However, assessments collected prior to this timeframe that the investigator judges to be clinically relevant to the participant's current state can be utilized in the study and do not need to be repeated. For medically unstable participants, screening activities (e.g., labs or vital signs) should be collected as close to IP initiation as possible.
- The planned duration of treatment is 2 days which includes a 12-hour taper.

- The planned duration for the follow-up period following IP discontinuation with or without a taper is approximately 4 weeks. The follow-up period study assessments/procedures will be collected every 24 hours through 120 hours (or until hospital discharge) and at hospital discharge with weekly visits/contacts at Week 1, 2, 3, and 4. Weeks 1,2, 3, and 4 visits can be conducted as inpatient visits, if the participant is still in the hospital, or as telephone visits, if the participant has been discharged. Attempts should be made to have discharged participants return for one of these visits in person.

Endpoints:

Primary Endpoints:

- Proportion of participants with SE cessation within 30 minutes of IP initiation without medications for the acute treatment of SE*
- Proportion of participants with no progression to IV anesthesia for 36 hours following IP initiation

SE cessation will be assessed by the investigator based on clinical and EEG features. Training will be provided to guide and help standardize decisions across clinical sites. In addition, a central reader blinded to treatment assignment will review EEG recordings retrospectively and corroborate the accuracy of interpretation.

*Medications for the acute treatment of SE are defined as AEDs administered to abort ongoing SE or prevent imminent recurrence of SE based on clinical or EEG evidence. This definition excludes maintenance doses of AEDs or medications with anticonvulsant properties used for other reasons, such as procedural sedation.

Key Secondary Endpoints:

- Time to SE cessation following IP initiation
- Proportion of participants with no progression to IV anesthesia for 72 hours following IP initiation

Other Secondary Endpoints:

- Proportion of participants with any escalation of treatment in the first 24 hours following IP initiation, i.e., any medication other than IP administered for the acute treatment of SE in the first 24 hours
- Time to treatment escalation following IP initiation (any other medication used for acute treatment of SE)
- Time to initiation of anesthesia for SE treatment through the final study follow-up visit/contact
- Proportion of participants who develop SRSE through the final study follow-up visit/contact
- Seizure burden through 72 hours following IP initiation
- Level of responsiveness as assessed by the FOUR Score Scale
- Level of sedation/agitation as assessed by the RASS
- Clinician Global Impression-Improvement (CGI-I)
- Level of functioning as assessed by the mRS
- Level of functioning as assessed by the EuroQoL (EQ-5D-5L)
- Proportion of participants with mRS $\geq$3 at the time of hospital discharge
- Proportion of participants whose treatment does not progress to IV anesthesia during the follow-up period

Healthcare Utilization Endpoints:

- Time on positive pressure ventilation after IP initiation
- Proportion of participants requiring positive pressure ventilation initiated during IP infusion
- Length of stay in the intensive care unit and in-hospital after IP initiation
- Discharge destination (location where the participant resides at the last follow-up visit assessment)
- Proportion of participants requiring artificial ventilation

Open-Label Phase Endpoints

If the study transitions to an open-label phase, all endpoint assessments as described for the double-blind phase will be summarized using descriptive statistics and no formal hypothesis testing will be performed.

Safety Endpoints:

Safety and tolerability will be assessed by physical examinations, clinical laboratory tests, ECGs, vital signs, use of concomitant medications, and occurrence of AEs

Statistical Methods:

The statistical analysis plan (SAP) will provide the complete details for the analysis and reporting of the data from the study.

Analysis of Primary Endpoint (Double-Blind Phase)

The primary efficacy objective of this study is to assess the efficacy of ganaxolone plus standard of care versus placebo plus standard of care in producing rapid and durable SE cessation without the need for treatment escalation to IV anesthesia for at least 36 hours following IP initiation.

Since the primary objective is a composite objective, in order to establish effectiveness of ganaxolone, the superiority of ganaxolone versus placebo added to standard of care would need to be established for the following co-primary endpoints:

1. Proportion of participants with SE cessation as determined by the investigator within 30 minutes of IP initiation without medications for the acute treatment of SE
2. Proportion of participants with no progression to IV anesthesia for 36 hours following IP initiation

Analysis of the response rates observed for each co-primary efficacy endpoint will be conducted using logistic regression methods. The model will include terms for treatment group and baseline STESS as a covariate. The analysis will be based on the intent to treat (ITT) population. Model-based point estimates (i.e., odds ratio), 95% confidence intervals and p-values will be reported. In addition, the point estimate of difference of the proportions of participants achieving either and both co-primary endpoints between two treatment arms will be provided. The 95% confidence interval will be provided using Clopper-Pearson method.

Analysis of Key Secondary Endpoints (Double-Blind Phase)

The following key secondary endpoints will be analyzed:

1. Time to SE cessation following IP initiation
2. Proportion of participants with no progression to IV anesthesia for 72 hours following IP initiation

If the primary endpoints are statistically significant, the analysis of key secondary efficacy endpoints will be performed sequentially in the order listed above.

The time to SE cessation will be analyzed using the Kaplan-Meier method.[20] The comparison of the survival curves between treatment groups will be conducted by a log-rank test. The second key secondary endpoint will be analyzed using the same statistical model as pre-specified for the co-primary endpoints.

Further details will be provided in the SAP.

Data Monitoring Committee

Emerging study data will be reviewed on a regular basis by an independent Data Monitoring Committee (DMC). The mission of the DMC is to safeguard the interests of study participants and to ensure the integrity and credibility of the trial. To enable the DMC to achieve its mission, it will have ongoing access to efficacy and safety data and information regarding quality of trial conduct and will ensure that the confidentiality of these data is protected. A DMC charter will provide the principles and guidelines for the DMC process.

Sample Size

The planned sample size for the study was 124 participants randomized in a 1:1 ratio. This sample size assumed at least a 75% response rate with ganaxolone treatment for each of the co-primary endpoints and no more than a 45% response rate with placebo. With 62 participants randomized to each treatment arm, there would be at least 90% power for each co-primary endpoint to achieve statistical significance at a 2-sided 5% level of significance.

Interim Analysis

An interim analysis was planned when two-thirds of the ITT population have completed 72 hours of efficacy assessments on the co-primary and key secondary endpoints (approximately 41 participants per arm). The overall type I error rate (i.e., alpha=0.05, 2-sided) will be controlled using a power family alpha spending function, with a 2-sided nominal alpha level of 0.0293 at the interim analysis. The interim analysis will be performed by an independent statistician who is not involved in study operation or study conduct.

The interim analysis was performed by an independent statistician who was not involved in study operation or study conduct and was based on 83 participants who had completed the primary and key secondary efficacy assessments. The DMC recommended may continue without modification.

Further details will be provided in the SAP.

STUDY SCHEDULE(S)

Table 1. Schedule of Assessments (Double-Blind and Open-Label Phases)

Periods/Day/ Duration	**Screening [a] Day -1 to Day 1 Predose through screening**	**Dosing Day 1 IP initiation 0 through 24 hours following IP initiation**				**Dosing Day 2 24 hours through 36 hours following IP initiation**		**Taper Day 2 (12 hours) Starts at 36 hours following IP initiation**	**IP Discontinuation**	**IP Discontinuation Follow-up [b]**							**Early Termination**
Visit	**1**	**2**				**3**			**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11 – 14**	**98**
Timepoint		**Minutes (m) /Hours (h) following IP initiation**							**With or without Taper**	**Hours following IP Discontinuation**					**Hospital Discharge**	**Weekly follow-up (Week 1, 2, 3, & 4)**	**ET**
	-0	**60 m**	**2 h**	**6 h**	**10 h**	**24 h**	**36 h**	**48 h**	Collected prior to or as close to IP discontinuation as possible	**24**	**48**	**72**	**96**	**120**		6 ± 3 14 ± 3, 21 ± 3, and 28 ± 3 days following IP discon	
Informed consent/assent	✔																
Inclusion/exclusion criteria	✔																
Demography and medical, including seizures or SE etiology and medication history[c]	✔																
Physical exam[d]	✔						✔		✔	✔					✔		✔
STESS	✔																
Vital signs[e]	✔	✔	✔	✔	✔	✔	✔		✔	✔					✔		✔
RASS[f]	✔	✔	✔	✔	✔	✔	✔		✔	✔	✔	✔	✔	✔	✔	✔	✔
FOUR Score[f]	✔	✔	✔	✔	✔	✔	✔		✔	✔	✔	✔	✔	✔	✔	✔	✔
Safety 12 lead ECG[g]	✔		✔						✔	✔					✔		✔
Cardiodynamic 12 lead ECG monitoring (sub study only)[h]	———						●										
Biochemistry, hematology, and AEDs[i]	✔								✔	✔					✔	✔	✔

Table 1. Schedule of Assessments (Double-Blind and Open-Label Phases)

Periods/Day/ Duration	**Screening [a] Day -1 to Day 1 Predose through screening**	**Dosing Day 1 IP initiation 0 through 24 hours following IP initiation**				**Dosing Day 2 24 hours through 36 hours following IP initiation**		**Taper Day 2 (12 hours) Starts at 36 hours following IP initiation**	**IP Discontinuation**	**IP Discontinuation Follow-up [b]**							**Early Termination**
Visit	**1**	**2**				**3**			**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11 – 14**	**98**
Timepoint		**Minutes (m) /Hours (h) following IP initiation**							**With or without Taper**	**Hours following IP Discontinuation**					**Hospital Discharge**	**Weekly follow-up (Week 1, 2, 3, & 4)**	**ET**
	-0	**60 m**	**2 h**	**6 h**	**10 h**	**24 h**	**36 h**	**48 h**	Collected prior to or as close to IP discontinuation as possible	**24**	**48**	**72**	**96**	**120**		6 ± 3 14 ± 3, 21 ± 3, and 28 ± 3 days following IP discon	
Urine chemistry (N-acetyl-β-D-glucosaminidase (NAG), β2-microglobulin, and Creatinine)[k]	✔									✔					✔	✔	✔
Coagulation[k]	✔									✔					✔		✔
Routine Urinalysis[i]	✔								✔	✔					✔	✔	✔
Drugs of abuse, including alcohol[l]	✔																
Pregnancy test (FCBP only)[l]	✔																
EEG[m]	→	→	→	→	→	→	→	→	→	→							
Blood Gas[n]																	
CGI-S	✔																
CGI-I[o]					✔	✔			✔	✔	✔	✔	✔	✔	✔	✔	✔
Seizure Description Questionnaire-predose[p]	✔																
Status Epilepticus Cessation Questionnaire[q]										✔		✔					
Super Refractory Status Epilepticus Questionnaire (SRSE)[r]																✔	
EuroQol (EQ-5D-5L)[s]														✔	✔	✔	✔
mRS										✔	✔	✔	✔	✔	✔	✔	✔
AEs/SAEs[u]		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	

Table 1. Schedule of Assessments (Double-Blind and Open-Label Phases)

Periods/Day/ Duration	**Screening [a] Day -1 to Day 1 Predose through screening**	**Dosing Day 1 IP initiation 0 through 24 hours following IP initiation**				**Dosing Day 2 24 hours through 36 hours following IP initiation**		**Taper Day 2 (12 hours) Starts at 36 hours following IP initiation**	**IP Discontinuation**	**IP Discontinuation Follow-up [b]**							**Early Termination**
Visit	**1**	**2**				**3**			**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11 – 14**	**98**
Timepoint		**Minutes (m) /Hours (h) following IP initiation**							**With or without Taper**	**Hours following IP Discontinuation**					**Hospital Discharge**	**Weekly follow-up (Week 1, 2, 3, & 4)**	**ET**
	-0	**60 m**	**2 h**	**6 h**	**10 h**	**24 h**	**36 h**	**48 h**	Collected prior to or as close to IP discontinuation as possible	**24**	**48**	**72**	**96**	**120**		6 ± 3 14 ± 3, 21 ± 3, and 28 ± 3 days following IP discon	
Concomitant medication[u]		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Healthcare Utilization Questionnaires[v]		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	

Discon = discontinuation; ET = Early Termination; ECG = electrocardiogram; IP = investigational product;; FCBP = females of childbearing potential; EEG = electroencephalograms; AE = adverse event; SAE = serious AE; STESS = Status Epilepticus Severity Score; RASS = Richmond Agitation and Sedation Scale; FOUR Score = Full Outline of UnResponsiveness Score; AED = antiepileptic drug; CGI-S = Clinical Global Impression of Severity; CGI-I = Clinical Global Impression of Improvement; mRS = modified Rankin Scale

a. The screening period is from the time participant/participant's parent/guardian/LAR consent is obtained (or deferred, if allowed by law) to immediately prior to IP initiation However, assessments collected prior to this timeframe that the investigator judges to be clinically relevant to the participant's current state can be utilized in the study and do not need to be repeated. For medically unstable participants, screening activities (e.g., labs or vital signs) should be collected as close to IP initiation as possible.
b. The planned duration for the follow-up period after IP is discontinued is approximately 4 weeks. Study assessments/procedures will be collected every 24 hours through 120 hours (or until hospital discharge) and at the time of hospital discharge followed by weekly follow-up visits at Week 1, 2, 3 and 4. Weeks 1, 2, 3 and 4 visits can be conducted as an inpatient visit, if the participant is still in the hospital, or as a telephone contact, if the participant has been discharged. Attempts should be made to have discharged participants return for one of these visits to be in person for clinical laboratory sample collection and RASS & FOUR Score assessments which can only be performed in person.
c. Demography, medical history, including seizures or SE etiology, and medication history will be collected prior to IP initiation but can be collected whenever feasible before the end of the taper.
d. Physical exam should be obtained from the participant's chart or completed predose (screening) or, if not available, collect within 2 hours following IP initiation, and at 36 hours, if clinically indicated, following IP initiation. Collect at the time of IP discontinuation (+/- 1 hour), either at the end of the taper or if the IP administration is stopped without a taper and 24 hours (+/- 1 hour) following IP discontinuation and at the time of hospital discharge. For participants who terminate early from the study, collect at the time of early termination (whenever possible). The investigator may conduct at any other time based on clinical judgment.
e. Vital signs including blood pressure, pulse, respiratory rate, temperature, and oxygen saturation should be collected predose (screening), 60 minutes (+/- 15 min), 2 (+/- 15 min), 6, 10, 24, and 36 hours (+/- 2 hour) following IP initiation. Collect at the time of IP discontinuation (+/- 1 hour), either at the end of the taper or if the IP administration is stopped without a taper and 24 hours (+/- 2 hours) following IP discontinuation, and at the time of hospital discharge. For participants who terminate early from the study, collect at the time of early termination (whenever possible). The investigator may collect at any other time based on clinical judgment. Weight and height should be collected predose (screening) for calculation of BMI inclusion criterion, if feasible. If not collected predose (screening), collect prior to the end of the first 24 hours of the follow-up period.
f. RASS and FOUR score scales should be collected predose (screening),60 minutes (+/- 15-min), 2, 6, 10 (+/- 30 minutes), 24 and 36 hours (+/- 1 hour) following IP initiation. Collect at the time of IP discontinuation (+/- 1 hour), either at the end of the taper or if the IP administration is stopped without a taper. Collect 24 (+/- 1 hour), 48, 72, 96, and 120 hours (+/- 2 hours) following IP discontinuation and at the time of hospital discharge. Collect at the weekly follow-up visits (Week 1, 2, 3, or 4) for hospitalized participants and for participants who have been discharged (whenever possible). For participants who terminate early from the study (whenever possible), collect at the time of early termination.
g. ECG should be collected predose (screening) and 2 hours (+/- 30 min) following IP initiation. Collect at the time of IP discontinuation (+/- 1 hour), either at the end of the taper or if the IP administration is stopped without a taper and 24 hours (+/- 1 hour) following IP discontinuation and at the time of hospital discharge. For participants who terminate early from the study, collect at the time of early termination (whenever possible). The investigator may collect any other time based on clinical judgment.
h. Cardiodynamic 12 lead ECG monitoring. Select sites will participate in a sub study using a continuous 12 lead ECG recorder which should be started approximately 60 minutes prior to IP initiation and should continue for 36 hours following IP initiation. For more details refer to Appendix 5.
i. Clinical labs, hematology, serum chemistry (including creatinine, blood urea nitrogen, creatinine clearance calculation [if available], estimated glomerular filtration rate [eGFR] calculation [if available]), and concomitant AED levels (fosphenytoin/phenytoin, valproic acid, levetiracetam, lacosamide, phenobarbital, or brivaracetam, if collected per standard of care) and Routine Urinalysis (including urine protein, and microscopic examination, if any abnormal value is observed on the urine dipstick test) should be collected predose (screening), if unable to collect predose, collect within 2 hours following IP initiation. Collect at the time of IP discontinuation (+/- 1 hour), either at the end of the taper or if the IP administration is stopped without a taper and 24 hours (+/- 1 hour) following IP discontinuation and at the time of hospital discharge. Collect at the weekly follow-up visits (Week 1, 2, 3, or 4) for hospitalized participants and for participants who have been discharged (whenever possible). For participants who terminate early from the study, collect at the time of early termination (whenever possible). Collect in the event of an SAE. The investigator may collect at any other time based on clinical judgment.
j. Urine chemistry sample for N-acetyl-β-D-glucosaminidase (NAG),β2-microglobulin, and creatinine should be collected predose (screening), if unable to collect predose, collect within 2 hours following IP initiation, 24 hours (+/- 1 hour) following IP discontinuation and at the time of hospital discharge. Collect at one of the weekly follow-up visits (Week 1, 2, 3, or 4) for hospitalized participants and when possible, for participants who have been discharged. For participants who terminate early from the study, collect at the time of early termination (whenever possible). Urine samples will be stored frozen unless otherwise dictated or revised in the Biospecimen Manual.
k. Clinical coagulation (including fibrinogen, activated partial thromboplastin time [APTT], prothrombin time [PT] and international normalize ratio [INR]) should be collected predose (screening), if unable to collect predose, collect within 2 hours following IP initiation, 24 hours (+/- 1 hour) following IP discontinuation and at the time of hospital discharge. For participants who terminate early from the study, collect at the time of early termination (whenever possible). The investigator may collect at any other time based on clinical judgment.
l. A urine or serum sample for drugs of abuse testing should be collected predose per the institution standard of care. A urine or serum sample for alcohol testing should be collected, if medically indicated. A urine or serum sample for pregnancy testing for females who are of childbearing potential, should be collected predose (screening). If unable to collect sample(s) at predose, collect as soon as possible following IP initiation. Enrollment is not contingent upon results. However, if a participant has a positive test result, it will be at the investigator's discretion to weigh the risks versus benefits for enrollment or continued participation. If the investigator decides to discontinue the IP, refer to the taper directions in the Investigational Product, Dose and Mode of Administration section. If the institution requires the pregnancy test results be obtained prior to IP initiation, the institution guidelines will be followed. The investigator may collect at any other time based on clinical judgment.
m. EEG is required for confirmation of CSE and NCSE diagnosis. Continuous EEG recording should be utilized for all participants and should start at least 60 minutes before IP initiation and continue through the end of the first 24 hours of the follow-up period.

n. Blood gas, arterial or venous, if collected to manage the participant's care from the time of SE diagnosis through the first end of the first 24 hours of the follow-up period, the eCRF should be completed. If samples are not collected, a sample is not required. If a decision is made to intubate the participant between IP initiation through the end of the first 24 hours of the follow-up period, a blood gas sample should be collected. The sample should be collected immediately prior to or as close as possible to the time of intubation.
o. CGI-I should be collected 10 and 24 hours (+/- 1 hour) following IP initiation. Collect at time of IP discontinuation (+/- 1 hour), either at the end of the taper or if the IP administration is stopped without a taper. Collect 24 (+/- 1 hour), 48, 72, 96, and 120 hours (+/- 2 hours) following IP discontinuation and at the time of hospital discharge. Collect at Week 1, 2, 3, and 4 follow-up visits/contacts. For participants who terminate early from the study, collect at the time of early termination (whenever possible).
p. Seizure Description Questionnaire should be collected predose (screening) as close as possible prior to IP initiation.
q. Status Epilepticus Cessation Questionnaire should be collected as close as possible to 24 and 72 hours following IP initiation.
r. Super Refractory Status Epilepticus (SRSE) Questionnaire should be collected as close as possible to the diagnosis of SRSE and no later than the final study follow-up visit/contact.
s. EuroQoL (EQ-5D-5L) should be collected at 120 hours (+/- 2 hours) following IP discontinuation and at the time of hospital discharge. Collect at Week 2, 3, and 4 follow-up visit/contacts. For participants who terminate early from the study, collect at the time of early termination (whenever possible).
t. mRS should be collected 24 (+/- 1 hour), 48, 72, 96, and 120 hours (+/- 2 hours) following IP discontinuation and at the time of hospital discharge. Collect at Week 2, 3, and 4 follow-up visits/contacts. For participants who terminate early from the study, collect at the time of early termination (whenever possible).
u. AEs will be collected from the time of IP initiation until the final study follow-up visit/contact via non-direct questioning. Concomitant medications will be collected during the same time period. All AEs and associated concomitant medications will be collected through the final study follow-up visit/contact. For participants who terminate early from the study, prior to discontinuation as much information as is available should be recorded for ongoing AEs/SAEs, new AEs/SAEs, and their associated concomitant medications, especially those that may have led to the early termination. Each AED administered within 14 days of IP initiation will be recorded and the reason for administration through the final study follow-up visit/contact.
v. Healthcare Utilization Questionnaires include the Hospitalization Questionnaire and the Positive Pressure Ventilation (PPV) and Intubation Questionnaire. The Hospitalization Questionnaire should be collected at hospital discharge or at final study visit/contact. The need for non-invasive or invasive ventilatory support within 24 hours prior to IP initiation and following IP initiation and within 48 hours following IP discontinuation should be collected as close as possible to the event.

Table 2. Investigational Product Infusion and Pharmacokinetic Sample Collection (Double-Blind and Open-Label Phases)

Periods/Day/ Duration	**Screening Day -1 to Day 1 Predose through screening**	**Dosing Day 1 IP initiation 0 through 24 hours following IP initiation**				**Dosing Day 2 24 hours through 36 hours following IP initiation**		**Taper Day 2 (12 hours) Starts at 36 hours following IP initiation**	**IP Discontinuation With or without Taper**	**IP Discontinuation Follow-up**
Visit	**1**	**2**				**3**		**3**	**4**	**5**
IP infusion[a]		✔				✔		✔		
Timepoint		**Minutes (m) /Hours (h) following IP initiation**								**Hours following IP Discontinuation**
	-0	**60 m**	**2 h**	**6 h**	**10 h**	**24 h**	**36 h**			**24 h**
Pharmacokinetic blood sample collection[b]		✔	✔	✔	✔	✔	✔		✔	✔

IP = investigational product

a. Investigational product will be administered as a 48-hour continuous infusion, which includes an initial 3-minute bolus and ends with a 12-hour taper.

b. Blood sample collection (venous or arterial) for pharmacokinetic analysis (ganaxolone and Captisol®) will occur at 60 minutes (± 5 min), then at 2, 6 (± 5 min), 10, 24 and 36 hours (± 2 hours) following IP initiation. Collect at the time of IP discontinuation (± 1 hour), either at the end of the taper or if the IP administration is stopped without a taper (e.g., when the participant progresses to IV anesthesia for seizure/SE treatment), and 24 hours (± 2 hour) following IP discontinuation. Variable PK collection time between IP initiation and the end of the first 24 hours in the follow-up period, where possible, collect a PK sample at the time of an SAE (related or not related); Pharmacokinetic samples should be collected from the contralateral peripheral access or the arterial line and avoid collecting samples downstream of the IP infusion. The location of IP access and location of PK sample collection should be documented in the participant's chart. If the PK sample cannot be collected due to poor venous or arterial access and the IP infusion site is the only viable option, the sample should not be collected and the reason for non-collection documented in the participant's source. Pharmacokinetic samples will be stored frozen as per the Biospecimen Manual.

1 BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

Status epilepticus (SE) is defined as a prolonged, self-sustaining seizure or recurrent seizures without intervening recovery of consciousness.[1] The International League Against Epilepsy (ILAE) has further defined SE as a condition resulting either from the failure of mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to prolonged seizures.[2] The minimum duration of seizures constituting SE is typically defined as 5 minutes for convulsive SE (CSE) and 10 minutes for non-convulsive SE (NCSE).[3] The ILAE has proposed definitions that encompass the time at which seizures become self-sustaining (t1) and a time when neurologic damage results (t2). For GCSE, these are 5 and 30 minutes, respectively; for nonconvulsive SE (NCSE), they are 10 and 60 minutes.[2]

In general, SE incidence varies from 9.9 to 41/100,000 per year with a bimodal age distribution. The youngest and oldest patients suffer from SE most often, specifically those in the first decade of life (14.3/100,000) and those over 60 years of age (28.4/100,000).[21] While the etiologies tend to be unique to specific age groups, the basic approach to treatment is similar across all ages and etiologies.[22,23] Treatment is largely focused on rapid SE cessation, including initiation of drugs to terminate seizures and reversal of conditions that may lower seizure threshold. Potentiating GABAergic inhibition is a key mechanism to achieve rapid seizure cessation in both adults and children.

If not treated immediately, prolonged seizure activity can result in permanent neuronal damage and contribute to the high morbidity and mortality associated with SE.[8,24,25] Mortality due to SE can range from 3% to 40% depending on etiology, age, type of SE and its duration.[26] Previous studies have shown that seizures cause neuronal death via excitotoxic mechanisms as a result of excessive neuronal activity.[1] Furthermore, CSE is associated with many complications, including cardiac arrhythmias, rhabdomyolysis, pulmonary edema, electrolyte and glucose imbalance, and temperature disturbances.[27]

Status epilepticus often occurs in the setting of pre-existing epilepsy, but it can also be caused by cerebral injury in individuals with no prior history of seizures.[8] In patients with chronic epilepsy, low blood concentration of antiepileptic drugs (AEDs) is a common cause of SE.[1] Other recognized causes of SE include, but are not limited to, stroke, anoxia or hypoxia, metabolic causes, and alcohol or drug withdrawal.[1,8]

Status epilepticus can be classified into 2 subtypes: Convulsive SE and NCSE.[8,24] Convulsive SE is characterized by continuous or repetitive tonic-clonic seizures without interictal recovery of full consciousness. Nonconvulsive SE is defined as prolonged continuous electrographic seizure activity without convulsive clinical symptoms or a series of nonconvulsive seizures without complete interictal clinical recovery. If CSE is prolonged, clinical manifestations may evolve to those of NSCE, a stage sometimes referred to as “subtle convulsive status epilepticus”.[28,6]

Additionally, SE can be categorized based on its refractoriness to treatment. The first-line standard of care medications for SE are benzodiazepines which, depending on the agent used, may be administered intravenously, intramuscularly or via the buccal route.[13] While these agents

have demonstrated efficacy in early SE, a recent study found that 25% and 36% of subjects with SE did not respond to intramuscular (IM) midazolam or intravenous (IV) lorazepam, respectively.[29] Early SE that is refractory to first line treatment is termed established SE (ESE). Only two-thirds of subjects with SE respond to the first treatment, and evidence shows that prolonged seizures can result in permanent neuronal damage and contribute to the high morbidity and mortality associated with SE.[30]

Refractory SE (RSE) is defined as SE resistant to treatment with one first-line AED (benzodiazepines) and one second-line AED such as IV fosphenytoin/phenytoin, valproic acid or levetiracetam.[11,31] The prognosis worsens with progression to RSE, with mortality in approximately one-third of patients and another one-third suffering from chronic neurologic sequalae.[14,32,33]

If second-line IV AEDs fail, IV anesthetic agents must be used to induce therapeutic coma to attempt control of SE.[1] Midazolam, propofol, pentobarbital or other anesthetics are administered, and coma is maintained for 24 hours or longer, after which the dose of the anesthetic agent is reduced to determine whether seizure activity has been aborted. Repeated courses of IV anesthesia may be attempted to control SE, with longer duration of IV anesthesia associated with a worse prognosis.[15] SE that fails treatment with a course of IV anesthesia is classified as super-refractory SE (SRSE), which is associated with increased length of hospitalization and higher costs of care.[34] SRSE represents only 13% of hospital admissions for SE but is responsible for 56% of costs. Mortality in SRSE is 40%, compared to 15% for RSE and 10% for non-refractory SE.

A recently completed study assessed the neurosteroid, brexanolone (allopregnanolone), compared to placebo in the treatment of SRSE (ClinicalTrial.gov NCT02477618). The study failed to meet its primary endpoint, the proportion of patients successfully weaned from IV anesthetics (43.9% vs. 42.4% for brexanolone and placebo, respectively, p=0.8775). The failure of brexanolone to treat SRSE may have been due to the severity or stage of progression of SE or to other factors. There has not been a controlled clinical trial of an AED for RSE.

An important aspect of SE diagnosis and treatment is the use of electroencephalographic (EEG) monitoring. EEG is necessary to determine the adequacy of SE therapy, particularly in NCSE, which often has no clinical manifestations to guide treatment. After control of CSE, subclinical electrographic seizure activity can be detected in up to 48% of patients.[35] If IV anesthesia is required, the EEG is used to assess whether depth of sedation is sufficient. The presence of a burst-suppression pattern on EEG is indicative of adequate levels of anesthesia for control of SE.

1.2 Product Background and Clinical Information

Nonclinical Data

The biological effects of ganaxolone (GNX) have been assessed in numerous in vitro and in vivo models and non-clinical pharmacodynamics (PD), pharmacokinetics (PK), and toxicology studies conducted in mice, rats, rabbits, monkeys, and dogs.[36]

The most common effect following treatment with GNX in toxicology studies was dose-related sedation, an expected pharmacological effect of a positive modulator of $GABA_A$ receptors. In both the oral (PO) and IV programs, there was little evidence of target organ or systemic toxicity associated with either single- or multiple-dose treatment with GNX. No functional or anatomic changes within hematopoietic tissue or any specific organ such as liver, kidney or gastrointestinal (GI) systems were seen in the repeat-dose studies.

Ganaxolone was not teratogenic in rats or mice and did not significantly affect the development of offspring. Ganaxolone had no effects on fertility and early embryonic development in rats. No potential for genotoxicity was detected. Treatment of neonatal rats with GNX produced expected signs of sedation but did not affect development or demonstrate any postmortem changes.

In rats continuously dosed with IV GNX for 14 days, no GNX-related changes were noted in clinical pathology parameters or histopathology examination. There was no evidence of local irritation when GNX was given IV or peri-venously in preclinical studies. Furthermore, IV GNX did not cause hemolysis and was compatible with human plasma.

The anticonvulsant activity of GNX was established in multiple in vivo models of seizure activity in rats and mice. The results from these studies show that GNX blocks seizure propagation, elevates seizure threshold, and can reverse seizures with delayed administration.

Ganaxolone, administered IV, was also evaluated and shown to be effective in models of SE.[37] These evaluations were conducted in rats and SE was induced by lithium pilocarpine administration. Seizure response was measured by EEG activity, behavioral convulsions, and seizure related mortality. In these studies, the administration of GNX was delayed up to 60 minutes after SE onset. Seizures at this time point after SE onset are resistant to benzodiazepine treatment and are considered to represent a treatment resistant version of SE. Ganaxolone, administered IV, produced a long-lasting reduction in EEG seizure response, behavioral convulsions, and also decreased seizure related mortality. In a study in which a subtherapeutic dose of GNX was co-administered with a subtherapeutic dose of diazepam, a synergistic effect on reduction of EEG seizure was observed. In comparison to IV administered allopregnanolone, GNX produced a longer lasting reduction in seizure activity. These preclinical data provide the support for the clinical evaluation of GNX in SE subjects.

Ganaxolone administered IV was also evaluated for effects on EEG patterns in otherwise normal (non-epileptic) rats. In one study, GNX was administered at a dose of 3 mg/kg every 30 minutes for 5 doses (total: 15 mg/kg). Under this dosing paradigm, GNX produced a complex EEG profile. Shortly after dosing, brief (~1 sec) periods of intense EEG activity with a peak frequency of around 10 Hz were observed. EEG power was increased in the GNX compared to the vehicle group from 0–50 Hz and reduced from 50–96 Hz. This EEG is consistent with a sedation EEG pattern. Rats still responded to painful stimuli. Thus, GNX did not produce an anesthetic response. In the second study, GNX was administered IV at 3 mg/kg every 3 minutes. Under this dosing paradigm, GNX produced a burst suppression-like EEG pattern after 4 doses (12 mg/kg). Rats were sedated, but still responded to tail pinch stimuli indicating that GNX did not cause a full anesthetic response.

The toxicity of Captisol® was evaluated in juvenile male and female Sprague Dawley rats dosed via twice daily (BID) subcutaneous injection (1000, 2500, and 5000 mg/kg/day) from Postnatal

Day (PND) 14 through PND 35 (Study 00398517). Endpoints included mortality, clinical signs, body weights, body weight gains, food consumption, organ weights, and macroscopic and microscopic examinations. All males and females survived to the scheduled necropsies. No remarkable clinical observations were noted during the detailed clinical observations or 1–2 hours following the first daily dose at any dose level. Nonadverse lower mean weight gain and corresponding food consumption was noted in the 5000 mg/kg/day group males and nonadverse microscopic findings in the kidneys, adrenal glands, axillary lymph node, and injection sites were observed in the 1000, 2500, and 5000 mg/kg/day group males and females. The epithelial cell vacuolation in the kidneys was not considered severe and histiocytic vacuolation in the adrenal gland, axillary lymph node, and injection sites were due to a biologic response to the presence of foreign material at the injection sites. At the recovery necropsy, microscopic findings persisted in the kidneys, adrenal glands, axillary lymph node, and injection sites, but with a general decrease in severity, suggesting partial recovery.

Based on the lack of adverse effects in males and females at all dose levels tested, a dose level of 5000 mg/kg/day (2500 mg/kg/dose BID) was considered to be the no-observed-adverse-effect level (NOAEL) for juvenile toxicity of Captisol® in rats.

Clinical Data

In 20 completed Phase 1 studies, 319 healthy volunteers received GNX doses of 50 to 2,000 mg/day for periods of up to 2 weeks.

In the 20 completed Phase 2/3 clinical studies, 1,238 study participants have received GNX, including adults with epilepsy, migraine and post-traumatic stress disorder, and children with epilepsy and Fragile X syndrome. There are 109 pediatric study participants currently enrolled in 2 ongoing epilepsy trials (CDKL5-deficiency disorder and PCDH19-related epilepsy).

The overall frequency of treatment-emergent adverse events (TEAE) in company-sponsored placebo-controlled studies was 61.7% (613/993) in study participants who received GNX and 51.8% (330/637) in those who received placebo. The most frequently reported TEAEs in GNX-treated participants were somnolence, dizziness, fatigue, and headache. All of these events, except for headache, which occurred more frequently in GNX- than placebo-treated study participants. CNS-related adverse events were dose-related, with the majority occurring at doses ≥500 mg/day. The majority of TEAEs were not unexpected based on the mechanism of action of GNX and were non-serious, mild to moderate in severity and did not lead to discontinuation of treatment.

No clinically significant trends in electrocardiogram (ECG) intervals, vital signs, or physical or neurologic examinations have been noted, and no mean changes from baseline in clinical laboratory results have been identified. Overall, there have been only a few clinically significant individual changes from baseline in laboratory measurements in GNX trials. In the completed, placebo-controlled Phase 1, 2, and 3 studies, 0.3% of subjects treated with GNX and 0.5% of subjects treated with placebo exhibited elevated liver function tests during the study (aspartate transaminase or alanine transaminase >3 times the upper limit of normal [ULN]). There have been no cases attributed to GNX fulfilling criteria for Hy's law.

In controlled clinical trials of GNX, 1.1% of subjects receiving placebo and 1.7% of subjects receiving GNX reported an AE of rash. However, rash led to discontinuation in GNX-treated subjects in 6 cases (0.6%) compared to no cases (0%) in placebo-treated subjects. Two subjects participating in a Phase 2 study investigating GNX in treatment of epilepsy developed an SAE of rash. Both events resolved after discontinuation of the IP.

Ganaxolone is rapidly absorbed into plasma and readily moved into breast milk. The effects of GNX on milk production and the breastfed infant are unknown. After cessation of the infusion, plasma GNX levels are expected to drop rapidly, but it is possible that low, subtherapeutic levels persist for several days as GNX is slowly released from tissues. Therefore, a washout period of 45 days is required following cessation of GNX treatment before breastfeeding. Previous toxicology studies in animals focusing on prenatal and neonatal development have not demonstrated toxicities associated with GNX. Ganaxolone has been administered to infants with severe forms of epilepsy as early as 4 months of age.

In clinical trials involving administration of GNX over several weeks, the IP has been tapered off over a 1- to 2- week period. There have been no reports of withdrawal symptoms emerging after cessation of GNX.

Always refer to the latest version of the GNX Investigator's Brochure (IB) for the overall risk/benefit assessment and the most accurate and current information regarding metabolism, pharmacokinetics, efficacy, and safety of GNX.

2 STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the study

Few drugs are approved for the treatment of SE and an urgent need for evidence-based, efficacious therapies remains, particularly for patients with RSE who have failed treatment with benzodiazepines and one or more second-line AEDs.[13] There is no evidence from randomized, controlled trials to support the use of one AED over another in any but the earliest stage of SE, in which benzodiazepines such as IV lorazepam or IM midazolam have been demonstrated to be effective.[29] The Established Status Epilepticus Treatment Trial (ESETT) demonstrated that three commonly used AEDs were ineffective in over half of patients with established status epilepticus (ESE), and none were superior to the others in stopping seizures.[9] There is limited evidence from retrospective case series suggesting potential utility for IV levetiracetam or lacosamide in RSE[38,39] though interpretability is limited by the retrospective nature of the data, lack of control groups and potential confounding by use of concomitant treatments.

Ganaxolone is the 3β-methylated synthetic analogue of the neuroactive steroid allopregnanolone. It differs from other GABAergic agents in that it binds to both synaptic and extrasynaptic $GABA_A$ receptors at a binding site distinct from benzodiazepines or barbiturates.[17] Resistance to treatment in SE has been attributed to the internalization of postsynaptic $GABA_A$ receptors and increase in synaptic density of glutamate receptors.[12] This alteration of receptor trafficking may underlie a shift in the balance of excitation and inhibition resulting in the perpetuation of SE.

Because prolonged seizures result in a reduction of $GABA_A$-mediated synaptic inhibition, antiepileptic treatments that rely on enhancing intrasynaptic $GABA_A$ neurotransmission become less effective the longer SE continues. Because of its action at extrasynaptic $GABA_A$ receptors, which are not downregulated with progression of SE, ganaxolone has the potential for therapeutic benefit when benzodiazepines and barbiturates are likely to be ineffective. Because of its mode of action, as well as its extensive safety record, ganaxolone represents a promising alternative to current treatments for SE.

The potential utility of ganaxolone for treatment of SE is also supported by the results of a phase 2, open-label study in 17 patients with RSE (Study 1042-SE-2001). Ganaxolone was administered IV via a bolus dose and concurrent initiation of a 48 to 96-hour infusion according to one of three dosing regimens as outlined in Table 3.

Table 3. Enrollment in Study 1042-SE-2001 Dose Level Cohorts

Cohort	Dose of GNX/day	Duration at target level ≥500 ng/mL (hours)	Number of patients per cohort
Low	500 mg/day	4	5
Medium	650 mg/day	0	4
High	713 mg/day	8	8

GNX = ganaxolone.

The median age of enrolled patients was 56.9 years (range 23 to 88 years) and 53% were female. Causes of SE included vascular disease (stroke or intracranial hemorrhage, N = 7), brain tumors (N = 4), alcohol withdrawal or drug overdose (N = 2), metabolic disturbances (N = 2) or autoimmune causes (N = 2). In two patients, the etiology of SE was unknown.

The majority of patients (N = 12) had NCSE, one of whom had converted from convulsive to non-convulsive SE. Study participants had failed a mean of 2.9 IV AEDs, including first-line treatment with benzodiazepines. The mean number of second-line IV AEDs was 2.1, including phenytoin, fosphenytoin, valproate, lacosamide and levetiracetam. All of the patients had received either lacosamide or levetiracetam, or both.

None of the 17 enrolled patients required treatment with IV anesthetics through 24 hours following initiation of ganaxolone, the primary efficacy endpoint of the study. The median time to SE cessation was 5 minutes from initiation of ganaxolone (N = 15 evaluable patients); 14/15 achieved SE cessation within 30 minutes and one achieved SE cessation at approximately 4 hours. Post hoc analysis of EEG monitoring data indicated that maintenance of an infusion rate producing a blood ganaxolone concentration of 500 ng/mL for 8 hours, and not 4 hours, resulted in sustained suppression of epileptiform activity. The dosing regimen in the present study is designed to maintain a ganaxolone concentration ≥500 ng/mL for the first 12 hours of IP infusion. It will also achieve plasma concentrations that replicate those associated with anticonvulsant effects in preclinical SE models and that are therefore expected to demonstrate anticonvulsant properties in humans.

The ganaxolone IV to be used in this study is a proprietary formulation that is solubilized with Captisol® (betadex sulfobutyl ether sodium), with the dose of Captisol® not exceeding 50 grams per day.

Among the 17 enrolled subjects who received GNX, the most common TEAE were somnolence (5 subjects, 29.4%), hypotension (4 subjects, 23.5%), and hypokalemia (3 subjects, 17.6%). Severe TEAEs were reported in 6 subjects (35.3%). The most frequently (reported in 2 or more subjects [i.e., ≥10%]) reported severe TEAEs by system organ class were Nervous System Disorders, reported in 4 subjects (23.5%). Refer to the GNX IB for detailed safety information.

2.2 Study Objectives

2.2.1 Primary Objective

- To evaluate the efficacy and safety of ganaxolone IV for the treatment of SE after failure of two or more antiseizure medications.

2.2.2 Secondary Objectives

- To assess the time to SE cessation following ganaxolone administration.
- To evaluate the sustained efficacy of ganaxolone IV beyond the 48-hour treatment period as assessed by prevention of progression to IV anesthesia for the treatment of SE.

2.2.3 Exploratory Objectives

- To determine the effect of ganaxolone on healthcare utilization.
- To assess the effect of ganaxolone on doses of other antiseizure treatments and changes in seizure burden.
- To evaluate the effect of ganaxolone on quality of life, functional status, and level of responsiveness.

3 STUDY DESIGN

3.1 Study Design and Flow Chart

This is a double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of ganaxolone IV solution in SE, with an option to transition to open-label treatment to obtain additional safety data following a demonstration of efficacy at the interim analysis, data monitoring committee (DMC) recommendation, and Sponsor agreement. The term “participant” will be used in place of “subject” in accordance with the FDA glossary which states these terms may be used interchangeably.

3.1.1 Double-blind Phase

Approximately 160 participants were planned to be screened to randomize approximately 124 study participants at least 12 years of age with SE. Randomization stopped at 100 patients for business reasons. Randomized participants will receive ganaxolone IV solution or placebo, referred to as investigational product (IP), in a 1:1 ratio added to SE standard of care.

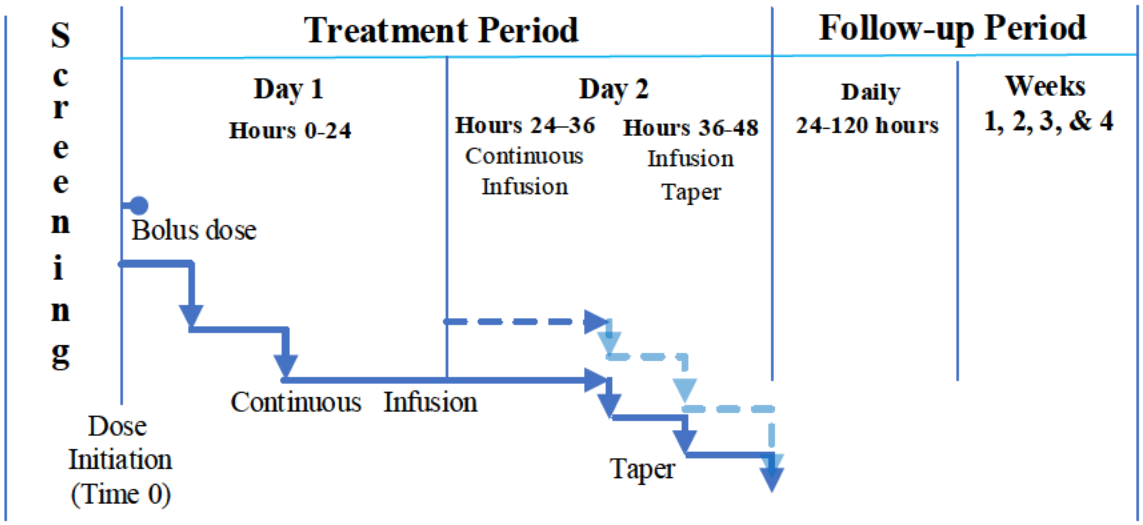
Potential participants may be identified in the emergency department, ICU or other units in the hospital and will be consented/assented or deferred, where allowed by law and then screened for inclusion/exclusion criteria prior to being randomized to start IP treatment.

Investigational product will be added to standard of care following failure of any two or more antiseizure treatments (benzodiazepine and 1 IV AED or 2 IV AEDs). Investigational product will be administered as a 48-hour continuous infusion, which includes an initial 3-minute bolus and ends with a 12-hour taper.

After the IP has been discontinued (with or without taper), the follow-up period study assessments/procedures will be collected every 24 hours through 120 hours (or until hospital discharge) and at the time of hospital discharge followed by weekly follow-up visits/contacts at Week 1, 2, 3, and 4.

Weeks 1, 2, 3, and 4 visits can be conducted as an inpatient visit for participants who are still in the hospital, or as a telephone contact for participants who have been discharged. Attempts should be made to have discharged participants return for one of these visits to be in person. In total, each participant will be followed for approximately 4 weeks following IP initiation.

Figure 1. Study Design Flow Chart



Treatment is planned to be 2-days (including a 12-hour taper).

Hours 24-36 should start with an infusion rate of 20mg/hr with dose adjustments allowed up to 45mg/hr. Upon IP discontinuation (with or without taper) participant will continue into the Follow-up Period

Total participation is expected to be approximately 4 weeks.

3.1.2 Open-label Phase

As described in Section 10.7, an interim analysis will be conducted when two-thirds of the ITT population have completed 72 hours of efficacy assessments (approximately 41 participants per arm). Based upon the interim analysis results, recommendation from the DMC, and agreement from the Sponsor, the study will either continue without modification or will transition to enrollment in an open-label phase. All participants enrolled subsequently will receive open-label ganaxolone IV solution added to SE standard of care. The screening, duration of the treatment and follow-up periods as well as the study schedule remain the same for participants enrolled under either the double-blind or open-label phases as described above and in Figure 1.

Approximately 60 to 100 study participants will receive ganaxolone IV in the double-blind and open-label phases combined.

3.2 Interim Analysis

As described in Section 10.7, an interim analysis will be conducted when two-thirds of the ITT population have completed 72 hours of efficacy assessments (approximately 41 participants per arm). Based upon the interim analysis results, recommendation from the DMC, and agreement from the Sponsor, the study will either continue without modification or will transition to enrollment in an open-label phase. All participants enrolled in the open-label phase will receive open-label ganaxolone IV solution added to SE standard of care. The screening, duration of the treatment, and follow-up periods, as well as the study schedule, would remain the same for participants enrolled under either the double-blind or open-label phases as described above and in Figure 1. Approximately 60 to 100 study participants are planned to receive ganaxolone IV in the double-blind and open-label phases combined.

3.3 Duration and Study Completion Definition

The maximum duration of study participation is expected to be approximately 4 weeks.

The study completion date is defined as the date the final participant, across all sites, completes their final study assessment/procedure; this includes the follow-up visit/contact, whichever is later. The study completion date is used to ascertain timing for posting and reporting of study results.

3.4 Sites and Regions

This multicenter study is to be conducted in the United States, Canada, and Australia, with approximately 100 sites planned to participate.

4 STUDY POPULATION

Each participant/participant's parent/guardian/legally authorized representative (LAR) must participate in the informed consent process and provide written informed consent/assent, unless allowed by law, e.g., deferred consent, before any procedures specified in the protocol are performed. Consent/assent will be administered per institution IRB/EC policy and may vary across sites, i.e., some sites may be able to consent/assent over the phone or other communication methods. Informed consent/assent for participants who are known to be at risk for SE may be obtained prior to a SE event. The period the pre-consent/assent is valid will be determined by institution IRB/EC. However, reconsenting will be needed should the consent/assent be updated at any point during the study.

4.1 Inclusion Criteria

The participant will not be considered eligible for the study without meeting all the criteria below.

1. Participant, participant's parent, guardian, or LAR must provide signed informed consent/assent, and once capable (per institution guidelines), there must be documentation of consent/assent by the participant demonstrating they are willing and aware of the investigational nature of the study and related procedures. Where allowed by law, where the patient lacks the capacity to make informed decisions regarding his/her medical treatment options, the treating clinician may follow their deferred consenting practices. The clinician will make the final decision based on the best interests of the patient.
2. Male or females 12 years of age and older at the time of the first dose of IP.
3. SE meeting the following criteria:
    a. A diagnosis of SE with or without prominent motor features based on clinical and EEG findings according to the investigator's judgement, based on the following:
        i. For SE with prominent motor features: Clinical and EEG seizure activity indicative of convulsive, myoclonic or focal motor SE
        ii. For SE without prominent motor features (nonconvulsive SE): Appropriate clinical features and an EEG indicative of NCSE (see modified Salzburg criteria[19] in Appendix 3).
        iii. For any type of SE:
            - Approximately 6 minutes of cumulative seizure activity over a 30-minute period within the hour before IP initiation, AND
            - Seizure activity during the 30 minutes immediately prior to IP initiation.
    b. The treating clinician(s) anticipate that IV anesthesia is likely to be the next treatment for SE that persists following initiation of IP.
4. Participants must have received any two or more of the following agents for treatment of the current episode of SE administered at an adequate dose and for a sufficient duration, in the judgment of the investigator, to demonstrate efficacy (guidelines for adequate doses are provided in Appendix 2):
    - Benzodiazepines,
    - IV Fosphenytoin/phenytoin,
    - IV Valproic acid,
    - IV Levetiracetam,
    - IV Lacosamide,
    - IV Brivaracetam, or
    - IV Phenobarbital
5. BMI <40 or, if BMI is not able to be calculated at screening, participant is assessed by investigator as not morbidly obese.

4.2 Exclusion Criteria

Participants are excluded from the study if any of the following exclusion criteria are met.

1. Life expectancy of less than 24 hours.
2. Anoxic brain injury or an uncorrected rapidly reversable metabolic condition as the primary cause of SE (e.g., hypoglycemia <50 mg/dL or hyperglycemia >400 mg/dL).
3. Participants who have received high-dose IV anesthetics (e.g., midazolam, propofol, thiopental, or pentobarbital) during the current episode of SE for more than 18 hours, or who continue to have clinical or electrographic evidence of persistent seizures while receiving high-dose IV anesthetics.
4. Clinical condition or advance directive that would NOT permit use of IV anesthesia.
5. Participants known or suspected to be pregnant.
6. Participants with known allergy or sensitivity to progesterone or allopregnanolone medications/supplements.
7. Receiving a concomitant IV product containing Captisol® (marketed products listed in Appendix 4).
8. Known or suspected hepatic insufficiency or hepatic failure leading to impaired synthetic liver function.
9. Known or suspected stage 3B (moderate to severe; eGFR 44-30 mL/min/1.73m^2), stage 4 (severe; eGFR 29-15 mL/min/1.73m^2), or stage 5 (kidney failure; eGFR <15 mL/min/1.73m^2 or dialysis) kidney disease.
10. Use of an investigational product for which less than 30 days or 5 half-lives have elapsed from the final product administration. Participation in a non-interventional clinical study does not exclude eligibility.
11. Known or suspected history or evidence of a medical condition that, in the investigator's judgment, would expose participant to an undue risk of a significant adverse event or would interfere with assessments of safety or efficacy during the study.

4.3 Restrictions

Participants must abstain from the use of alcohol until the end of the 24-hour IP discontinuation follow-up period.

Females are prohibited from breastfeeding for 45 days after the last dose of IP.

4.4 Reproductive Potential

4.4.1 Female Contraception

Sexually active females of childbearing potential should be using an acceptable form of contraception and must be advised to use acceptable contraceptives throughout the study period and for 30 days after the last dose of IP. If hormonal contraceptives are used, they should be administered according to the package insert.

Females of childbearing potential who are not currently sexually active must agree to use acceptable contraception, as defined below, if they become sexually active during the period of the study and 30 days after the last dose of IP.

Female participants should be:

- Postmenopausal (12 consecutive months of spontaneous amenorrhea and ≥ age 51 years), or
- Surgically sterile (having undergone one of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy, or bilateral salpingectomy) and at least 6 weeks post-sterilization, or
- Should have a urine or serum sample collected for pregnancy testing prior to IP initiation. If not possible, collect as soon as possible following IP initiation. Enrollment is not contingent upon results. However, if a participant has a positive test result, it will be at the investigators' discretion to weigh the risks versus benefit for continued participation. If the institution requires the pregnancy test results be obtained prior to IP initiation, the institution guidelines will be followed.

Acceptable methods of contraception are:

- Intrauterine device plus condoms
- Double barrier methods (e.g., condoms and diaphragm with spermicidal gel or foam)
- Hormonal contraceptives (oral, patch, injectable, or vaginal ring), stabilized for at least 30 days prior to the study participation, plus condoms. Note: If participant becomes sexually active during the study, they should use one of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days.

Contraceptive measures such as Plan B™, sold for emergency use after unprotected sex, are not acceptable methods for routine use.

4.4.2 Male Contraception

Male participants must agree to take all necessary measures to avoid causing pregnancy in their sexual partners during the study and for 30 days after the last dose of IP. Medically acceptable contraceptives include surgical sterilization (such as a vasectomy) and a condom used with a spermicidal gel or foam.

Male participants should not donate sperm during the study and for 30 days after the last dose of IP.

4.5 Discontinuation of Participants

A participant may withdraw, or their parent, guardian, or LAR may withdraw the participant from the IP administration and/or the study at any time for any reason without prejudice to their future medical care by the physician or the institution. The investigator or Sponsor may withdraw the participant at any time (e.g., in the interest of participant safety). The investigator is encouraged to discuss withdrawal of a participant from IP with the Medical Monitor, when possible, unless due to progression to an IV anesthetic for seizure suppression.

4.5.1 Investigational product discontinuation

Participants who discontinue IP without a taper (e.g., were administered IP for less than 2 hours, progress to anesthesia for seizure suppression or discontinue IP due to safety or any other reason, except due to withdrawal of consent) will have the follow-up assessments/procedures collected

every 24 hours through 120 hours (or until hospital discharge) and at the time of hospital discharge, followed by weekly follow-up visits/contacts at Week 1, 2, 3 and 4.

4.5.1.1 Reasons for IP discontinuation include, but are not limited to, the following:

- Adverse event or imminent safety concern
- Medical procedure
- Lack of efficacy with progression to high dose IV anesthesia for seizure/SE control
- Lack of efficacy without progression to high dose IV anesthesia for seizure/SE control
- Progression to high dose IV anesthesia for reason not related to seizure/SE
- Death
- Consent withdrawal
- Physician decision (must be specified in the participant's source documents and electronic case report form [eCRF])
- Other (must be specified in the participant's source documents and eCRF).

4.5.1.2 Study Withdrawal

All participants reserve the right to withdraw from the clinical study at any time, as stated in the informed consent/assent form.

Participants who terminate early from the study (e.g., due to consent withdrawn), any outstanding procedures and the evaluations listed for the Early Termination Visit in Table 1 should be completed when early termination is being considered.

4.5.2 Participant Withdrawal Criteria

The Sponsor is not providing formal thresholds to discontinue a participant from the study. The Sponsor encourages the investigator to continuously assess any potential risks and benefits of participation during the entire study. The investigator should not hesitate to discontinue a participant from the clinical study if, according to the investigator's clinical judgment, the risks exceed any potential benefits. Reference examples below.

1. If the participant experiences worsening and persistent ventilatory depression despite routine clinical interventions (e.g., jaw thrust, chin lift or oxygen supplementation) that, in the judgment of the investigator, can be improved upon by discontinuation of the IP, the investigator may choose to discontinue such participant from the study. If positive ventilatory support is initiated and the participant is stable as per the investigator's clinical judgment, IP may be continued.
2. ECG evidence of QT prolongation (QTcF >500 msec, or an increase of QTcF >60 msec above baseline to a value >480 msec on the 12 lead ECG, confirmed on a repeat 12-lead ECG taken after resting at least 5 minutes in a supine or semi recumbent position after the original finding of prolonged QTcF).
3. Kidney function impairment such that eGFR ≤44 mL/min/1.73m^2 and participant is not starting dialysis.

4. Any other adverse event or safety issue (e.g., severe persistent hypotension/hypertension or tachycardia/bradycardia) that suggests it is not in the participant's best interest to continue to receive IP.
5. Rash that is clinically significant and considered to be related to the IP (e.g., morbilliform, urticarial, papular).
6. Participant experiences an SAE considered to be related to the IP.

Decisions to discontinue from the study will be made by the investigator. If feasible, the reason for discontinuation should be discussed with the Medical Monitor prior to the participant's discontinuation unless due to the progression to anesthesia for seizure suppression.

4.5.3 Reasons for Study Discontinuation

The reason for study discontinuation must be determined by the investigator and recorded in the participant's medical record and in the eCRF. If a participant is withdrawn for more than one reason, each reason should be documented in the source document and the most clinically relevant reason should be entered in the eCRF.

Reasons for discontinuation include, but are not limited to, the following:

- Adverse event
- Protocol deviation
- Consent withdrawal
- Lost to follow-up
- Lack of efficacy
- Death
- Physician decision (must be specified in the participant's source documents and eCRF)
- Other (must be specified in the participant's source documents and eCRF)

4.5.4 Participants Lost to Follow-up Prior to Last Scheduled Visit

A minimum of three documented attempts must be made to contact any participant lost to follow-up at any timepoint prior to the last scheduled contact (office visit or telephone contact). At least one of these documented attempts must include a written communication sent to the participant's last known address via courier or mail (with an acknowledgment of receipt request) asking that they return to the site for final safety evaluations. If a contact is not made, the participant should be classified as Lost to Follow-up in the eCRF. However, if contact is made but the participant refuses or is unable to come to the final safety evaluation, they should be classified as Other and the reason documented in the eCRF.

5 PRIOR AND CONCOMITANT TREATMENT

5.1 Prior Treatment

Prior treatment includes all non-study treatment (including AEDs) administered within 14 days of IP initiation (or pharmacokinetic equivalent of five half-lives, whichever is longer).

Treatments including but not limited to herbal treatments, vitamins, surgical implants (such as Vagus nerve stimulator), and prescribed medications, if available, must be recorded on the appropriate eCRF page.

Benzodiazepines, AEDs and Anesthesia Medications

- Prior to IP initiation (not experiencing a seizure event)
    - Medications administered during this timeframe will be collected per the medication order
- Prior to IP initiation (for the current SE event)
    - Medications administered during this timeframe will be collected separately (i.e., each dose administered will be collected separately)

Vasopressors

- The administration of a continuous IV vasopressor infusion in the 24-hours prior to IP initiation will be collected in the Prior and Concomitant Medication eCRF

5.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between the date of the first dose of IP and the final study follow-up visit/contact.

Concomitant treatment information must be recorded on the appropriate eCRF page.

Benzodiazepines, AEDs and Anesthesia Medications

- During IP administration and for 120 hours of the follow-up period
    - Medications administered during this timeframe will be collected separately (i.e., each dose administered will be collected separately)
- Follow-up period (starts 120 hours following IP discontinuation)
    - Medications administered during this timeframe will be collected per the medication order

Vasopressors

- Administration of a continuous IV vasopressor infusion during IP administration or within 24 hours following IP discontinuation will be collected in the Prior and Concomitant Medication eCRF.

For some of the concomitant medications only the highest dose administered will be required in the eCRF. Reference the eCRF Completion Guidelines for guidance.

5.2.1 Permitted Treatment

To qualify for inclusion (Section 4.1), the participant must have received an acute treatment with any two or more of the following agents for treatment of the current episode of SE: benzodiazepines, IV fosphenytoin/phenytoin, IV valproic acid, IV levetiracetam, IV lacosamide, IV phenobarbital, IV brivaracetam, or IV phenobarbital. Taking any of these drugs alone or in combination is acceptable. Fosphenytoin/phenytoin will be counted as one (1) IV AED. Levetiracetam and brivaracetam will be counted as two (2) IV AEDs.

If the participant is receiving an oral AED to manage a chronic medical condition, (e.g., epilepsy, migraine, or neuropathic pain), the AED is acceptable and may continue unchanged. This maintenance treatment does not count towards the SE treatment failures required to qualify for this study.

The site will record the reason for each AED dose during IP administration in the appropriate CRF page.

5.2.2 Prohibited Treatment

If a participant progresses at any time during the study to an IV anesthetic (e.g., midazolam, propofol, thiopental, or pentobarbital) given with the primary intent specifically to treat seizures or achieve burst suppression IP administration will be discontinued without taper but the participant will continue in the study. Additional details can be found in Section 4.5.

Concomitant use of IV products containing Captisol® during IP administration is prohibited (see exclusion criterion #7 and Appendix 4).

6 INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The IP is ganaxolone IV solution, 1 mg/mL, or placebo which will be provided in 500 mL glass bottles with a grey stopper, purple flip-off cap and aluminum overseal. Each 500 mL bottle contains 425 mL of a sterile solution. The IP is provided as a unit dose bottle. Placebo will only be used for the double-blind phase of the study. Should the study transition to open-label, the ganaxolone IV solution administered as IP will be identical to the ganaxolone IV solution administered during the double-blind phase.

The active formulation consists of a sterile solution of ganaxolone drug substance that has been solubilized by complexation with Captisol® (Betadex Sulfobutyl Ether Sodium). The drug product is terminally heat-sterilized.

On 01 June 2022 the Drug Enforcement Administration (DEA) issued its interim final rule placing ganaxolone, including its salts, in schedule V of the Controlled Substances Act. The DEA drug code for Ganaxolone (commercial name, Ztalmy) is 2401.

For more details on the composition of the ganaxolone IV solution, 1 mg/mL refer to the Pharmacy Manual.

6.1.1 Blinding the Treatment Assignment

6.1.2 Double-Blind Phase

During the double-blind phase of the study, all participating staff involved in the evaluation and execution of the study will remain blinded to the participant's treatment assignment.

6.1.3 Open-Label Phase

If the study transitions to an open-label phase (refer to Section 10.7**)**, blinding will not be applicable for new participants enrolled in the open-label phase of the study.

6.2 Administration of Investigational Product(s)

6.2.1 Interactive Response Technology for Investigational Product Management

Interactive Response Technology (IRT) will be utilized for the following tasks:

- IP allocation (double-blind phase only)
- Randomization (double-blind phase only)
- Supply management
- Inventory management and supply ordering
- Expiration date tracking
- Returns
- Emergency unblinding (double-blind phase only)

Details of the system and a system user manual will be provided for the investigator files at each site.

6.2.2 Allocation of Participants to Treatment

6.2.2.1 Double-Blind Phase

The actual treatment given to individual participants is determined by a randomization schedule. Participant identification numbers are assigned prior to dosing. Within each site (numbered uniquely within a protocol), participant numbers are assigned in the sequence of participant presentation for study participation. To allow for timely delivery of IP to the hospital unit, the IP bottles may be allocated for use in the IRT prior to the participant meeting all eligibility criteria to avoid impact to standard of care. Investigational product will not be administered until eligibility has been determined. Enrollment is defined as the initiation of IP infusion.

6.2.2.2 Open-Label Phase

All eligible participants enrolled under the open-label phase of the study will receive ganaxolone IV solution added to SE standard of care. No randomization will occur.

As per the double-blind phase, within each site, participant numbers will be assigned in the sequence of participant presentation for study participation. Investigational product will not be

administered until eligibility has been determined. Enrollment is defined as the initiation of IP infusion.

6.2.3 Dosing

Once consent/assent has been obtained or deferred, where allowed by law and if the participant meets protocol entry criteria, IP will be added to standard of care.

Participants must have received any two or more of the following agents for the treatment of the current episode of SE (benzodiazepine and one IV AED or two IV AEDs), administered at an adequate dose and for a sufficient duration, in the judgment of the investigator, to demonstrate efficacy (guidelines for adequate doses are provided in Appendix 2):

- Benzodiazepines,
- IV Fosphenytoin/phenytoin,
- IV Valproic acid,
- IV Levetiracetam,
- IV Lacosamide,
- IV Brivaracetam, or
- IV Phenobarbital

Administering fosphenytoin/phenytoin will be counted as one (1) AED. Administering levetiracetam and brivaracetam will be counted as two (2) AEDs.

Investigational product will be administered as a 48-hour continuous infusion, which includes an initial 3-minute bolus and ends with a 12-hour taper.

The investigator will confirm that the participant meets clinical and EEG criteria for SE during the 60-minute period prior to IP initiation and will reconfirm that ongoing ictal activity is present within 30 minutes immediately prior to IP initiation.

Investigational product should be administered through a dedicated peripheral or central IV line or a dedicated lumen of a multi-lumen catheter. Infusion lines should be changed according to institution standard practices. The maximum time an IP bottle can be hung at the participant's bedside for administration is 24 hours.

Note: At any time, the infusion rate of IP may be temporarily decreased or permanently stopped for safety reasons.

Status epilepticus cessation will be assessed by the investigator based on clinical and EEG features. Training will be provided to guide and help standardize decisions across clinical sites. In addition, during the double-blind phase, a central reader blinded to treatment assignment will review EEG recordings retrospectively and corroborate accuracy of interpretation. If the study transitions to open-label treatment after a demonstration of efficacy at the interim analysis, a central reader will still review the EEG recordings retrospectively and corroborate accuracy of interpretation but will not be blinded to treatment assignment given that all participants will be receiving open-label ganaxolone IV solution.

6.2.3.1 Participants weighing at least 40 kg:

- A 30 mg bolus dose (over ~3 minutes) will be administered with a continuous infusion of 80 mg/hour for 2 hours followed by a continuous infusion rate of 40 mg/hour for 10 hours, and then 20 mg/hour for the remaining 12 hours of Day 1.
- On Day 2, from 24 to 36 hours following IP initiation, the continuous infusion rate of 20 mg/hour can be increased up to a maximum rate of 45 mg/hour until the start of the taper at 36 hours. The infusion rate will be determined by the investigator to best manage seizure relapse and cannot exceed the rate of 45 mg/hour between 24- and 36- hours following IP initiation.
- To taper IP, beginning 36 hours following IP initiation, the infusion rate will be reduced by 33.3% every 4 hours until the infusion is stopped or until the infusion rate becomes too low to sustain the IV line.
- Note: If, according to the investigator's clinical judgment, IP taper needs to start sooner than 36 hours after initiation, the infusion rate will be decreased by 33.3% of the rate at the beginning of the IP taper every 4 hours.
- At the time the IP infusion is discontinued, the participant will progress to the follow-up period assessments/procedures.

Table 4. Dosing for Participants ≥40 kg (on a mg/hour basis)

Days	Start Time from IP Initiation	IP Dose	IP Infusion Rate (mL/hour)	Duration
Day 1	0 hours: bolus dose via syringe or infusion pump	30 mg[a]	N/A	3 minutes (0.05 hours)
Day 1	0 hours through 2 hours following IP initiation: continuous infusion, started with bolus	80 mg/hr	80	2 hours
Day 1	2 hours through 12 hours following IP initiation	40 mg/hr	40	10 hours
Day 1	12 hours through 24 hours following IP initiation	20 mg/hr	20	12 hours
Day 2[b]	24 hours through 36 hours following IP initiation	20 - 45 mg/hr	20 - 45	12 hours
	Taper			
Day 2[c]	36 through 48 hours following IP initiation (12-hour taper)	13 - 30 mg/hr	13 - 30	4 hours
		9 - 20 mg/hr	9 - 20	4 hours
		6 - 13 mg/hr	6 - 13	4 hours

IP = investigational product.

a. The 30 mg bolus is administered over ~3 minutes.

b. On Day 2 (24 through 36 hours), the continuous infusion rate can be increased from 20 mg/hour to a maximum rate of 45 mg/hour at any time, if needed, to manage seizure relapse or other medical reason.

c. To taper the IP, the infusion rate at the 36-hour following IP initiation timepoint will be reduced by 33.3% every 4 hours until the infusion rate is stopped or if the infusion rate becomes too low to sustain the infusion line, at which point it will be stopped. The first taper will be 33.3% from the current infusion rate (e.g., if the current infusion rate is 20 mg/hr, the first taper will be 13 mg/hr) the second taper will be 33.3% from the first tapered infusion rate (e.g., if the current infusion rate is 20 mg/hr, the second taper will be 9 mg/hr), and the final taper will be 33.3% from the previous tapered infusion rate (e.g., if the current infusion rate is 20 mg/hr, the final taper will be 6 mg/hr). If, in the investigator's judgment, the taper needs to start at an earlier timepoint during the treatment period, the infusion rate at the start of the first taper will be decreased by 33.3% every 4 hours as described.

6.2.3.2 Participants weighing <40 kg will be dosed on a per kilogram basis:

- A 0.75 mg/kg bolus dose (over ~3 minutes) will be administered with a continuous infusion at a dose of 2.0 mg/kg/hour for 2 hours followed by a continuous infusion dose of 1.0 mg/kg/hour for 10 hours, and 0.5 mg/kg/hour for the remaining 12 hours of Day 1.
- On Day 2, 24 to 36 hours following IP initiation, the continuous infusion rate of 0.5 mg/kg/hour can be increased up to a maximum of 1.125 mg/kg/hour until the start of IP taper at 36 hours. The infusion rate will be determined by the investigator to best manage seizure relapse and cannot exceed the rate of 1.125 mg/kg/hour during hours 24 to 36 of Day 2 at any time.
- To taper IP, beginning 36 hours following IP initiation, the infusion rate will be reduced by 33.3% every 4 hours until the infusion is stopped or until the infusion rate becomes too low to sustain the IV line.

  Note: If, according to the investigator's clinical judgment, IP taper needs to start sooner than 36 hours after initiation, the infusion rate will be decreased by 33.3% of the rate at the beginning of the IP taper every 4 hours.

- At the time the IP infusion is discontinued the participant will progress to the follow-up period assessments/procedures.

Table 5. Dosing for Participants <40 kg (on a mg/kg/hour basis)

Days	Start Time from IP Initiation	IP Dose	IP Infusion Rate (mL/kg/hour)[a]	Duration
Day 1	0 hours: bolus dose via syringe or infusion pump	0.75 mg/kg[b]	N/A	3 minutes
Day 1	0 hours through 2 hours following IP initiation continuous infusion, started with bolus	2.0 mg/kg/hr	2.0	2 hours
Day 1	2 hours through 12 hours following IP initiation	1.0 mg/kg/hr	1.0	10 hours
Day 1	12 hours through 24 hours following IP initiation	0.50 mg/kg/hr	0.50	12 hours
Day 2[c]	24 hours through 36 hours following IP initiation	0.50 – 1.125 mg/kg/hr	0.50 - 1.125	12 hours
	Taper			
Day 2[d]	36 through 48 hours following IP initiation (12-hour taper)	0.34 – 0.75mg/kg/hr	0.34 - 0.75	4 hours
		0.22 – 0.51mg/kg/hr	0.22 - 0.51	4 hours
		0.15 – 0.34mg/kg/hr	0.15 - 0.34	4 hours

IP = investigational product.

a. Reference the Pharmacy Manual for IP infusion rates based on mg/kg/hour dosing.
b. The 0.75 mg/kg bolus is administered over ~ 3 minutes.
c. On Day 2 (24 through 36 hours), the continuous infusion dose can be increased from 0.5 mg/kg/hour to a maximum dose of 1.125 mg/kg/hour at any time, if needed, to manage seizure relapse or other medical reason.
d. To taper the IP, the infusion rate at the 36-hour following IP initiation timepoint will be reduced by 33.3% every 4 hours until the infusion rate becomes too low to sustain the infusion line, at which point it will be stopped. The first taper will be 33.3% from the current infusion rate (e.g., if the current infusion rate is 0.50 mg/kg/hr, the first taper will be 0.34 mg/kg/hr), the second taper will be 33.3% from the first tapered infusion rate (e.g., if the current infusion rate is 0.50 mg/kg/hr, the second taper will be 0.22 mg/kg/hr), and the final taper will be 33.3% from the previous tapered infusion rate (e.g., if the current infusion rate is 0.5 mg/kg/hr, the final taper will be 0.15 mg/kg/hr). If, in the investigator's judgment, the taper needs to start at an earlier timepoint during the treatment period, the infusion rate at the start of the first taper will be decreased by 33.3% every 4 hours as described.

6.2.4 Investigational Product Infusion Precautions

Throughout the study, heart rate and rhythm, blood pressure, and oxygen saturation are monitored. Investigational product may be temporarily or permanently discontinued, if clinically indicated, for treatment of persistent hypotension (sustained systolic blood pressure <90 mmHg), cardiac arrhythmia or oxygen desaturation.

Due to Captisol® presence in the IV formulation of the IP, renal function will be monitored throughout the study. In addition to standard and accepted biomarkers of renal function (i.e., creatinine clearance and estimated glomerular filtration ratio [eGFR]), urinary exploratory biomarkers of renal function (N-acetyl-β-D-glucosaminidase [NAG], β2-microglobulin, and creatinine) will be monitored throughout the study and reviewed by the DMC.

6.2.5 Medical Oversight

Participants will require close medical monitoring as defined by local institutional practice guidelines for the treatment of patients with the diagnosis of seizures or status epilepticus.

Telemedicine

Telemedicine is an acceptable practice for conducting protocol-driven assessments/procedures as defined by local institutional practice guidelines.

6.2.6 Investigational Product Tapering (One or More May Apply)

Scenarios for stopping IP without a taper may include:

- Participants who receive IP for less than 2 hours
- Investigational product infusion is discontinued or interrupted (e.g., for safety concerns related or not related to IP or due to planned medical procedures), and a decision is made not to restart the infusion
- If at any time during IP administration the participant progresses to an anesthetic with the primary intent specifically to treat seizures or achieve burst suppression
- For other safety reasons based on the investigator's clinical judgment

6.2.7 Dose Adjustments and Interruptions

Investigational product dose (infusion rate) decreases, and interruptions are discouraged during treatment. However, if there is an urgent medical need (e.g., severe hypotension, severe sedation) or standard of care requires a procedure for which the infusion rate would need to be temporarily decreased or interrupted (e.g., MRI) it should be kept as short as possible and should not exceed 2 hours. If the interruption is >2 hours, the Medical Monitor should be consulted before restarting the infusion.

Note:

- After a dose (infusion rate) decrease or interruption, the investigator's clinical judgment of risk/benefit will determine IP administration or discontinuation.
- Investigational product discontinuation does not affect participation in the study. All participants should be followed until they reach the final study follow-up visit/contact or consent is withdrawn.
- In cases when IP discontinuation is considered (e.g., severe sedation), when possible, the Medical Monitor should be contacted prior to IP discontinuation.
- If the decision is made to restart IP, the infusion should be restarted at the rate matching the rate at the corresponding nominal time, counted from the start of the IP infusion on Day 1 (Time 0). Investigational product bolus or "catch-up" dose to deliver the IP that was missed during the interruption should not be administered.
- Infusion rate increases above those specified in the protocol are not allowed at any time during infusion. This is to ensure daily Captisol® and ganaxolone limits are maintained at ≤50 g/day or 1.25 g/kg/day (in participants weighing <40 kg) and ≤833 mg/day or 20.825 mg/kg/day (in participants weighing <40 kg), respectively.

6.2.8 Unblinding the Treatment Assignment

6.2.8.1 Double-Blind Phase

During the study, the treatment assignment must not be broken except in emergency situations in which the identification of the IP is required for further treatment of the participant. If possible, the investigator should contact the Medical Monitor before unblinding. However, this should not delay unblinding in case of an emergency. The investigator should contact the Medical Monitor as soon as possible after the investigator has unblinded the participant.

If the treatment assignment is broken, the date, the signature of the person who broke the code, and the reason for breaking the code are recorded in the source documents. Upon breaking the blind, the participant will have the follow-up period assessments/procedures, and the follow-up visits/contacts at Weeks 1, 2, 3, and 4. The IRT will record all unblinding events.

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling

Labels containing study information and bottle identification are applied to the IP containers.

Each 500 mL bottle contains no less than (NLT) 425 mL of IP at a ganaxolone concentration of 1 mg/mL or placebo. (Note: placebo is only applicable for the double-blind phase). A label is applied to each bottle with information on strength, manufacturing batch numbers or job number, storage conditions, and name of the manufacturer, as well as a warning that the drug is intended for research only.

The IP will be dispensed to qualified staff members who will administer the IP to the participant.

All IP is labeled with a minimum of the following: protocol number, unique bottle number, dosage form (including product name and quantity in pack), directions for use, storage conditions, batch number and/or packaging reference, the statements “Caution: New Drug—Limited by Federal (or US) Law for Investigational Use” and “Keep out of reach of children,” and the Sponsor’s name and address. No information should be visible, which could potentially unblind the IP (only applicable for the double-blind phase). The label may be updated per local requirements.

Additional labels (e.g., those used when dispensing marketed product) may be applied to the IP bottle to satisfy local or institution requirements, but must not:

- Contradict the clinical study label.
- Obscure the clinical study label.

Sponsor approval is not required to make this change.

6.3.2 Packaging

IP solution for administration will be provided to the site as individual bottles containing ganaxolone IV solution 1 mg/mL, or placebo. (Note: placebo is only applicable to the double-blind phase).

Changes to Sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the Sponsor.

6.3.3 Storage

The investigator has overall responsibility for ensuring that IP is stored in a secure, limited access location in accordance with applicable requirements under the Controlled Substance Act (CSA) and Drug Enforcement Administration (DEA) regulations. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. Investigational products are distributed by the pharmacy or by a nominated member of the study team. Details on how to store the IP can be found in the Pharmacy Manual. Prior to administration inspect the IP for particulate matter, cloudiness, and discoloration. If any of these is present, do not use and notify the Sponsor.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring of the IP is required at the storage location to ensure that the IP is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained. The temperature should be monitored continuously by an in-house system, by a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (i.e., certified min/max thermometer) would require manual resetting upon each recording. The Sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The Sponsor will determine the ultimate impact of excursions on the IP and will provide supportive documentation, as necessary. Under no circumstances should the product be dispensed to participants until the impact has been determined and the product is deemed appropriate for use by the Sponsor.

The Sponsor should be notified immediately if there are any changes to the storage area of the IP that could affect the integrity of the product(s), such as fumigation of a storage room.

6.4 Investigational Product Accountability

Investigators will be provided ample amounts of the IP to carry out this protocol for the agreed number of participants. The investigator or designee will acknowledge receipt of the IP, documenting shipment content and condition. Accurate records of all IP dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has the overall responsibility for dispensing/administering IP. Where permissible, tasks may be delegated to a qualified designee (e.g., pharmacist) who is adequately

trained in the protocol and who works under the supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or their designee (as documented by the investigator in the applicable study delegation of authority form) will place the IP administration orders and confirm that the IP is only administered to participants included in this study following the procedures set out in the study protocol. Each participant will be given only the IP carrying their treatment assignment. All dispensed medication will be documented in the eCRFs and/or other IP record.

No IP stock or returned inventory from a Marinus-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the Sponsor. If such transfer is authorized by the Sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The Sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records.

At the end of the study, or as instructed by the Sponsor, all unused stock will be sent to a nominated contractor on behalf of the Sponsor for destruction or will be destroyed by the site. Investigational product being returned to the Sponsor's designated contractor must be counted and verified by clinical site personnel and the Sponsor (or designated CRO). For unused supplies for which the original tamper evident feature is verified as intact, the tamper evident feature must not be broken, and the labeled amount is to be documented in lieu of counting. Shipment return forms, when used, must be signed prior to shipment from the site. Returned IP must be packed in a tamper evident manner to ensure product integrity. Contact the Sponsor for authorization to return any IP prior to shipment. Shipment of all returned IP must comply with local, state, and national laws.

Investigational product administered to the participant will be destroyed upon completion of the individual bottle administration according to institution standard procedures.

With the written agreement of the Sponsor, unused stock may be destroyed at the site or a local facility. In this case, destruction records identifying what was destroyed, when, and how must be obtained with copies provided to the Sponsor. Destruction of IP must be in accordance with local, state, and national laws.

Based on entries in the IP accountability forms, it must be possible to reconcile IP delivered with those used and returned. All IP must be accounted for, and all discrepancies investigated and documented to the Sponsor's satisfaction.

6.5 Participant Compliance

The IP will only be administered by appropriately trained site staff. Investigational product accountability must be assessed at the container/packaging level for unused IP that is contained within the original tamper evident sealed container (e.g., bottles) or at the individual count level for opened containers/packaging. The pharmacist/nominated person will record details on the IP accountability form.

7 STUDY PROCEDURES

7.1 Study Schedule

The study schedule will remain the same under both the double-blind and open-label phases. See Table 1 and Table 2 for details regarding scheduled assessments and procedures in this study.

The following "priority order" will be in effect when more than one procedure or assessment is required at a timepoint:

1. Spontaneous or solicited AE reporting
2. Vital signs
3. Pharmacokinetic sample collection
4. Clinical laboratory tests
5. Physical examination

NOTE: Blood sampling for pharmacokinetic evaluation should be performed at the precise protocol scheduled time. Actual sampling time(s) must be accurately recorded in the source document and appropriate eCRF.

7.1.1 Screening Period

7.1.1.1 Screening

Potential participants may be identified in the emergency department, ICU, or other units in the hospital, and will be consented/assented and then screened for inclusion/exclusion criteria prior to being enrolled to start IP treatment.

Procedures specific to this protocol and not otherwise considered standard of care, will not be performed until written informed consent/assent from the participant/participant's parent/guardian/LAR has been appropriately obtained or deferred, where allowed by law. Consent for participants who are at risk for SE may be obtained prior to occurrence of SE, this is also referred to as pre-consenting. Additional details on consent/assent can be found in Section 11.3.1.

7.1.1.2 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened once they have been designated as a screen failure during the same episode of SE. Participants who have failed screening in a prior episode of SE may be rescreened if they experience a new SE event.

7.1.2 Treatment Period

7.1.2.1 Investigational Product Initiation Through Taper (Day 1 to Day 2)

Eligible SE participants will be enrolled to receive either ganaxolone IV solution or placebo (double-blind phase) or ganaxolone IV solution (open-label phase) added to SE standard of care. Investigational product will be administered as a 48-hour continuous infusion, which includes an initial 3-minute bolus and ends with a 12-hour taper.

The investigator will confirm that the participant meets clinical and EEG criteria for SE during the 60-minute period prior to IP initiation and will reconfirm that ongoing ictal activity is present within 30 minutes immediately prior to IP initiation. Following IP initiation, the standard duration of treatment is 2 days (48 hours) which includes a 12-hour taper as described in Section 6.

7.1.3 Follow-up Period (starting at IP discontinuation through Week 4)

Participants will have the follow-up period assessments/procedures collected following IP discontinuation (with or without taper) as noted in Section 3. Assessments/procedures will be collected every 24 hours through 120 hours (or until hospital discharge) and at the time of hospital discharge, followed by weekly follow-up visits/contacts at Week 1, 2, 3 and 4.

Participants who discontinue IP without a taper, e.g., were administered IP for less than 2 hours, progress to anesthesia for seizure suppression or discontinue IP due to safety or any other reason, except due to withdrawal of consent, will have the follow-up assessments/procedures collected every 24 hours through 120 hours (or until hospital discharge) and at the time of hospital discharge, followed by weekly follow-up visits/contacts at Week 1, 2, 3 and 4.

The follow-up period for this protocol is approximately 4 weeks. Week 1, 2, 3, and 4 visits may be conducted as an inpatient visit, if the participant is still in the hospital, or as a telephone contact, if the participant has been discharged. Attempts should be made to have discharged participants return for one of these visits to be in person. The participant/participant's parent/guardian/LAR, as appropriate, will receive a follow-up contact weekly approximately 7 ± 3, 14 ± 3, 21 ± 3, and 28 ± 3 days following the IP discontinuation date. If the hospital discharge visit corresponds to the Week 1, 2, 3, or 4 (± 3 days) visits, it can take the place of the weekly visit.

During these follow-up period visits/contacts, the site will follow-up on all SAEs and non-serious AEs, AE resolution that occurs, and concomitant medications. Adverse events and SAEs that are not resolved at the time of contact will be followed to closure (see Section 8.1). Table 1 lists the assessments that should be collected during the follow-up visits/contacts.

7.1.4 Additional Care of Participants After the Study

No aftercare is planned for this study. Participants should follow their physician's care plan and referral guidance.

7.2 Study Evaluations and Procedures

7.2.1 Demographic and Other Baseline Characteristics

The following demographic data will be recorded:

- Date of birth
- Sex
- Ethnic origin (Hispanic or Latino or not Hispanic or Latino)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other, Pacific Islander, White, or Other)

7.2.2 Efficacy

Efficacy will be evaluated by collecting the following assessments as noted in Table 1.

The name and address of each third-party vendor (e.g., central EEG reader) used in this study will be maintained in the investigator's and Sponsor's files.

7.2.2.1 Electroencephalogram (EEG)

An EEG is required for confirmation of CSE and NCSE diagnosis. Continuous EEG monitoring should be used for all study participants and should start before IP initiation to obtain a baseline assessment and should continue through the end of the first 24 hours of the follow-up period (i.e., 24 hours following IP discontinuation).

Sites will be offered the use of a rapid EEG device to assist with screening and enrollment of participants with NCSE. It is preferred that a conventional EEG is used for the purpose of confirming inclusion criterion #3 and EEG monitoring during IP administration.

In situations when a conventional EEG is not immediately available, the rapid EEG may be used to confirm inclusion criterion #3 and enroll the participant. Since the rapid EEG has a limited battery life, it should be switched to a conventional EEG within several hours but not earlier than 90 minutes after IP initiation to allow uninterrupted collection of EEG for the 30-minute SE cessation co-primary endpoint. It will be at the investigator's discretion if the use of the rapid EEG will benefit their site. The device should be used according to institution standard practices. All devices utilized in the study will have received FDA 510(k) clearance. It will be at the investigator's discretion if they feel the device will benefit their site and if any institutional approvals are needed to utilize the device. A copy of the device user manual and system specifications will be on file at any site utilizing the device.

7.2.2.2 Status Epilepticus Severity Score (STESS)

The STESS is a prognostic score relying on 4 outcome predictors (age, history of seizures, seizure type and extent of consciousness impairment).

7.2.2.3 Clinical Global Impression of Severity and Improvement (CGI-S and CGI-I, respectively)

The CGI-S and CGI-I assess overall health and functional status of a participant. Participant and clinician rater versions indicate general worsening or improvement on a seven-point Likert-like scale. For specific collection timepoints reference Table 1.

7.2.2.4 Richmond Agitation and Sedation Scale (RASS)

The RASS is a medical scale used to measure the agitation or sedation level. For specific collection timepoints reference Table 1.

7.2.2.5 The Full Outline of UnResponsiveness (FOUR) Score

The FOUR Score is a tool designed to assess patients with impaired level of consciousness. There are four parameters evaluated in order to cover domains of neurological function: eye response, motor response, brainstem reflex and respiration. For specific collection timepoints reference Table 1.

7.2.2.6 Seizure Description Questionnaire

The Seizure Description Questionnaire is a descriptive questionnaire that captures the clinical features of SE prior to IP initiation using ILAE 2015 classification. This questionnaire should be collected as close as possible to IP initiation. Reference Table 1.

7.2.2.7 Status Epilepticus Cessation Questionnaire

For this study, SE Cessation is defined as the beginning of the first 30-minute epoch following IP initiation in which SE burden is no longer fulfilled (<20% ictal burden and is at least 50% less during the 30 minutes prior to IP initiation). This questionnaire should be collected as close as possible to 24 and 72 hours following IP initiation. Reference Table 1.

7.2.2.8 Super Refractory Status Epilepticus Questionnaire

The definition of SRSE is SE that is continuous or recurs during or after the SE treatment with IV anesthesia for 24 hours or longer. This questionnaire should be collected as close as possible to the diagnosis of SRSE and no later than the final study follow-up visit/contact. Reference Table 1.

7.2.2.9 Modified Rankin Scale (mRS)

The mRS is a commonly used 6-point scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurology disability. The mRS should be assessed at the timepoints noted in Table 1.

7.2.2.10 EuroQol (EQ-5D-5L)

The EQ-5D-5L is a descriptive system of health-related quality of life states consisting of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For specific collection timepoints reference Table 1.

7.2.3 Safety

Safety will be evaluated by collecting the following assessments as noted in Table 1.

If a third-party vendor is used for any safety analysis, then the name and address of each third-party vendor will be maintained in the investigator's and Sponsor's files.

7.2.3.1 Medical, Seizure or SE, and Medication History

Medical history will include the following:

- Previous and concomitant illnesses, surgeries, and medications
- Family history
- History of drug and alcohol abuse
- Seizure or SE etiology

7.2.3.2 Physical Examination

A physical examination will be performed at the timepoints described in Table 1 by a qualified licensed physician, physician's assistant, or nurse practitioner.

The physical examination will include a review of the following body systems:

- General appearance
- Skin
- Head, eyes, ears, nose, and throat
- Spine, neck, and thyroid
- Musculoskeletal
- Respiratory
- Cardiovascular
- Neurologic
- Abdomen (including liver and kidneys)
- Other systems as appropriate

Abnormalities identified at the first PE thought to be present prior to IP initiation will be documented in the participant's source documents and in the medical history eCRF. Conversely, abnormalities identified at the first PE that are thought to develop following IP initiation should be recorded as AEs on the AE eCRF page, as deemed by the investigator.

Changes after the first PE will be recorded as AEs on the AE eCRF page, as deemed by the investigator.

7.2.3.3 Adverse Event Collection

Participants and their parent/guardian/LAR will be questioned in a general way to ascertain if AEs have occurred (e.g., "Have you had any health problems since your last visit?"). Adverse events will be collected from the time of IP initiation through the final study follow-up visit/contact.

Refer to Section 8, Adverse and Serious Adverse Events Assessment.

7.2.3.4 Vital Signs

Vital signs include blood pressure, pulse, respiration rate, oxygen saturation, and temperature. Ideally, noninvasive automated monitoring of vitals should be started at screening and continue through the end of the first 24 hours of the follow-up period. If not continuously monitored, vitals should be assessed as stated in Table 1 including collection for participants who stop IP without a taper or terminate early from the study.

Noninvasive blood pressure (systolic and diastolic) and pulse rate will be measured by an automated blood pressure device after the participant has been in a supine position for at least 5 minutes. Ideally, the same arm should be used for all measurements.

Any deviations from the predose (screening) vital signs that are deemed clinically significant based on investigator judgment should be recorded as AEs.

Weight and height should be collected predose (screening) for calculation of the BMI inclusion criterion, if feasible. If not collected at screening, they will need to be collected prior to the end of the first 24 hours of the follow-up period.

7.2.3.5 Electrocardiography (ECG)

A 12 lead ECG should be collected after the participant has been in a supine position for at least 5 minutes.

If abnormal results are observed, the investigator will assess clinical significance and determine whether the results should be recorded as an AE.

The timepoints for ECG collection is noted in Table 1.

7.2.3.6 Cardiodynamic 12-Lead Electrocardiography (ECG) Monitoring

Select sites will participate in a sub study using a continuous 12 lead ECG recorder. For more details refer to Appendix 5.

7.2.3.7 Clinical Laboratory Evaluations

All clinical laboratory assays will be performed according to the institution's laboratory normal procedures. If there are laboratory collections that are not done by the institution's laboratory, the institution should follow their standard procedures for sending samples to their reference laboratories for analysis (e.g., AEDs). The collection timepoints are detailed in Table 1. Reference ranges are to be supplied by the laboratory and will be used to assess the clinical laboratory data for clinical significance and out of range pathologic changes. The investigator should assess out of range clinical laboratory values, indicating if the values are clinically significant or not clinically significant. Abnormal clinical laboratory values that are unexpected or not explained by the participant's clinical condition may, at the discretion of the investigator or Sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

Urine Chemistry

Urine samples for N-acetyl-β-D-glucosaminidase (NAG), β2-microglobulin, and creatinine will be collected at the times specified in Table 1. Urine samples will be stored frozen. Details regarding sample collection, processing, storage, and shipment to the bioanalytical vendor are described in the Biospecimen Manual.

Drugs of Abuse Testing

A urine or serum sample for drugs of abuse testing should be collected per the institution standard of care and prior to IP initiation. A urine or serum sample for alcohol testing should be collected if medically indicated. If medically indicated, the investigator may expand testing for additional drugs of abuse above the institution's standard of care. If unable to collect predose, collect as soon as possible following IP initiation. However, if a participant tests positive, it will be at the investigator's discretion to weigh the risks versus benefits for enrollment or continued participation. If the investigator decides to discontinue the IP, refer to Section 4.5.

Pregnancy Test

As described in Table 1 and Section 4.4, a urine or serum pregnancy test should be collected for all females of childbearing potential prior to IP initiation, and if pregnancy is suspected. If unable to collect predose, collect as soon as possible following IP initiation. Enrollment is not contingent upon results. However, if a participant has a positive test result, it will be at the investigator's discretion to weigh the risks versus benefits for continued participation. If the investigator decides to discontinue the IP, please refer to Section 4.5. If the institution requires the pregnancy test results be obtained prior to IP initiation, the institution guidelines will be followed.

Blood Gas

All blood gas samples arterial or venous, if collected, will be at the investigator's discretion to manage care. If collected from the time of SE diagnosis through the end of the first 24 hours of the follow-up period, the eCRF should be completed. If samples are not collected, a sample will not be required.

If a decision is made to intubate the participant between IP initiation through the end of the first 24 hours of the follow-up period, a blood sample should be collected. The sample should be collected immediately prior to or as close as possible to the time of intubation.

The clinical laboratory tests performed as part of the protocol are listed in Table 6.

Table 6. Clinical Laboratory Tests

Hematology	Coagulation	Biochemistry	Urinalysis
Hemoglobin (Hb) Hematocrit (Hct) Red blood cell count (RBC) White blood cell count; total and differential (WBC) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Platelet count WBC Differential % Basophils % Eosinophils % Lymphocytes % Monocytes % Neutrophils Basophil count Eosinophil count Lymphocyte count Monocyte count Neutrophil count	Fibrinogen Activated partial thromboplastin time (aPTT) Prothrombin time (PT) International normalized ratio (INR)	Sodium Potassium Calcium Glucose Total protein Albumin Creatinine Blood urea nitrogen (BUN) Total Bilirubin Alkaline phosphatase (ALP) Aspartate transaminase (AST) Alanine transaminase (ALT) Total cholesterol[1] Estimated Glomerular Filtration Rate (eGFR), if available Creatinine Clearance calculation, if available **Urine Chemistry** N-acetyl-β-D-glucosaminidase [NAG] B2-microglobulin Creatinine **Antiepileptic drug levels (AEDs; per institution standard of care)** fosphenytoin/ phenytoin, valproic acid, levetiracetam, lacosamide, phenobarbital or brivaracetam	pH Protein Blood Ketones Glucose Bilirubin Specific gravity If *any abnormal value* is observed on the urine dipstick test, the sample should be further analyzed with urine microscopy: WBC RBC Cellular casts Granular casts Hyaline casts **Urine or Serum Drugs of Abuse Testing (per institution standard of care)** Phencyclidine Opioids[2] Cannabinoids[3] Methamphetamine/Amphetamine Cocaine Barbiturates Benzodiazepines Alcohol, if medically indicated **Urine or Serum Pregnancy**

1. Total cholesterol level, if collected per standard of care, should be collected predose (screening).
2. May be limited to drug class or list specific drug such as oxycodone, methadone, heroin.
3. May be limited to drug class or list specific substance such as THC.

7.2.4 Others

7.2.4.1 Clinical Pharmacology Blood Sample Collection and Handling Procedures

Blood samples for pharmacokinetic analysis (PK) will be collected at the times specified in Table 2. The Sponsor's expectation is that the investigator will ensure that every effort is made to collect all PK blood samples at the precise protocol scheduled time. Pharmacokinetic blood collection must not deviate from the nominal collection time set forth in the protocol by more than ± 5 minutes for samples drawn within 6 hours following IP initiation or by more than ± 2 hours for samples drawn beyond 36 hours following IP initiation. Samples drawn outside these parameters will be considered a protocol deviation.

Venous blood samples (2 mL) will be drawn from indwelling catheters or by direct venipuncture into K_2EDTA Vacutainer® tubes (lavender top), capped, mixed by inversion (×10), and chilled immediately on crushed ice. If using indwelling catheters, they should be kept patent with isotonic saline and the saline should be withdrawn (1 mL) and discarded before the blood sample is taken. Use of topical anesthesia to reduce the pain of an indwelling catheter is permitted and, if used, should be documented as a concomitant medication. If venous blood sample collection is not possible an arterial sample may be collected. The type of sample will be recorded in the source documents and eCRF.

Pharmacokinetic samples should be collected from the contralateral peripheral access or the arterial line and avoid collecting samples downstream of the IP infusion. The location of IP access and location of PK sample collection should be documented in the participant's source. If the PK sample cannot be collected due to poor venous access and the IP infusion site is the only viable option, the sample should not be collected and the reason for non-collection documented in the participant's source.

Details regarding sample collection, processing, storage, and shipment to the bioanalytical vendor are described in the Biospecimen Manual. The freezer temperature where these samples are stored must be controlled, monitored, and recorded during the storage period until the samples are shipped on dry ice to the bioanalytical vendor for analysis. The Sponsor must be notified of any temperature excursions.

7.2.4.2 Shipment of Plasma Pharmacokinetic Samples

Unless agreed upon by the Sponsor, within approximately 1 week after participants complete the first 24 hours of the follow-up period, the site will ship the primary plasma samples to the bioanalytical vendor. Upon notification of receipt of the primary samples by the bioanalytical vendor, the backup samples will be shipped to the bioanalytical laboratory. Refer to the Biospecimen Manual for details regarding sample shipping.

7.2.4.3 Plasma Drug Assay Methodology

Plasma concentrations will be measured using the most current validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) method. Other metabolites may be monitored or quantitated as appropriate. Raw data will be stored in the archive of the designated bioanalytical laboratory.

Table 7. Volume of Blood to Be Drawn from Each Participant

Assessment		Sample Volume (mL) [a]	Number of Required Collection Timepoint Samples	Number of Variable Collection Timepoint Samples	Total Volume (mL)
Safety [b]	Biochemistry (with indwelling catheter)	8.5	5	3	42.5 to 68
	Hematology	4.0	5	3	20 to 32
	Coagulation	5.1	3	1	15.3 to 20.4
Pharmacokinetic samples (with indwelling catheter) [c]		3.0	8	0	24
Blood gas (for intubation only) [b]		1.0	0	1	1
Total mL					140.3 to 190.4

a. If a catheter is used, the first milliliter (mL) collected is to be discarded, then the required volume is collected into the appropriate tube for the assessment. This additional 1 mL has been added the biochemistry and pharmacokinetic collections noted in the table. This assumes the hematology, coagulation, and AED samples will be collected at the same times as the biochemistry samples. The collection volume for coagulation testing at sites ranged from 2.7mL to 7.5.0mL, as such the median volume of 5.1mL was used for the table calculation.
b. See Table 1 for sample collection timepoints. There are required collection timepoints for all participants and variable collection timepoints that only apply in specific situations. The two different types have been separated in the table to show the maximum and minimum number of sample collections for a participant.
c. Blood samples for pharmacokinetic analysis will be collected as noted in Table 2.
d. Venous or arterial samples are acceptable.

Table 8. Volume of Blood to Be Drawn from Each Participant (Pediatric Institution Sample Volumes)

Assessment		Sample Volume (mL) [a]	Number of Required Collection Timepoint Samples	Number of Variable Collection Timepoint Samples	Total Volume (mL)
Safety [b]	Biochemistry (with indwelling catheter)	2.0	5	3	10 to 16
	Hematology	1.0	5	3	5 to 8
	Coagulation	1.0	3	1	3 to 4
Pharmacokinetic samples (with indwelling catheter) [c]		3.0	8	0	24
Blood gas (for intubation only) [b]		1.0	0	1	1
Total mL					36 to 40

a. If a catheter is used, the first milliliter (mL) collected is to be discarded, then the required volume is collected into the appropriate tube for the assessment. This additional 1 mL has been added to the biochemistry and pharmacokinetic collections noted in the table. This assumes the hematology, coagulation, and AED samples will be collected at the same times as the biochemistry samples.
b. See Table 1 for sample collection timepoints. There are required collection timepoints for all participants and variable collection timepoints that only apply in specific situations. The two different types have been separated in the table to show the maximum and minimum number of sample collections for a participant.

c. Blood samples for pharmacokinetic analysis will be collected as noted in Table 2. Venous or arterial samples are acceptable.

During the study, it is expected that some sites (e.g., pediatric institutions) will collect smaller volumes of blood from participants per local laboratory standards. The ranges in Table 7 and Table 8 reflect the possible range for adult and child versus a pediatric only institution. The total blood volume drawn from pediatric participants for all safety and pharmacokinetic sampling will be approximately 36 mL and will not exceed 40 mL. The total blood drawn from adult participants will be approximately 140.3 mL and will not exceed 190.4 mL.

As noted in Table 1, several of the collection points are considered optional; however, to provide the most conservative estimate of the blood volume drawn, these optional collections have been included in Table 7 and Table 8.

Note: The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment. When more than one blood assessment is to be done at a single timepoint/period, if they require the same type of collection tube, the assessments may be combined.

7.3 Healthcare Utilization Questionnaires

The Healthcare Utilization Questionnaires include the Hospitalization Questionnaire and the Positive Pressure Ventilation (PPV) and Intubation Questionnaire. The Hospitalization Questionnaire should be collected at hospital discharge or at final study visit/contact. The need for non-invasive or invasive ventilatory support within 24 hours prior to IP initiation and following IP initiation and within 48 hours following IP discontinuation should be collected as close as possible to the event.

8 ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An AE is any untoward medical occurrence in a clinical investigation participant who has been administered a pharmaceutical product; it does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP product, whether or not related to the IP.[40]

As this study allows for pre-consenting of participants, all AEs will be collected from the time of IP initiation until the final study follow-up visit/contact stated in Section 7.1. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be recorded on the AE eCRF page and in source documents. In addition to untoward AEs, unexpected benefits outside the IP indication should also be recorded on the AE eCRF page.

All AEs must be followed for the durations described below. For AEs followed to closure, this indicates that an outcome is reached, stabilization is achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

For participants who terminate early from the study, prior to discontinuation as much information as possible as is available should be recorded for AEs/SAEs and their associated concomitant medication, especially those that may have led to the early termination.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event, including the start and stop dates for each change in severity. An event that changes in severity should be recorded as a new event. Worsening of pretreatment events, after initiation of the IP, must be recorded as new AEs on the appropriate eCRF page.

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the research participant.

Severe: A type of AE that interrupts usual activities of daily living, that significantly affects clinical status, or that may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A physician/investigator must make the assessment of the relationship between the IP and each AE. The investigator should decide whether, in their medical judgment, there is a reasonable possibility that the event may have been caused by the IP. If there is no valid reason for suggesting a relationship, the AE should be classified as "not related." Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause and effect relationship between the IP and the occurrence of the AE, the AE should be considered "related." The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship definition
Related	The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the participant's medical condition, other therapies, or accident.
Not related	The event can be readily explained by other factors, such as the participant's underlying medical condition, concomitant therapy, or accident, and no plausible temporal or biologic relationship exists between the investigational product and the event.

8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the study in the eCRF. Outcomes are as follows:

- Fatal
- Not recovered/not resolved
- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Unknown

8.1.4 Symptoms of the Disease Under Study

Symptoms of the disease under study should not be classified as AEs as long as they are within the normal day to day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE. Specifically, SE signs and symptoms that were present at study entry and that varied in intensity over the duration of study treatment are not considered AEs unless in the investigator's opinion there is an *unexpected* worsening of the events. However, if all seizure activity resolved and the participant returned to baseline status, but SE recurred, the event would then be recorded as an SAE.

8.1.5 Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory, vital sign, or ECG assessment can represent an AE if the change is clinically significant or if, during treatment with the IP, a shift of a parameter is observed from a normal value to an abnormal value, or there is a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range (either while continuing treatment or following IP discontinuation), and the range of variation of the respective parameter within its reference range must be taken into consideration.

At the end of the treatment phase, for participants who complete the study and do not progress to an IV anesthetic for seizure suppression, if there are abnormal clinical laboratory, vital sign, or ECG values that were not present in the pretreatment assessments closest to the start of IP initiation, further investigations should be performed until the values return to within the reference range or until a plausible explanation (e.g., concomitant disease) is found for the abnormal values.

The investigator should decide, based on the above criteria and the clinical condition of a participant, whether a change in a clinical laboratory, vital sign, or ECG parameter is clinically significant and therefore represents an AE.

8.1.6 Pregnancy

As this study allows for pre-consenting of participants, all pregnancies are to be reported from the time of IP initiation until the defined follow-up period stated in Section 7.1.

Any report of pregnancy for any female study participant or the partner of a male study participant must be reported within 24 hours to the Marinus Drug Safety vendor using the Pregnancy Report Form. If a participant has a positive test result, it will be at the investigator's discretion to weigh the risks versus benefits for continued participation.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days after delivery.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported as outlined in Section 8.2 of the protocol using the Marinus SAE Fax Cover Letter. Non-serious AEs are to be reported as per clinical eCRF Completion Guidelines. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE to the Marinus Drug Safety vendor as outlined in Section 8.2 of the protocol using the Marinus SAE Fax Cover Letter. The test date of the first positive serum/urine β-human chorionic gonadotropin test or ultrasound result will determine the pregnancy onset date.

8.1.7 Medication Errors and Other Reportable Information

Medication errors made in prescribing, dispensing, administering, or use of an IP must be reported as protocol deviations. An overdose is a medication error and is defined as administration of IP exceeding the prespecified total daily dose of the IP which for this study is set by a 50 g/day (1.25 g/kg/day in participants weighing <40 kg) Captisol® limit which corresponds to a maximum of 833 mg/day (20.825 mg/kg/day in participants weighing <40 kg) ganaxolone.

If a medication error results in a Captisol®/ganaxolone overdose, this is a protocol deviation that may have the potential to affect the safety of the affected participant. The administration of lower doses of the IP as a result of an IP rate decrease or as part of IP discontinuation are not considered medication errors and are permitted by protocol.

In addition to medication errors the following events are considered other reportable information and are reportable to the Marinus Drug Safety vendor within 15 days of awareness of the event using the Medication Errors and Other Reportable Information Report Form. A copy of the Report Form (and any applicable follow-up reports) must also be sent to the Medical Monitor using the details specified in the emergency contact information section at the beginning of the protocol:

- Accidental exposure
- Lactation exposure
- Product Misuse

All IP provided in this study will be administered by appropriate site staff.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The Reference Safety Information for this study is the Ganaxolone IB, which the Sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Marinus Drug Safety vendor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of medication errors and other reportable information (see Section 8.1.7) unless the event results in an SAE.

The investigator must complete, sign, and date the Marinus SAE Fax Cover Letter and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested) and fax or email the form to the Marinus Drug Safety vendor. A copy of the Marinus SAE Fax Cover Letter (and any applicable

follow-up reports) must also be sent to the Medical Monitor using the details specified in the emergency contact information section of the protocol.

8.2.3 Serious Adverse Event Definition

An SAE is any untoward medical occurrence (whether considered to be related to IP or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for preexisting conditions that have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, a complication resulting from a hospitalization for an elective or previously scheduled surgery that meets serious criteria must be reported as an SAE.
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, they jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

As this study allows for pre-consenting of participants, all SAEs (regardless of relationship to study) are collected from the time of IP initiation until the final study follow-up visit/contact stated in Section 7.1 and must be reported to the Marinus Drug Safety vendor within 24 hours of the first awareness of the event.

In addition, any SAE considered "related" to the IP and discovered by the investigator at any interval after the study has completed must be reported to the Marinus Drug Safety vendor within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the date the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the participant following IP initiation or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the participant's death (i.e., the SAE was noted as the primary cause of death) must have fatal checked as an outcome, with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the participant's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the participant's death or any ongoing events at the time of death, unless another IP action was previously taken (e.g., the IP was interrupted, reduced, or withdrawn), the action taken with the IP should be recorded as "dose not changed" or "not applicable" (if the participant never received the IP). The IP action of "withdrawn" should not be selected solely as a result of the participant's death.

8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The Sponsor or its delegate is responsible for notifying the relevant regulatory authorities in the US of related, unexpected SAEs. For ex-US countries, the Sponsor will comply with local laws and requirements with regard to SAE reporting.

In addition, the Sponsor or its delegate is responsible for notifying active sites and central IRBs of all related, unexpected SAEs occurring during all interventional studies across the ganaxolone program.

The investigator is responsible for notifying the local IRBs, local EC, or the relevant local regulatory authority of all SAEs that occur at their site as required.

9 DATA MANAGEMENT

9.1 Data Collection

The investigator's authorized site personnel must enter the information required by the protocol in the eCRF. A study monitor will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered in the eCRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site prior to enrollment (e.g., site initiation or other type of visit, investigator meeting, or other planned training). Once a participant is enrolled, the site should initiate data entry within 5 days of enrollment with the goal of having all protocol required data entered within 5 days of the participant's last follow-up visit/contact.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the eCRF Completion Guidelines. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Data Monitoring Committee (DMC)

The emerging study data will be reviewed on a regular basis by an independent DMC. The mission of the DMC will be to safeguard the interests of study participants and to enhance the integrity of the trial. To enable the DMC to achieve its mission, it will have ongoing access to efficacy and safety data and information regarding quality of trial conduct and will ensure that the confidentiality of these data are protected. A DMC charter will provide the principles and guidelines for the DMC process.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Analysis Process

The statistical analysis plan (SAP) will provide the complete details for the analysis and reporting of the data from the study.

To preserve the integrity of the statistical analysis and study conclusions, the SAP will be finalized and approved prior to database lock for the interim analysis and prior to the Sponsor being unblinded to treatment assignments. All deviations from or changes to the SAP following database lock will be described in detail and summarized in the final clinical study report.

10.2 Sample Size Determination

Approximately 124 participants will be randomized and qualified for the study. The sample size is based on the assumption of at least 75% response rate to ganaxolone treatment for each of the co-primary endpoints and no more than 45% response rate to placebo treatment and 1:1 randomization ratio.

With 62 participants randomized to each treatment arm, there would be at least 90% power for each co-primary endpoint to achieve statistical significance at 2-sided 5% level of significance.

10.3 Analysis Populations

The following population are defined:

Population	Description
Safety	All participants who received IP.
Intent to Treat (ITT)	All randomized participants in the double-blind phase of the study who received IP and had at least one non-missing efficacy assessment.
Per Protocol (PP)	All participants in the ITT population without major protocol deviations related to co-primary endpoint efficacy assessments.
Open-Label (if applicable)	All enrolled participants who received open-label IP (should the study transition to open-label).

10.4 Statistical Analyses

The SAP will be finalized prior to database lock (DBL) and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

10.4.1 Primary Endpoints (Double-Blind Phase)

The primary efficacy objective of this study is to assess the efficacy of ganaxolone plus standard of care versus placebo plus standard of care in producing rapid and durable SE cessation without the need for treatment escalation to IV anesthesia for at least 36 hours following IP initiation.

Since the primary efficacy objective is a composite objective, in order to establish effectiveness of ganaxolone and support approval, the superiority of ganaxolone vs placebo added to standard of care would need to be established for the following co-primary endpoints:

1. Proportion of participants with SE cessation within 30 minutes of IP initiation without medications for the acute treatment of SE
2. Proportion of participants with no progression to IV anesthesia for 36 hours following IP initiation

SE cessation will be determined by the investigator based on clinical and EEG features (see Appendix 1 for SE cessation guide). Training will be provided to guide and help standardize decisions across clinical sites. In addition, a retrospective, confirmatory analysis of time of SE cessation will be performed by a central EEG reader blinded to treatment assignment.

Medications for the acute treatment of SE are defined as AEDs administered to abort ongoing SE or prevent imminent recurrence of SE based on clinical or EEG evidence. This definition excludes maintenance doses of AEDs or medications with anticonvulsant properties used for other reasons, such as procedural sedation.

Both co-primary efficacy endpoints must be statistically significant to claim the study being positive. No ordering is involved in the hypothesis testing of the two co-primary endpoints.

The efficacy analysis of the response rates observed for each co-primary endpoint will be conducted by using logistic regression methods. The model will include terms for treatment group and baseline STESS as a covariate. The analysis will be based on the ITT population. Model-based point estimates (i.e., odds ratio), 95% confidence intervals and p-values will be reported. In addition, the point estimate of difference of the proportions of participants achieving either and both co-primary endpoints between two treatment arms will be provided. The 95% confidence interval will be provided using Clopper-Pearson method.[41]

Due to the nature of the disease and short observational period, occurrence of intercurrent events is expected to be low, and thus a treatment policy approach is planned for the co-primary analyses.

10.4.2 Key Secondary Endpoints (Double-Blind Phase)

The following key secondary endpoints will be analyzed:

1. Time to SE cessation following IP initiation
2. Proportion of participants with no progression to IV anesthesia for 72 hours following IP initiation

If the primary endpoints are statistically significant, the key secondary endpoints will be compared between ganaxolone and placebo treatment groups based on the ITT population with a hierarchical testing progress at the same alpha level of the primary endpoints. Each key secondary endpoint will only be tested if the prior endpoint is statistically significant.

The time to SE cessation endpoint will be analyzed using the Kaplan-Meier method.[20] The comparison of the survival curves between treatment groups will be conducted by a log-rank test.

The second key secondary endpoint will be analyzed using the same statistical model as pre-specified for the co-primary endpoints.

10.4.3 Other Secondary Endpoints

The following secondary endpoints will be analyzed:

- Proportion of participants with any escalation of treatment in the first 24 hours following IP initiation, i.e., any medication other than IP for the acute treatment of SE in the first 24 hours
- Time to treatment escalation following IP initiation (any other mediation used for acute treatment of SE)

- Time to initiation of anesthesia for SE treatment through the final study follow-up visit/contact
- Proportion of participants who develop SRSE through the final study follow-up visit/contact
- Seizure burden through 72 hours following IP initiation
- Level of responsiveness as assessed by the FOUR Score Scale
- Level of sedation/agitation as assessed by the RASS
- Clinician Global Impression-Improvement (CGI-I)
- Level of functioning as assessed by the mRS
- Level of functioning as assessed by the EuroQoL (EQ-5D-5L)
- Proportion of participants with mRS ≥3 at the time of hospital discharge
- Proportion of participants whose treatment does not progress to IV anesthesia for 4 weeks following IP initiation

10.4.4 Healthcare Utilization Endpoints

If the key secondary endpoints are statistically significant, analysis of the first healthcare utilization endpoint, time on positive pressure ventilation, will be performed. The time on positive pressure ventilation endpoint will be analyzed using the Kaplan-Meier method. The comparison of the survival curves between treatment groups will be conducted by a log-rank test.

- Time on positive pressure ventilation after IP initiation.
- Proportion of participants requiring positive pressure ventilation initiated during IP infusion.
- Length of stay in the intensive care unit and in hospital after IP initiation.
- Discharge destination (location where the participant is living at the last follow-up assessment).

The other healthcare utilization endpoints will be summarized descriptively.
Further details are provided in the SAP.

10.4.5 Open-Label Endpoints

If the study transitions to the open-label phase, all endpoint assessments as described for the double-blind phase will be summarized using descriptive statistics and no formal hypothesis testing will be performed. Efficacy analyses performed for the open-label phase of this study will be based on the Open-Label (OL) population.

10.5 Safety Analyses

Adverse Events will be coded using the Medical Dictionary for Regulatory Activities. The number of events, incidence, and percentage of treatment-emergent AEs will be calculated overall, by system organ class, by preferred term, and by treatment group in the double-blind phase, and summarized overall if the study transitions to open-label. Treatment emergent AEs will be further summarized by severity and relationship to IP. Adverse events related to IP, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized and listed.

Physical examinations, clinical laboratory tests, vital signs, ECG findings, use of concomitant medications will be summarized by treatment group in the double-blind phase, and summarized overall if the study transitions to open-label.

10.6 Pharmacokinetic Analyses

The PK population will include all participants who have received at least 1 dose of IP and who have had at least 1 sample collected and a valid bioanalytical result obtained. The following plasma pharmacokinetic parameters for ganaxolone and Captisol will be calculated as data allows and as appropriate using noncompartmental approaches:

- Maximum plasma concentration (C_{max})
- Time of maximum concentration (T_{max})
- Area under the concentration versus time curve from time 0 to t hours (AUC_{0-t})
- Area under the concentration versus time curve from time 0 to infinity (AUC_{inf})
- Clearance (CL). Calculated as dose/AUC_{inf}.

Pharmacokinetic variables will be computed using WinNonlin Professional, version 5.2 or similar software. Actual elapsed sampling times relative to IP administration will be used for the estimation of pharmacokinetic metrics. Additional parameters may be calculated on discretion of the pharmacokineticist, pending review of the data.

10.7 Interim Analyses

An interim analysis was planned when two-thirds of the ITT population have completed 72 hours of efficacy assessments on the co-primary and key secondary endpoints (approximately 41 participants per arm). The overall type I error rate (i.e., alpha=0.05, 2-sided) will be controlled using a power family alpha spending function, with a 2-sided nominal alpha level of 0.0293 at the interim analysis. The interim analysis will be performed by an independent statistician who is not involved in study operation or study conduct.

The interim analysis was performed by an independent statistician who was not involved in study operation or study conduct and was based on 83 participants who had completed the primary and key secondary efficacy assessments. The DMC recommended that the study may continue without modification.

To control the overall type I error rate (i.e., a two-sided alpha level of 0.05), the alpha value for the final analysis will be adjusted by the final sample size. For example, if the final analysis sample size is 100, the two-sided alpha level for the final analysis is 0.0410.

Further details will be provided in the SAP.

11 SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, International Council for Harmonisation (ICH), European Union (EU) Directives and its updates, and local ethical and legal requirements.

The name and address of each third-party vendor (e.g., CRO) used in this study will be maintained in the investigator's and Sponsor's files, as appropriate.

11.1 Sponsor's Responsibilities

11.1.1 Good Clinical Practice (GCP) Compliance

The study Sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all current, applicable industry regulations, ICH GCP Guidelines, and EU Directives, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study Sponsor and/or the company organizing/managing the research on behalf of the Sponsor to inspect study data, participants' medical records, and eCRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The Sponsor ensures that local regulatory authority requirements are met before the start of the study. The Sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of IP for shipment to the site.

11.1.2 Public Posting of Study Information

The Sponsor, or their designee, is responsible for posting appropriate study information on applicable websites such as ClinicalTrials.gov and Europe's website - Eudract.ema.europa.eu. Information included in clinical study registries may include participating investigator's names and contact information.

11.1.3 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The Sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance.

11.1.4 Study Suspension, Termination, and Completion

The Sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the Sponsor will ensure that applicable sites, regulatory agencies, and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study that has been posted to a designated public website will be updated accordingly.

11.2 Investigator's Responsibilities

11.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with current ICH GCP Guidelines, EU Directives, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained personnel are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate the potential for recruiting the required number of suitable participants within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study related tasks, and shall, upon request of the Sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub investigators are provided to the study Sponsor (or designee) before starting the study.

If a potential research participant has a primary care physician, the investigator should, with the participant's consent, inform them of the participant's participation in the study.

A coordinating principal investigator is appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator (single site study) or coordinating principal investigator (multicenter study), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

11.2.2 Protocol Adherence and Investigator Agreement

The investigator and any sub investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those participants who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the Sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return or destroy all IP, containers, and other study materials in accordance with the Sponsor instructions. Upon study completion, the investigator will provide the Sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the Sponsor, applicable CRO, investigator, or, for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

11.2.3 Documentation and Retention of Records

11.2.3.1 Case Report Forms

Electronic CRFs are supplied by the Data Management vendor detailed in the investigator's and Sponsor's files, as applicable, and should be handled in accordance with the instructions from the Sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Electronic CRFs must be completed by the investigator or designee as stated in the site delegation log.

All data will have separate source documentation; no data will be recorded directly into the eCRF.

All data sent to the Sponsor must be endorsed by the investigator.

The clinical research associate (CRA)/study monitor will verify the contents against the source data according to the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

Incorrect paper source entries must be crossed with a single line as to not obscure the original entry. Corrections must be made adjacent to the item to be altered, initialed, and dated by an authorized investigator or designee as stated in the site delegation log. Overwriting of this information or use of liquid correction fluid is not allowed.

11.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to, the participant's medical file and original clinical laboratory reports.

All key data must be recorded in the participant's medical records.

The investigator must permit authorized representatives of the Sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The CRA/study monitor (and auditors, IRB/EC, or regulatory inspectors) may check the eCRF entries against the source documents. The consent form includes a statement by which the participant agrees to allow the monitor/auditor from the Sponsor or its representatives, national or local regulatory authorities, or the IRB/EC to have access to source data (e.g., participant's medical file, appointment books, original laboratory reports, X-rays, etc.).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any applicable regulatory authority or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the Sponsor.

11.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the FDA, other regulatory authorities, the Sponsor or its representatives, and the IRB/EC for each site.

11.2.3.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the Sponsor. The following information is collected: any significant payments from the Sponsor or subsidiaries, such as a grant to fund ongoing research, compensation in the form of equipment, or retainer for ongoing consultation or honoraria; any proprietary interest in IP; and any significant equity interest in the Sponsor or subsidiaries as defined in 21 Code of Federal Regulations 54 2(b) (1998).

11.3 Ethical Considerations

11.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent and assent, where applicable, from all study participants prior to any study related procedures, including screening assessments. As the disease under consideration is a life-threatening condition for which participants presenting may not be capable of providing consent or assent for themselves, a parent/guardian/LAR will be required to sign upon identification of the participant for study participation. Consent/assent will be administered according to institution IRB/EC policy and may vary across sites, i.e., some sites may be able to consent/assent over the phone or other communication methods. At the first opportunity, consent and assent should be obtained from the participant directly. Alternatively, consent and assent for participants who are at risk for SE may be obtained prior to an SE event through a pre-consenting process. The period of time the pre-consent/assent is valid will be determined by each institutions IRB/EC. However, reconsenting will be required should the consent/assent be updated at any point during the study.

All consent and assent documentation must be in accordance with applicable regulations and GCP. Each participant, participant's parent, guardian, or the LAR, as applicable, is requested to sign and date the participant's informed consent form/assent or a certified translation, if applicable, after the participant, participant's parent, guardian, or LAR has received and read (or been read) the written participant information and received an explanation of what the study involves, including but not limited to the objectives, potential benefits and risk, inconveniences, and the participant's rights and responsibilities. A copy of the informed consent and assent documentation (i.e., a complete set of participant information sheets and fully executed signature pages) must be given to the participant, participant's parent, guardian, or the LAR, as applicable.

This document may require translation into the local language. Signed consent forms must remain in each participant's study file and must be available for verification at any time.

The investigator provides the Sponsor with a copy of the consent form and assent that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the Sponsor prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (i.e., Sponsor or coordinating investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample participant information and consent document provided by the Sponsor, the documentation supporting this requirement must be provided to the Sponsor.

11.3.2 Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent and assent documents (approved by the Sponsor or their designee), relevant supporting information, and all types of participant recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

Prior to implementing changes in the study, the Sponsor and the IRB/EC must approve any revisions of all informed consent/assent documents and amendments to the protocol unless there is a participant safety issue.

Investigational product supplies will not be released until the Sponsor or designee has received written IRB/EC approval of and copies of revised documents.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case, at least once a year. This can be done by the Sponsor or investigator for sites within the EU, or for multicenter studies, it can be done by the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any SAEs and significant AEs.

11.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with the Health Insurance Portability and Accountability Act (HIPAA). A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the CRO/Sponsor. All sites, laboratories, or entities providing support for this study, must, where applicable, comply with General Data Protection Regulation (GDPR) for purposes of data protection and privacy.

The confidentiality of records that may be able to identify participants will be protected in accordance with applicable laws, regulations, and guidelines.

After participant, participant's parent, guardian, or the LAR have consented to take part in the study, the Sponsor and/or its representatives review the medical records and data collected during the study. These records and data may, in addition, be reviewed by others, including the following: independent auditors who validate the data on behalf of the Sponsor; third parties with whom the Sponsor may develop, register, or market ganaxolone; national or local regulatory authorities; and the IRB/EC that gave approval for the study to proceed. The Sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of participants' identities.

Participants are each assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the Sponsor in verifying the accuracy of the data (e.g., to confirm that laboratory results have been assigned to the correct participant).

The results of studies containing participants' unique identifying numbers, relevant medical records, and possibly initials and dates of birth will be recorded. They may be transferred to, and used in, other countries that may not afford the same level of protection that applies within the countries where this study is conducted. The purposes of any such transfer would include to support regulatory submissions, to conduct new data analyses to publish or present the study results, and to answer questions asked by regulatory or health authorities.

11.5 Study Results/Publication Policy

Marinus will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Marinus adheres to external guidelines (e.g., Good Publication Practices 2) when forming a publication steering committee, which may be done for large, multicenter Phase 2 to 4 and certain other studies as determined by Marinus. The purpose of the publication steering committee is to act as a noncommercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Marinus products or projects must undergo appropriate technical and intellectual property review, with Marinus' agreement to publish prior to release of information. The review is aimed at protecting the Sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint, or shared rights, the principal investigator grants the Sponsor a perpetual, irrevocable, royalty free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure, including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral, or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the Sponsor that is necessary to include in any publication of study results or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the Sponsor's confidential information shall be submitted for publication without the Sponsor's prior written agreement to publish and shall be given to the Sponsor for review at least 60 days prior to submission for publication. If requested in writing by Marinus, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the Sponsor in conjunction with the Sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the Sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the Sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors current standards. Participation as an investigator does not confer any rights to authorship of publications.

12 REFERENCES

1. Lowenstein, D. and Alldredge, B. (1998). Status epilepticus. *New England Journal of Medicine*, 338: 970-76.

2. Trinka, E., Cock, H., Hesdorffer, D., Rossetti, A., Scheffer, I., Shinnar, S., Shorvon, S. and Lowenstein, D. (2015). A definition and classification of status epilepticus-Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia,* 56: 1515-23.

3. Falco-Walter, J. and Bleck, T. (2016). Treatment of established status epilepticus. *Journal of Clinical Medicine*, 5 (5): 49.

4. Bhattacharjee, A. and Hirsch, N. (2015). Management of status epilepticus. *Anaesthesia & Intensive Care Medicine*, 16: 159-60.

5. Treiman, D. (2014). Status epilepticus. Daroff, R. and Aminoff, M. (editors). *Encyclopedia of the Neurological Sciences* (Academic Press: Oxford, UK).

6. Treiman, D. (2007). Treatment of convulsive status epilepticus. *International Review of Neurobiology*, 81: 273-85.

7. Koubeissi M, Alshekhlee A. (2007). In-hospital mortality of generalized convulsive status epilepticus: a large scale US sample. Neurology, 69: 886-893.

8. Glauser, T., Shinnar, S., Gloss, D., Alldredge, B., Arya, R., Bainbridge, J., Bare, M., Bleck, T., Dodson, W.E., and Garrity, L. (2016). Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the Guideline Committee of the American Epilepsy Society. *Epilepsy Currents*, 16: 48-61.

9. Kapur, J., Elm, J., Chamberlain, J., Barsan, W., Cloyd, J., Lowenstein, D., Shinnar, S., Conwit, R., Meinzer, C., Cock, H., Fountain, N., Connor, J., Silbergleit, R., Nett and Pecarn Investigators. (2019). Randomized trial of three anticonvulsant medications for status epilepticus. *New England of Journal Medicine*, 381: 2103-13.

10. Kapur, J. and Macdonald, R. (1997). Rapid seizure-induced reduction of benzodiazepine and Zn2+ sensitivity of hippocampal dentate granule cell GABAA receptors. *Journal of Neuroscience*, 17: 7532-40.

11. Mayer, S., Claassen, J., Lokin, J., Mendelsohn, F., Dennis, L. and Fitzsimmons, B.F. (2002). Refractory status epilepticus: frequency, risk factors, and impact on outcome. *Archives of Neurology*, 59: 205-10.

12. Niquet, J., Baldwin, R., Suchomelova, L., Lumley, L., Naylor, D., Eavey, R. and Wasterlain, C. (2016). Benzodiazepine-refractory status epilepticus: pathophysiology and principles of treatment. *Annals of the New York Academy of Sciences*, 1378: 166-73.

13. Trinka, E., Höfler, J., Leitinger, M. and Brigo, F. (2015). Pharmacotherapy for status epilepticus. *Drugs*, 75: 1499-521.

14. Hocker, S., Britton, J., Mandrekar, J., Wijdicks, E. and Rabinstein, A. (2013). Predictors of outcome in refractory status epilepticus. *JAMA Neurology*, 70: 72-77.

15. Shorvon, S. and Ferlisi, M. (2012). The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. *Brain*, 135: 2314-28.

16. Sutter, R., Marsch, S., Fuhr, P., Kaplan, P. and Rüegg, S. (2014). Anesthetic drugs in status epilepticus: risk or rescue?: a 6-year cohort study. *Neurology*, 82: 656-64.

17. Nohria, V. and Giller, E. (2007). Ganaxolone. *Neurotherapeutics*, 4: 102-05.

18. Rogawski, M., Loya, C., Reddy, K., Zolkowska, D. and Lossin, C. (2013). Neuroactive steroids for the treatment of status epilepticus. *Epilepsia*, 54(suppl 6): 93-98.

19. Leitinger, M., Trinka, E., Gardella, E., Rohracher, A., Kalss, G., Qerema, E., Höfler, J., Hess, A., Zimmermann, G., Kuchukhidze, G., Dobesberger, J., Langthaler, P., Beniczky, S. (2016). Diagnostic accuracy of the Salzburg EEG criteria for non-convulsive status epilepticus: a restrospective study. *The Lancet Neurology*, 15:1054-62.

20. Kaplan, E. and Meier, P. (1958). Nonparametric estimation from incomplete observations. *Journal of the American Statistical Association*; 53: 457-481.

21. Jędrzejczak J, Mazurkiewicz-Bełdzińska M, Szmuda M, et al. Convulsive status epilepticus management in adults and children: Report of the Working Group of the Polish Society of Epileptology. Neurol Neurochir Pol. 2018;52(4):419-426.

22. Chiarello D, Duranti F, Lividini A, et al. Clinical characterization of status epilepticus in childhood: a retrospective study in 124 patients. Seizure. 2020;78:127-133.

23. Marawar R, Basha M, Mahulikar A, et al. Updates in Refractory Status Epilepticus. Crit Care Res Pract. 2018;2018:9768949.

24. Brophy, G., Bell, R., Claassen, J., Alldredge, B., Bleck, T., Glauser, T., Laroche, S., Riviello, Jr., J., Shutter, L., Sperling, M., Treiman, D., Vespa, P. and Committee Neurocritical Care Society Status Epilepticus Guideline Writing. (2012). Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care*, 17: 3-23.

25. Treiman, D. (2008). Importance of early recognition and treatment of generalized convulsive status epilepticus. *The Lancet Neurology*, 7: 667-68.

26. Knake, S., Hamer, H. and Rosenow, F. (2009). Status epilepticus: a critical review. *Epilepsy and Behavior*, 15: 10-4.

27. Rossetti, A. and Lowenstein, D. (2011). Management of refractory status epilepticus in adults: still more questions than answers. *The Lancet Neurology*, 10: 922-30.

28. DeLorenzo, R., Waterhouse, E., Towne, A., Boggs, J., Ko, D., DeLorenzo, G., Brown, A. and Garnett, L. (1998). Persistent nonconvulsive status epilepticus after the control of convulsive status epilepticus. *Epilepsia*, 39: 833-40.

29. Silbergleit, R., Durkalski, V., Lowenstein, D., Conwit, R., Pancioli, A., Palesch, Y. and Barsan, W. (2012). Intramuscular versus intravenous therapy for prehospital status epilepticus. *New England Journal of Medicine*, 366: 591-600.

30. Treiman, D. (2001). GABAergic mechanisms in epilepsy. *Epilepsia*, 42(Suppl. 3): 8-12.

31. Rossetti, A., Logroscino, G. and Bromfield, E. (2005). Refractory status epilepticus: effect of treatment aggressiveness on prognosis. *Archives of Neurology*, 62: 1698-702.

32. Neligan, A. and Shorvon, S. (2010). Frequency and prognosis of convulsive status epilepticus of different causes: a systematic review. *Archives of Neurology*, 67: 931-40.

33. Sutter, R., Kaplan, P. and Rüegg, S. (2013). Outcome predictors for status epilepticus-what really counts. *Nature Reviews Neurology*, 9: 525-34.

34. Strzelczyk, A., Ansorge, S., Hapfelmeier, J., Bonthapally, V., Erder, M. and Rosenow, F. (2017). Costs, length of stay, and mortality of super-refractory status epilepticus: A population-based study from Germany. *Epilepsia*, 58: 1533-41.

35. Claassen, J., Hirsch, L., Emerson, R. and Mayer, S. (2002). Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. *Epilepsia*, 43: 146-53.

36. Ganaxolone Investigator's Brochure. (December 2021). Radnor, PA: Marinus Pharmaceuticals, Inc.

37. Saporito, M., Gruner, J., DiCamillo, A., Hinchliffe, R., Barker-Haliski, M., White, H. (2019). Intravenously administered ganaxolone diazepam-resistant lithium-pilocarpine-induced status epilepticus in rats: comparison with allopregnanolone. *Journal of Pharmacology and Experimental Therapeutics*, 368: 326-337.

38. Albers, J., Moddel, G., Dittrich, R., Steidl, C., Suntrup, S., Ringelstein, E. and Dziewas, R. (2011). Intravenous lacosamide-an effective add-on treatment of refractory status epilepticus. *Seizure*, 20: 428-30.

39. Moddel, G., Bunten, S., Dobis, C., Kovac, S., Dogan, M., Fischera, M., Dziewas, R., Schabitz, W., Evers, S. and Happe, S. (2009). Intravenous levetiracetam: a new treatment alternative for refractory status epilepticus. *Journal of Neurology, Neurosurgery and Psychiatry*, 80: 689-92.

40. International Conference on Harmonisation (ICH) Guidance E2A March 1995. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

41. Clopper, C., Pearson, E.S. (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika, 26 (4): 404-413.

13 APPENDICES

APPENDIX 1 STATUS EPILEPTICUS CESSATION GUIDE

Status epilepticus cessation will be based on investigator judgment, guided by the following clinical and electrographic features:

1. The first 30-minute SE free period after IP initiation denotes the onset of SE cessation
2. Electrographically SE cessation should coincide with the beginning of the first 30-minute epoch of EEG which demonstrates seizure burden <20% and at least 50% less than during the 30 minutes prior to IP initiation
3. For the first co-primary endpoint only, SE cessation observed without administration of medications for the acute treatment of SE* from the time of IP initiation through 30 minutes following the onset of SE cessation

*Medications for the acute treatment of SE are defined as AEDs administered to abort ongoing SE or prevent imminent recurrence of SE based on clinical or EEG evidence. This definition excludes maintenance doses of AEDs or medications with anticonvulsant properties used for other reasons, such as procedural sedation.

APPENDIX 2 THERAPEUTIC DOSES OF BENZODIAZEPINES AND 2ND LINE IV AEDS

Benzodiazepines	
Drug Name	***Dose***
Diazepam	• 0.15-0.2 mg/kg IV up to 10 mg per dose • may repeat in 5 minutes
Diazepam (rectal)	• 0.2-0.5 mg/kg, maximum 20 mg/dose
Lorazepam	• 0.1 mg/kg IV up to 4 mg/dose • may repeat in 5-10 minutes
Midazolam	• 0.2 mg/kg IM, maximum 10 mg/dose

2nd line IV AEDs	
Drug Name	***Dose***
Phenytoin (PHT)/ fos-phenytoin (fPHT)	• PHT loading dose: 15-20 mg/kg IV given once, which can be followed by additional 10 mg/kg IV after 20 minutes if there is no response to the initial dose • PHT maintenance dose: 100 mg IV q6-8 hours (adjusted based on treatment response or blood levels) • fPHT loading dose: 18-20 mg PE/kg with a maximum infusion rate of 150 mg PE/min IV • Maintenance dose should begin 12 hours after loading dose • fPHT, maintenance dose: 5 mg PE/kg/day IM/IV divided daily TID
Valproic acid (VPA)	• Loading dose: 20-40 mg/kg IV at an infusion rate of 6 mg/kg/min • Maintenance dose: 10-20 mg/kg/day divided in BID-TID dosing
Levetiracetam (LEV)	• Loading dose: 20-60 mg/kg • Maintenance dose: 1000-3000 mg/day or 20 mg/kg/day
Brivaracetam (BRI)	• Loading dose: 2-4 mg/kg
Lacosamide (LAC)	• Loading dose: 400-600 mg IV • Maintenance dose: 20-300 mg BID
Phenobarbital (PHEN)	• Loading dose: 15-20 mg/kg IV • Maintenance dose: 1-4 mg/kg/day

The doses cited above are based on the published literature and should serve as guidance only.

References:

Aicua-Rapun, I., Andre, P., Rossetti, A.O., Decosterd, L.A., Buclin, T. & Novy, J. (2019) Intravenous brivaracetam in status epilepticus: Correlation between loading dose, plasma levels and clinical response. *Epilepsy Res,* **149**, 88-91.

Brophy, G.M., Bell, R., Claassen, J., Alldredge, B., Bleck, T.P., Glauser, T., Laroche, S.M., Riviello, J.J., Jr., Shutter, L., Sperling, M.R., Treiman, D.M., Vespa, P.M. & Neurocritical Care Society Status Epilepticus Guidelines Writing, C. (2012). Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care,* **17**, 2-23.

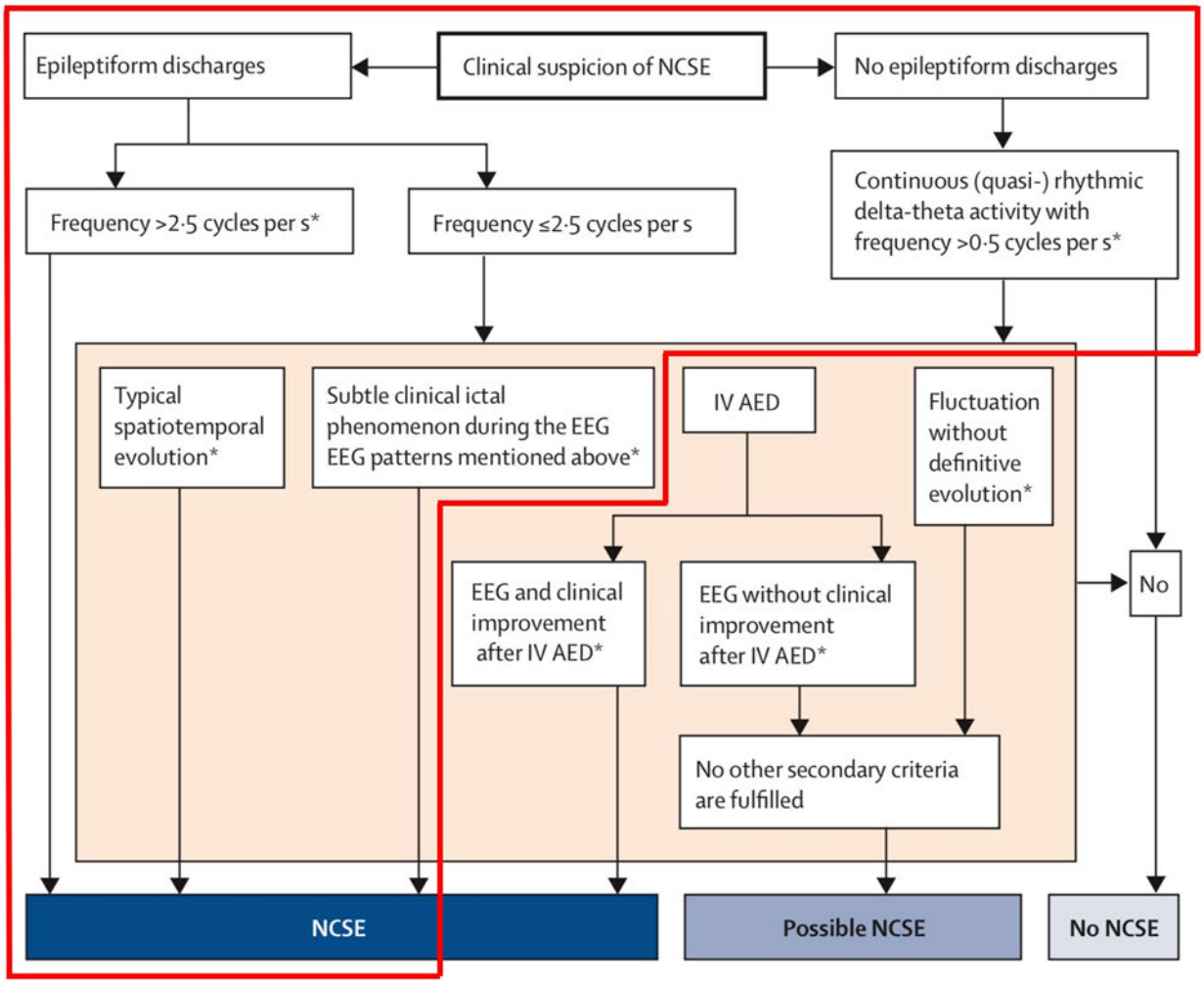
Glauser, T., Shinnar, S, Gloss, D., Alldredge, B., Arya, R., Bainbridge, J., Bare, M., Bleck, T., Dodson, W.E., Garrity, L., Jagoda, A., Lowenstein, D., Pellock, J., Riviello, J., Sload, E. & Treiman, D.M. (2016) Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society. *Epilepsy Curr,* **16**, 48-61.

Wasim, M. & Husain, A.M. (2015 Nonconvulsive seizure control in the intensive care unit. *Curr Treat Options Neurol,* **17**, 340.

APPENDIX 3 SALZBURG EEG CRITERIA FOR NCSE

Patients with known epileptic encephalopathy should have an increase in prominence or frequency of the features above when compared to baseline and observable change in clinical state.

Participants in RED box are eligible for enrollment.



Beniczky S et al. Epilepsia 2013;54 (suppl 6): 28-29; Leitinger M et al. Lancet Neurol 2016;15:1054-62. Image reproduced with permission from publisher.

APPENDIX 4 GLOBAL-MARKETED PRODUCTS CONTAINING CAPTISOL®

The following table lists the commonly found but not exhaustive list of products containing Captisol®

Product	Active/Dosage Form
VFEND IV	voriconazole for injection
GEODON/ZELDOX IM	ziprasidone mesylate for injection
ABILIFY IM	aripiprazole injection
NEXTERONE	amiodarone injection
KYPROLIS	carfilzomib for injection
NOXAFIL injection	posaconazole injection
EVOMELA	melphalan for injection
CARNEXIV	carbamazepine injection
BAXDELA intravenous	delafloxacin meglumine for injection
ZULRESSO CIV	brexanolone injection
Generic 'VFEND IV'	voriconazole for injection
REMIVIR, VEKLURY	Remdesivir

APPENDIX 5 CARDIODYNAMIC 12 LEAD ELECTROGRAPHIC (ECG) MONITORING

Select sites will participate in a sub study using a continuous 12 lead ECG recorder which should start approximately 60 minutes prior to IP initiation and should continue for 36 hours following IP initiation.

Periods/Day/ Duration	**Screening Day -1 to Day 1 Predose through screening**	**Dosing Day 1 IP initiation 0 through 24 hours following IP initiation**	**Dosing Day 2 24 hours through 36 hours following IP initiation**	**Taper Day 2 (12 hours) Starts at 36 hours following IP initiation**
IP infusion		✔	✔	✔
Timepoint	**-60 minutes**	**0 through 24 hours following IP initiation**	**24 hours through 36 hours following IP initiation**	**36-48 hours following IP initiation**
Cardiodynamic 12 lead ECG monitoring	✔	✔	✔	✔

Replicate ECGs will be extracted from the recorder devices by the ECG vendor at 3 timepoints prior to IP initiation (-45, -30 and -15 minutes) at least 1 minute apart within + 3 minutes window. Post dose replicate ECGs will be extracted by the ECG vendor at timepoints that match the PK collection times. Whenever the ECG extraction and PK or clinical safety lab sample collection timepoints are close together, the ECG extraction will be performed prior to the PK or clinical safety lab sample collection.

Reference the Cardiodynamic ECG Manual for further details.

APPENDIX 6 SUMMARY OF CHANGES FROM PROTOCOL AMENDMENT 1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **14July2020**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
Added Murray Maytom, as the back-up emergency contact		Emergency Contact Information
Clarified that the administration of an anesthetic for seizure suppression should be given at an adequate dose and for an adequate duration to induce anesthesia		Synopsis; Section 6.2.6
Revised the sentence regarding the central reader to include 'confirmatory' analysis and that the central reader is blinded to treatment assignment		Synopsis, Section 6.2.3
Removed 'and neurological' from physical examination as the neurological assessment is included in the physical examination		Synopsis, Table 1, Section 7.2.3.2
Added the following timepoints to the Richmond Agitation and Sedation Scale (RASS) and the Full Outline of UnResponsiveness (FOUR) Score Scale: 60 minutes (+/- 15 min), 2, 6 hours (+/- 30 min), and 36 hours (+/- 1 hour)		Synopsis, Table 1
Added the following sample collection timepoints for Coagulation: For participants who terminate early from the study (whenever possible), collect at the time of early termination and as close as possible to the end of the IP administration and the investigator may collect at any other time based on clinical judgment		Synopsis, Table 1
Added the following timepoints to the Seizure Description Questionnaire (following IP initiation): At the time of hospital discharge and Early Termination		Synopsis, Table 1
Reduced the duration for the Cardiodynamic 12 Lead ECG monitoring (substudy) from 48 to 36 hours following IP initiation		Synopsis, Table 1, Appendix 4
Added clarifying instructions that a urine microscopic should be collected if any abnormal value is observed from the dipstick test		Synopsis, Table 1
The following timepoints for sample collection for urine chemistry testing of N-acetyl-β-D-glucosaminidase [NAG] and β-microglobulin have been deleted: IP discontinuation and in the event of an SAE and collection at any other time based on clinical judgment. Added instructions that urine samples must be frozen and details regarding the collection, processing and shipment of samples to the bioanalytical vendor.		Synopsis, Table 1, Section 7.2.3.7
Clarified that blood gas collection can be arterial or venous and deleted 'including FIO_2.PaO_2 and arterial pH'		Synopsis, Table 1, Section 7.2.3.7
Euro QOL: added '-5L' to the questionnaire title		Synopsis, Table 1, Section
Seizure Description Questionnaire (Predose): added additional instructions when the questionnaire should be completed		Synopsis, Table 1, Section 7.2.2.8
Inclusion criteria #3: reduced the duration of continuous or cumulative, intermittent seizure activity in the 30-minute period immediately prior to		Synopsis, Section 4.1

IP initiation from 15 minutes to 6 minutes; and revised Convulsive SE criteria to include EEG seizure activity.	
Exclusion criteria #4: revised wording to 'Seizure burden or clinical state would NOT warrant IV anesthesia for seizure control over the next 24 hours'	Synopsis, Section 4.2
Defined medications for the acute treatment of SE	Synopsis, Section 104.1
Primary Endpoint: Revised the seizure burden to <20% and that the seizure burden is at least 50% less than during the 30 minutes prior to IP initiation	Synopsis, Section 10.4.1
Other Secondary Endpoints added clarifying text for Proportion of participants with any escalation of treatment in the first 24 hours following IP initiation	Section 10.4.3
Deleted all references of the Intent to Treat (ITT) population as per FDA comment to use mITT instead. Revised the description of the mITT population. Removed all references to Full Analysis Set (FAS)	Synopsis, Sections 10.3, 10.4.1
Added sentence that the reason for each AED dose during IP administration will be recorded in the appropriate CRF	Section 5.2.1
Appendix 3: Remdesivir added to the list of US-marketed products containing Captisol®	Section 13, Appendix 3
Additional grammatical, typographical errors and formatting revisions have been made in the document but are not identified here	

APPENDIX 7 SUMMARY OF CHANGES FROM PROTOCOL AMENDMENT 2

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2**	**Amendment Date** **19November2021**	**Global/Country/Site Specific** **Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Removed Murray Maytom, MD and added Henrikas Vaitkevicius, MD as the back-up emergency contact		Emergency Contact Information
Extended the study period from May 2022 to December 2022		Synopsis
Mortality rate changed from 3% to 40% to 3% to 26% based on current literature		Synopsis (Rationale)
Clarified that IP can be administered through a **"dedicated lumen of a multi-lumen catheter"**		Synopsis (Investigational Product, Dose and Mode of Administration); Section 6.2.3
Added Phenobarbital to the list of acceptable second-line IV AEDs to align with pediatric SOC		Synopsis (Investigational Product Dose and Mode of Administration); Inclusion Criteria #4 (Synopsis; Sections 4.1; 5.2; 6.2.3; Table 6; Appendix 1
Removed "without a pattern of improvement" and added that an EEG should be used to confirm SE immediately prior to IP initiation (bolus dose) to align with revised inclusion criteria #3		Synopsis (Investigational Product, Dose and Mode of Administration); Sections 6.2.3; 7.1.2.1
For participants <40 kg, the reference weight was changed from 70 kg to 40 kg to allow dose-proportional dosing in patients whose weight is close to the cut-off 40 kg.		Synopsis (Investigational Product, Dose and Mode of Administration); Section 6.2.3; Table 5
Medical oversight requirement revised to align with local institutional guidelines Added **"Telemedicine"** as an acceptable practice for conducting protocol-driven assessments/procedures to align with institution processes		Synopsis (Investigational Product, Dose and Mode of Administration); Section 6.2.5
Reduced the number of hours for IP interruptions from 6 to 2 hours to encourage earlier communication with the Sponsor Medical Monitors in cases when IP infusion was temporally discontinued		Synopsis (Investigational Product Dose and Mode of Administration); Section 6.2.7
Clarified that after IP discontinuation, the follow-up assessments/procedures will be collected q 24 hours through 120 hours (or until hospital discharge) as participants may be discharged prior to the 120 hour timeframe		Synopsis (Methodology); Table 1 footnote b; Sections 3.1; 4.5; 7.1.3
Clarified that the Physical Examination at 36 hours should be collected if medically indicated to allow the physical examination to be conducted at PI discretion if medically indicated only. This will reduce burden of assessment in situations when they are not medically needed		Synopsis (Methodology); Table 1 footnote d
Removed "and as close as possible to the end of the IP administration" for all procedures/assessments performed for participants who terminate early from the study as participants may terminate at any time during the study		Synopsis (Methodology); Table 1; footnotes d, e, f, g, j, k, o, q, r

Added "**if available**" for estimated glomerular filtration rate (eGRF) and calculated creatinine clearance and removed albumin as this analyte is not tested in a routine urinalysis; added phenobarbital to the list of AED level collection	Synopsis (Methodology); Table 1 footnote i; Table 6
Added "**if available**" for estimated glomerular filtration rate (eGRF) and calculated creatinine clearance and removed albumin as this analyte is not tested in a routine urinalysis; added phenobarbital to the list of AED level collection	Synopsis (Methodology); Table 1 footnote i; Table 6
Revised Drugs of Abuse testing and clarified that alcohol testing should be collected, if medically indicated to align with the institution SOC; T. Chol footnote 1 revised and footnote 2 and 3 added	Synopsis (Methodology); Table 1 footnote l; Table 6
Clarified that institution guidelines will be followed for pregnancy test results prior to IP initiation	Synopsis (Methodology); Table 1 footnote l; Sections 4.4.1; 7.2.3.7
Clarified that Electroencephalogram (EEG) is required for confirmation of **CSE** diagnosis; removed "If continuous EEG is not possible or needed to diagnose (for convulsive SE) it should be instituted at the earliest possible time following IP initiation (if a predose EEG was not performed for the diagnosis of convulsive SE) as this statement no longer applies Added **"Sites will be offered the use of a rapid EEG device to assist with screening of participants with NCSE. It is preferred that a conventional EEG is used for the purpose of confirming inclusion criterion #3 and EEG monitoring during IP administration. In situations when a conventional EEG is not immediately available, the rapid EEG may be used to confirm inclusion criterion #3. Since the rapid EEG has a limited battery life, it should be switched to a conventional EEG within several hours but not earlier than 90 minutes after IP initiation to allow uninterrupted collection of EEG for the 30-minute SE cessation co-primary endpoint. It will be at the investigator's discretion if the use of the rapid EEG will benefit their site. The device should be used according to institution standard practices**." This change will allow screening and enrollment based on a portable EEG device, Ceribell, (approved by the FDA), in situations when conventional EEG is not immediately available (e.g., during night hours).	Synopsis (Methodology), Table 1 footnote m; Section 7.2.2.1
Clarified where pharmacokinetic samples should be collected in relation to IP infusion site.	Synopsis (Methodology); Table 2 footnote b, Section 7.2.4.1
Seizure Description Questionnaire should be collected predose only and as close as possible to IP initiation; all timepoints following IP initiation have been removed to reduce the burden of assessments throughout the study and to decrease the amount of redundant information collected.	Synopsis (Methodology); Table 1 footnote p; Section 7.2.2.6
Status Cessation and Super Refractory Status Epilepticus Questionnaires and Sections 7.2.2.7 and 7.2.2.8, respectively added	Synopsis (Methodology); Table 1; footnote q & r, respectively
Health Utilization Questionnaires and Section 7.2.2.8 added to align with statistical endpoints	Synopsis (Methodology); Table 1; footnote v
The following inclusion criteria revised: #3. Removed "…without a pattern of improvement and at least 6 minutes of continuous or cumulative, intermittent seizure activity in the 30-minute period immediately prior to IP initiation, and either" replaced with **"…with seizure burden warranting imminent**	Synopsis (Inclusion/Exclusion Criteria); Section 4.1

progression to IV anesthesia for seizure control. Ictal patterns and burden defined below." Added **"Ictal burden of approximately 6 minutes or more within 30-minutes immediately prior to IP initiation is targeted"** These changes in inclusion criterion #3 were made to better align with practical aspects of assessment of seizure burden at the bedside and with the second co-primary efficacy endpoint (progression to IV anesthesia within 36 hours). #4. Added phenobarbital to the list of acceptable second-line IV AEDs to align with SOC in the pediatric population #5. Revised BMI from <35 to <40 The BMI cut-off was increased to allow enrollment of patients who are severely obese but not yet considered morbidly obese. BMI ≥40 is generally considered for the designation of "morbidly obese".	
The following exclusion criteria revised: #2. Replaced "uncontrolled" with "**rapidly reversible**" when describing a metabolic cause of SE, e.g., hypoglycemia as this better describes the condition like severe hypoglycemia #3.Removed "phenobarbital or ketamine" from the list of anesthetic agents and added **"with the primary intent specifically to treat seizures or achieve burst suppression"** as phenobarbital has been added as an approved 2nd line IV AED counted for failure (inclusion criterion #4) and ketamine is generally not considered an IV anesthetic that can produce burst suppression or indicate SRSE if fails to control seizures #5. Added (e.g., **directive Do Not Intubate**) at the end of the criterion #10. Added reporting unit for eGFR #11. Removed "**whichever is greater**" when describing the use of an investigational product; added "**Participation in a non-interventional clinical study does not exclude eligibility**"	Synopsis (Inclusion/Exclusion Criteria); Section 4.2 Synopsis (Investigational Product, Dose, and Mode of Administration); Sections 5.2.2; 6.2.6
Revised timeframe for recording prior medications, including AEDs, administered from 30 for prior medications (7 for AEDs) to 14 days to reduce the amount of data collected for this acute indication and focus only on the medications that are expected to be relevant to acute events	Synopsis (Methodology); Table 1 footnote u; Section 5.1
Revised the definition for medications for the acute treatment of SE with the addition of "…or prevent **imminent** recurrence of SE based on clinical or EEG evidence"	Synopsis (Endpoints); Section 10.4.1
Healthcare Utilization Endpoints - removed list of discharge locations as they were not aligned with the case report form	Synopsis (Endpoints); Section 10.4.4
Safety Endpoints – Removed "neurological" as this assessment is included in the physical examination; added "**use of concomitant medications, and occurrence of AEs**" to the safety analyses	Synopsis (Endpoints); Section 10.5
Removed "and status strata (CSE or NCSE) as fixed effects" from logistic regression model to avoid unstable estimation of the regression coefficient of status strata as the majority of the participants will be NCSE Added "**In addition, the point estimate of difference of the proportions of participants achieving either and both of the co-primary endpoints between two treatment arms will be provided.**	Synopsis (Analysis of Primary Endpoint); Section 10.4

The 95% confidence interval will be provided using Clopper-Pearson method" to facilitate interpretation of the treatment effect	
Clinical Data Added findings from May 2021 breastfeeding study that have become available after the initial date of this protocol.	Section 1.2
Added paragraph that describes the most common treatment emergent adverse events reported in the 1042-SE-2001 study	Section 2.1
Added Exploratory Objectives to align with the Synopsis	Section 2.2.3
Restrictions Removed "from consuming grapefruit, Seville oranges, starfruit or citrus derived products" based on current DDI data; revised the restriction period for use of alcohol until the "**end of the 24 hour IP discontinuation follow-up period"** based on the relatively short half-life of ganaxolone that is expected to be cleared from the body within 24 hours post discontinuation Clarified that breastfeeding is prohibited for 45 days after the last dose of IP	Section 4.3
Revised duration for males to avoid causing pregnancy in their sexual partner during the study and for **30 days** after the last dose of IP	Section 4.4.2
Added Section 4.5.1.1 Reason for IP Discontinuation	
Clarified that investigator clinical judgment should be used to determine if a participant should be discontinued from the study Revised participant withdrawal criteria related to ventilatory depression	Section 4.5.2
Revised Section header to Reason for **Study** Discontinuation	4.5.3
Added details for collecting benzodiazepines, AEDs, anesthesia, and vasopressors data for prior to and concomitant treatment	Sections 5.1, 5.2
Allocation of Participants to Treatment – clarified that randomization is defined as the initiation of IP infusion; provides flexibility for timing of randomization to avoid impact to SOC; emphasizes that IP administration cannot occur until eligibility criteria has been met	Section 6.2.2
Clarified that IWRS will record all unblinding events and removed instruction that "code breaks must be reported to the Clinical Research Organization (CR) and Sponsor"	Section 6.2.8
The protocol allows for additional labels to be applied to the IP to satisfy local or institution requirements; therefore, "on a case by case basis" was removed Removed the following paragraph "Identify the study participant by name…" and replaced with "Sponsor approval is not needed to make this change"	Section 6.3.1
Section header revised to "Follow-up Period (24 hours **following IP** to Week 4) for clarification purposes	Section 7.1.3
Section header revised to "Medical, **Seizure or SE**, and Medication History and added bullet "Seizure or SE Etiology" to be aligned with the data being collected	Section 7.2.3.1
Removed "A neurological examination should be performed at the time of assent/consent is administered to the participant for continued participation…" as a neurological assessment is part of the physical examination and, therefore, no need to specify each system	Section 7.2.3.2

Section header revised to "**Medication Errors**" and section content updated to align with events that may occur when administering the IV formulation; removed references of "abuse, misuse or overdose"; added Other Reportable Information; clarified that reports of Medication Errors and Other Reportable Information are subject to the 24-hour reporting requirement	Sections 8.1.7; 8.2.2
Removed paragraph that states that the IB has not been updated to include the 1 mg/mL ganaxolone IV formulation as the current IB includes this information	Section 8.2.1
Revised guidance for data entry of participant data in the electronic data capture system; removed reference to Data Management Plan (DMP) as this is an internal document	Sections 9.1 and 9.2
Revised the Analysis Population descriptions for Enrolled, Safety, Modified Intent to Treat (mITT) and Per Protocol (PP); added Randomized	Section 10.2
Removed "During the study, participants will receive usual SOC …" through "The comparison for statistical significance…."; Added "**Both co-primary efficacy endpoints must be statistically significant at 2-sided 5%..."** Added "In addition, the point estimate of difference…to align with statistical principles	Section 10.4
Clarified which data are included in the Safety Analyses	Section 10.5
Clarified that there is no formal interim analysis planned for this study and that the DMC is chartered to review the study data periodically without any hypothesis testing	Section 10.7
Reference 37 and 38 added	References
Salzburg Criteria: Illustration revised to clarify patient eligibility	Appendix 2
Clarified that the table listing the US-Marketed Products containing Captisol® is not an exhaustive list	Appendix 3
Added recording window for extraction of the 3 timepoints	Appendix 4
Added Appendix 5 Summary of changes from Protocol Amendment 1	
Additional grammatical, typographical errors and formatting revisions have been made in the document but are not identified here	

APPENDIX 8 SUMMARY OF CHANGES FROM PROTOCOL AMENDMENT 3

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **3**	**Amendment Date** **10June2022**	**Global/Country/Site Specific** **Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Added current Marinus logo		Cover Page
Updated Additional Contact Information from Bonnie Dettore to Shawn Ironside		Additional Contact Information
Expanded regions from United States to North America and other locations		Synopsis (Site(s) and Region(s)) and Section 3.3
Extended the study period from December 2022 to December 2023		Synopsis
Revised Primary Objective, removing "first-line benzodiazepines and two second-line IV antiepileptic drugs (AEDs" and adding **SE after failure of two or more antiseizure treatments** to align with the new definition of participant failure. The secondary and exploratory objectives were clarified by the following revisions: Secondary: • Removed, "Compare rates of IV anesthesia use through the final study follow-up visit/contact" and "Establish efficacy of ganaxolone on measures of seizure activity and overall functioning" • Added, "**To demonstrate sustained efficacy of IV ganaxolone beyond the 48-hour treatment period to prevent initiation of IV anesthesia** and **Establish the effect of ganaxolone on healthcare utilization**" Exploratory: • Removed, "Assess seizure burden, use of additional doses of AEDs for SE treatment, and level of responsiveness" and "Evaluate functional status, patient reported outcomes and healthcare resource utilization" Added, "**Assess the effect of ganaxolone on doses of other antiseizure treatments and changes in seizure burden**" and "**Evaluate the effect of ganaxolone on quality of life, functional status, and level of responsiveness**"		Synopsis (Objectives: Primary Analysis) and Sections 2.2.1, 2.2.2, and 2.2.3
To align with the revised inclusion criteria #1, language has been added throughout the document to clarify that where allowed by law, deferred consent can be utilized for study inclusion.		Synopsis (Investigational Product, Dose, and Mode of Administration), (Methodology), Sections 3.1, 4.0, 4.1, 6.2.3, 7.1.1.1

To align with the revised inclusion criteria all references to the text in the bullets below has been removed or revised to align with the updated inclusion criteria: • "following initial benzodiazepine treatment and administration of two or more second-line IV AEDs." • "after initial treatment with benzodiazepines and" • "Investigators should determine that doses of administered second-line AEDs were sufficient for treatment of SE." • "Antiepileptic drug doses utilized in the treatment of SE are provided in Appendix 1." In addition, the following have been updated throughout the protocol to align with the update inclusion criteria: • References to the participants receiving **any** two or more of the following **agents** for the **treatment** of the current episode of SE, administered at an adequate dose and **for a sufficient** duration, **in the judgment of the investigator, based on investigator judgment, at an adequate dose and for a sufficient duration** to **have** demonstrated efficacy: As previously described, IP will be added to SOC after "initial treatment with benzodiazepines and" **failure of any** two or more "second-line IV AEDs" **antiseizure treatments** (benzodiazepine and one IV AED or two IV AEDs). And **Benzodiazepine** has been added to the list of possible treatments a participant may fail prior to IP initiation and **IV** has been added to all the 2nd line IV AEDs	Synopsis (Investigational Product, Dose, and Mode of Administration), (Methodology), Sections 3.1, 5.2.1, 6.2.3
To align with the inclusion criteria, the original wording, "After meeting the criteria for SE (clinical and EEG) within 60 minutes prior to IP initiation, the presence of ictal activity SE (clinical and EEG) should be confirmed during the 30 minutes immediately prior to IP initiation (bolus dose). Has been updated to the following: **The investigator will confirm that the participant meets clinical and EEG criteria for SE during the 60-minute period** prior to IP initiation **and will reconfirm that ongoing ictal activity is present within** 30 minutes immediately prior to IP initiation.	Synopsis (Investigational Product, Dose, and Mode of Administration), Sections 6.2.3 and 7.1.2.1
Moved, "Status epilepticus cessation will be assessed by the investigator based on clinical and EEG features. Training will be provided to guide and help standardize decisions across clinical sites. In addition, a retrospective confirmatory analysis of EEGs will be performed by a central reader who is blinded to treatment assignment" from the Methodology section to the Endpoints section as, "**SE** cessation will be assessed by the investigator based on clinical and EEG **features (see Appendix 1 for seizure cessation guide).** Training will be provided to guide and help standardize decisions across clinical sites. In addition, a central reader blinded to treatment assignment **will review EEG recordings retrospectively and corroborate accuracy of interpretation**." And moved to Appendix 1, "*SE cessation will be determined by the investigator based on clinical and EEG findings. The criterion for time of electrographic seizure cessation will be the beginning of the first 30-minute epoch of EEG in which The seizure burden (percent of time during which there is electrographic seizure activity) is <20%" and "The seizure burden is at least 50% less than during the 30 minutes prior to IP initiation" to align the Endpoint section of the synopsis to align the Endpoints.	Synopsis (Methodology), (Endpoints), Section 6.3 2, Section 10.4.1
Expanded the Vital signs collection window from (+/- 1 hour) to (+/- 2 hour) for 24 hours (+/- 1 hour) following IP discontinuation timepoint. Removed the 12-hour and added a **10-hour** collection timepoint to better align with the RASS, FOUR Score, CGI-I, and PK collections.	Synopsis (Methodology), Table 1 footnote e

Removed the 12-hour and added a **10-hour** collection timepoint for the RASS and FOUR Score to better align with the Vital Sign, CGI-I, and PK collections.	Synopsis (Methodology), Table 1 footnote f
Removed the 36 hours (+/- 1 hour) following IP initiation for the 12 lead Electrocardiogram (ECG).	Synopsis (Methodology), Table 1 footnote g
Added clarification, concomitant AED levels only need to be collected if required per the standard of care. Removed all requirements for variable AED collections: <u>Variable AED collection times based on participant response</u>: Between IP initiation and at the end of the first 24 hours of the follow-up period, where possible, collect sample for AED level(s): I. If a decision is made to intubate II. After initial SE cessation, AED levels should be collected at time of first recurrence of seizure activity or SE	Synopsis (Methodology), Table 1 footnote i
Removed the weekly follow up visit Coagulation sample collection At the weekly follow-up visits (Week 1, 2, 3, or 4) for hospitalized participants and for participants who have been discharged (whenever possible).	Synopsis (Methodology), Table 1 footnote k
Removed the 4, 8, and 12-hour PK collections and added a **6 and 10 hour** collections to make the sample collections not intersect with an infusion change. Increased the collection window for 10, 24, and 36 hour samples to (+/- 2 hour) Removed requirements I, II, and IV for variable PK collections: <u>Variable PK collection times based on participant response:</u> Between IP initiation and at the end of the first 24 hours of the follow-up period, where possible, collect a PK sample: I. If a decision is made to intubate II. At the time of introduction of a new AED for safety/efficacy (not for AEDs given prophylactically for "transition/bridging") IV. After the initial SE cessation, collect a sample at the first instance of seizure activity or SE relapse and does not progress to anesthesia (e.g., midazolam, propofol, thiopental, or pentobarbital)	Synopsis (Methodology), Table 2 footnote b
Removed the 12-hour and added a **10-hour** collection timepoint for the CGI-I to better align with the Vital Sign, RASS, FOUR Score, and PK collections.	Synopsis (Methodology); Table 1 footnote o
Unified all references to mechanical or artificial ventilation to be positive pressure ventilation (PPV)	Synopsis (Methodology), (Endpoints), Sections 7.3, 10.4.2, and 10.4.4
The following inclusion criteria revised: As the study is expanding globally #1 was updated to allow for deferred consent to be obtained where allowed by law. **1.** Participant, participant's parent, guardian, or LAR must provide **signed informed** consent/assent, and once capable (per institutional guidelines), there must be documentation of consent/assent by the participant demonstrating they are willing and aware of the investigational nature of the study and related procedures. **Where allowed by law, if the patient lacks the capacity to make informed decisions regarding his/her medical treatment options, the treating clinician may follow their deferred**	Synopsis (Inclusion/Exclusion Criteria), Section 4.1

consenting practices. The clinician will make the final decision based on the best interests of the patient. #3 was completely deleted, and new wording added to clarify the requirement and better align with clinical practice of SE diagnosis **3. SE meeting the following criteria:** **a. A diagnosis of SE with or without prominent motor features based on clinical and EEG findings:** **i. Diagnosis is established by:** • **For SE with prominent motor features: Clinical and EEG seizure activity indicative of convulsive, myoclonic or focal motor SE** • **For SE without prominent motor features (nonconvulsive SE): Appropriate clinical features and an EEG indicative of NCSE (see modified Salzburg criteria[19] in Appendix 3)** **ii. For any type of SE:** • **At least 6 minutes of cumulative seizure activity over a 30-minute period within the hour before IP initiation, AND** • **Seizure activity during the 30 minutes immediately prior to IP initiation** **b. The treating clinician(s) anticipate that IV anesthesia is likely to be the next treatment for SE that persists following initiation of IP** #4 Revised to clarify the requirement and better align with clinical current practice that some patients may not be receiving benzodiazepines and would be started on second-line agents directly. "Participants must have received a benzodiazepine and two or more of the following second-line IV AEDs for treatment of the current episode of SE" was revised to "Participants must have received **any two or more of the following agents for treatment** of the current episode of SE" Benzodiazepine was added to the bulleted list of medications and IV was added to all the bulleted second-line IV AEDs: ○ **Benzodiazepines,** ○ **IV** Fosphenytoin/phenytoin, ○ **IV** Valproic acid, ○ **IV** Levetiracetam, ○ **IV** Lacosamide, ○ **IV** Brivaracetam, or ○ **IV** Phenobarbital	
The following exclusion criteria 2, 3, 4, 8, 11 revised #2 added "an uncorrected", to Anoxic brain injury or **an uncorrected** rapidly reversable metabolic condition as the primary cause of SE (e.g., hypoglycemia <50 mg/dL or hyperglycemia >400 mg/dL). #3 deleted the text, "with the primary intent to treat seizures or achieve burst suppression" and added the bolded text below Participants **who have received high-dose** IV **anesthetics** (e.g., midazolam, propofol, thiopental, or pentobarbital) **during the current episode of SE for more than 18 hours, or who continue to have clinical or electrographic evidence of persistent seizures while receiving high-dose IV anesthetics**.	Synopsis (Inclusion/Exclusion Criteria); Section 4.2

#4 and #5 were deleted and a new exclusion added: **Clinical condition or advance directive that would NOT permit use of IV anesthesia** The changes to exclusion #3, 4, and 5 were all made to simplify the protocol requirements around IV anesthetic use in this patient population. Due to the combining of exclusion #4 and 5, the remaining criteria have been renumbered. #7 "US-" was removed as the appendix now reflects the global marketed products containing Captisol® #8 **leading to impaired synthetic liver function** was added to hepatic restrictions to better define the medical condition and guide the investigators	
Clarified that while the screening period is from the time consent/assent is obtained (or deferred, if allowed by law) to immediately prior to IP initiation (excluding pre-consent). Assessments collected prior to this timeframe that the investigator judges to be clinically relevant to the participant's current state can be utilized in the study and do not need to be repeated. For medically unstable participants, screening activities (e.g., labs or vital signs) should be collected as close to IP initiation as possible.	Synopsis (Maximum Duration of Participant Involvement in the Study), Table 1 footnote a
Other Secondary Endpoint, Level of sedation has added **agitation** to better define the assessment collection.	Synopsis (Endpoints), Section 10.4.3
Added **Time on positive pressure ventilation to the Healthcare Utilization Endpoints** and moved Proportion of participants requiring positive pressure ventilation to the second bullet based on key opinion leader feedback of the rank of meaningful clinical response.	Synopsis (Endpoints), Section 10.4.4
Removed "Status epilepticus cessation will be based on investigator judgment, according to the following criteria: a. SE cessation of at least 30 minutes duration, and b. Without administration of medications for the acute treatment of SE from the time of IP initiation through 30 minutes following the onset of SE cessation" Removed "Key secondary endpoints will be compared between ganaxolone- and placebo-treated participants in the mITT population with a hierarchical testing process at the 5% level of significance. The analysis of secondary efficacy endpoints will use the order of endpoints listed above. Assuming that a statistically significant difference between groups was observed on both co-primary endpoints, the first key secondary endpoint will be compared between groups. If statistical significance is established on the first key secondary endpoint, then the testing process will proceed to the second key secondary endpoint." And replaced it with**, If the primary endpoints are statistically significant, the analysis of key secondary efficacy endpoints will be performed sequentially in the order as listed above. If the key secondary endpoints are statistically significant, analysis of the first healthcare utilization endpoint, time on positive pressure ventilation, will be performed.** Added that the time on positive pressure ventilation endpoints will be analyzed using the Kaplan-Meier method. Added an Interim Analysis section to the Synopsis:	Synopsis (Statistical Methods), Section 10.4.2 and 10.7

<table>
<tr><td>We plan to conduct an interim analysis when two-thirds of the subjects have completed the study (41 participants per arm). The overall type I error rate (i.e., alpha=0.05, two-sided) will be controlled using a power family alpha spending function, with a two-sided nominal alpha level of 0.0293 at the interim analysis. If one or both primary efficacy endpoints fail to reach statistical significance at the interim analysis, the same testing process will be repeated at the final analysis at the nominal alpha level of 0.0343. The interim analysis will be performed by an independent statistician who is not involved in study operation and conduct.
If study enrollment is proceeding at a rate that the study would be complete or nearly complete by the time an interim analysis is accomplished, the Sponsor may elect not to conduct it.
Further details will be provided in the SAP.</td><td></td></tr>
<tr><td>Updated the exclusion criterion reference from #8 to #7 to match the renumbering.</td><td>Section 5.2.2</td></tr>
<tr><td>Removed reference to the IP formulation and storage requirements as this information will be detailed in the pharmacy manual, “In addition to Captisol®, the formulation consists of water for injection (diluent), buffering agents (potassium phosphate, sodium phosphate) and sodium chloride (tonicity modifier).”
Quantitative Composition of Ganaxolone IV Solution, 1 mg/mL –
<table>
<tr><th>Component</th><th>Reference to Standards</th><th>Content per mL (mg/mL)</th><th>Concentration (%w/w)</th><th>Function</th></tr>
<tr><td>Ganaxolone</td><td>Marinus</td><td>1.00</td><td>0.097</td><td>Active ingredient</td></tr>
<tr><td>Betadex sulfobutyl ether sodium (Captisol®)</td><td>NF</td><td>59.74</td><td>5.817</td><td>Solubilizing agent</td></tr>
<tr><td>Potassium phosphate, monobasic (KH_2PO_4)</td><td>NF</td><td>2.46</td><td>0.239</td><td>Buffer agent[a]</td></tr>
<tr><td>Sodium phosphate, dibasic heptahydrate ($Na_2HPO_4.7H_2O$)</td><td>USP</td><td>2.78</td><td>0.271</td><td>Buffer agent[a]</td></tr>
<tr><td>Sodium chloride</td><td>USP</td><td>2.00</td><td>0.195</td><td>Tonicity modifying agent</td></tr>
<tr><td>Water for injection</td><td>USP</td><td>q.s. 1 mL</td><td>93.381</td><td>Diluent</td></tr>
</table>
NF = National Formulary; USP = United States Pharmacopeia; w/w = weight by weight.
a. Formulation pH = 6.4

To simplify the protocol and refer the reader to the Pharmacy Manual.

Added, “On 01 June 2022 the Drug Enforcement Administration (DEA) issued its interim final rule placing ganaxolone, including its salts, in schedule V of the Controlled Substances Act. The DEA drug code for Ganaxolone (commercial name, Ztalmy) is 2401.”

Also removed the storage requirements as the information is detailed in Section 6.3.3 (Storage)</td><td>Section 6.1</td></tr>
<tr><td>The Interactive Response Technology (IRT) features are being updated, and as a result, IP allocation has been added to the list of available tasks.
The following has been deleted:
Randomization consists of two steps. The participant will first be assigned a randomization number and assignment of IP bottles by the IRT followed by the initiation of IP. This second step of initiation of the IP means the patient is randomized.

The randomization number represents a unique number corresponding to IP allocated to the participant.</td><td>Section 6.2.1, 6.2.2</td></tr>
</table>

Individual participant treatment is automatically assigned by the IRT To allow for timely delivery of IP to the hospital unit, **the IP bottles** may be **allocated for use** in the IRT prior to the participant meeting all eligibility criteria to avoid impact to SOC. Investigational product will not be administered until eligibility has been determined. Enrollment is defined as the initiation of IP infusion.	
Added a reminder that the investigator is responsible for complying with the DEA and CSA regulations now that ganaxolone is a scheduled drug, "The investigator has overall responsibility for ensuring that IP is stored in a secure, limited access location in accordance **with applicable requirements under the Controlled Substance Act (CSA) and Drug Enforcement Administration (DEA) regulations."** Removed the temperature ranges, "The 1 mg/mL ganaxolone IV solution and placebo bottles should be stored at room temperature 15°C to 25°C (59°F to 77°F) until use. Excursions up to 30°C (86°F) that are less than or equal to 72 hours are allowed" and referred the site staff to the pharmacy manual for the storage requirements.	Section 6.3.3
To clarify the collection requirements if a weekly follow-up visit is close to the discharge visit the bold sentence has been added: The follow-up period for this protocol is approximately 4 weeks. Week 1, 2, 3, and 4 visits may be conducted as an inpatient visit, if the participant is still in the hospital, or as a telephone contact, if the participant has been discharged. Attempts should be made to have discharged participants return for one of these visits to be in person. The participant/participant's parent/guardian/LAR, as appropriate, will receive a follow-up contact weekly approximately 7 ± 3, 14 ± 3, 21 ± 3, and 28 ± 3 days following the IP discontinuation date. **If the hospital discharge visit corresponds to the Week 1, 2, 3, or 4 (± 3 days) visits it can take the place of the weekly visit.**	Section 7.1.3
Clarified that rapid EEG can be utilized to screen and enroll participations where a conventional EEG may not be available.	Section 7.2.2.1
Updated blood collection volumes to 48 to 59 mL for pediatric institutions and 140.3 to 190.4 mL for adult participants, based on the revisions to Table 1 and Table 2.	Section 7.2.4.3 (Tables 7 and 8)
The following text was added to the protocol to cover the expansion of the study to countries outside of the USA • **For ex-US countries, the Sponsor will comply with local laws and requirements with regard to SAE reporting** • European Public posting site, **Europe's website - Eudract.ema.europa.eu** • **All EU and UK based sites, laboratories, or entities providing support for this study, must, where applicable, comply with General Data Protection Regulation (GDPR) 2016/679 for the purposes of data protection and privacy.**	Sections 8.2.7, 11.1.2, and 11.4
Simplified the population definitions by removing the Enrolled and Randomized population definitions. Additional population data can be found in the SAP. Enrolled: All participants who signed the ICF and received a participant number. Randomized: All enrolled participants who received a randomization number and met all inclusion criteria and none of the exclusion criteria or received IP.	Section 10.3
Updated Reference 32 to the latest version of the investigator brochure	References
Updated the US-Marketed Products containing Captisol® to be the Global list of marketed products and removed the Sponsor	Appendix 4
Added Appendix 6 Summary of changes from Protocol Amendment 2	Appendix 6
Additional grammatical, typographical errors and formatting revisions have been made in the document but are not identified here	

APPENDIX 9 SUMMARY OF CHANGES FROM PROTOCOL AMENDMENT 4

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Date **13October2023**	**Global/Country/Site Specific** **Global**	
Description of Change and Rationale		**Section(s) Affected by Change**
Updated Additional Contact Information from Shawn Ironside to Kimberly Barber as Clinical Trial Manager and from Heather Van Heusen to Kathleen Cohen as Program Manager.		Additional Contact Information
The study was updated to include an option to transition to open-label treatment following the interim analysis of the study demonstrates efficacy. Updates were made as applicable throughout the protocol, including the following additions/clarifications: • Clarified that, based on the results of the interim analysis and recommendation from the DMC, the study will either continue as double-blind or will transition to open-label treatment. All participants subsequently enrolled will receive ganaxolone IV solution added to SE standard of care. • Clarified that the screening, duration of the treatment and follow-up periods as well as the study schedule remain the same for participants enrolled under either the double-blind or open-label phases. • Clarified that all references to randomization, placebo, blinding and unblinding are applicable to only the double-blind phase. • Open-Label Population added. • Clarified that all efficacy endpoints in the open-label phase will be summarized using descriptive statistics, and no formal hypothesis testing will be performed. • Revised the interim analysis section to include a transition to open-label treatment after a demonstration of efficacy, DMC recommendation, and Sponsor agreement. • Revised interim analysis to occur after two-thirds of the ITT population had completed 72 hours of efficacy assessments (approximately 41 participants per arm). • Number of participants to receive ganaxolone IV during both phases of the study specified as approximately 60 to 100 participants.		Throughout the document
The upper value of the mortality range for SE was changed from 26% to 40% to better reflect data from the literature.		Synopsis (Rationale)
Updated Status Epilepticus Cessation Questionnaire to be collected as close as possible to 24 and 72 hours following IP initiation		Synopsis (Safety and Assessments) Table 1, Section 7.2.2.7
Timing of the first weekly follow-up amended from 7 ± 3 to 6 ± 3 days.		Table 1
Additional background information relating to SE included. **In general, SE incidence varies from 9.9 to 41/100,000 per year with a bimodal age distribution. The youngest and oldest patients suffer from SE most often, specifically those in the first decade of life (14.3/100,000) and those over 60 years of age (28.4/100,000).[21] While the etiologies tend to be unique to specific age groups, the basic approach to treatment is similar across all ages and etiologies.[22,23] Treatment is**		Section 1.1

largely focused on rapid SE cessation, including initiation of drugs to terminate seizures and reversal of conditions that may lower seizure threshold. Potentiating GABAergic inhibition is a key mechanism to achieve rapid seizure cessation in both adults and children.	
Summary of nonclinical Captisol® data in rats added.	Section 1.2
Language for secondary objective updated to "To evaluate the sustained efficacy of ganaxolone IV beyond the 48-hour treatment period as assessed by prevention of progression to IV anesthesia for the treatment of SE" for clarity. Secondary objective "Determine the effect of ganaxolone on healthcare utilization" changed to an exploratory objective.	Synopsis (Objectives) Section 2.2
Expanded regions/sites to United States, Canada and Australia.	Synopsis (Site(s) and Region(s)) and Section 3.3
Inclusion criterion #3 updated to "approximately 6 minutes" for SE diagnosis as precise and prospective calculation of ictal burden by providers caring for patients at the bedside may result in delay of standard of care.	Synopsis (Inclusion and Exclusion Criteria) Section 4.1
The following exclusion criteria has been reinserted into Section 4.2 to align with the synopsis. **11. Known or suspected history or evidence of a medical condition that, in the investigator's judgment, would expose participant to an undue risk of a significant adverse event or would interfere with assessments of safety or efficacy during the study.**	Section 4.2
Inclusion of creatinine collection for urine chemistry evaluations alongside N-acetyl-β-D-glucosaminidase [NAG] and β2-microglobulin.	Synopsis (Safety and Assessments), Section 6.2.4, Section 7.2.3.7 (including Table 6)
The maximum dosing for Captisol® was clarified as 50 g/day **(1.25 g/kg/day in participants weighing <40 kg)** which corresponds to a maximum ganaxolone dose of 833 mg/day **(20.825 mg/kg/day in participants weighing <40 kg)**.	Synopsis (Rationale, Dose adjustments and interruptions), Section 6.2.7 Section 8.1.7
Pharmacokinetic blood collection time window updated for consistency within protocol and ganaxolone and Capitsol specified to be collected.	Synopsis (Safety and Assessments) Section 7.2.4.1
Total blood volume values corrected and assessment for IV AEDs row removed as no longer required per protocol.	Synopsis (Safety and Assessments) Section 7.2.4.3 and Table 8
Updated "Marinus Safety Department or its delegate" to Marinus **Drug** Safety **vendor**.	EMERGENCY CONTACT INFORMATION Sections 8.1.6, 8.1.7, 8.2.2, 8.2.4
Removed "A copy of the Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the Medical Monitor using the details specified in the emergency contact information section at the beginning of the protocol."	Section 8.1.6
Time to SE cessation following IP initiation designated as first key secondary endpoint. Secondary endpoint language expanded for consistency with primary endpoint to "**Proportion of participants with** no progression to IV anesthesia for 72 hours following IP initiation" and other secondary endpoint clarified as "**Proportion of participants whose treatment does not progress to** IV anesthesia for 4 weeks following IP initiation".	Synopsis (Endpoints, Statistical Methods) Section 10.4
Clarification added on the timing of the Healthcare Utilization endpoints as follows: • Time on positive pressure ventilation **after IP initiation**	Synopsis (Healthcare Utilization Endpoints) Section 10.4.4

• Proportion of participants requiring positive pressure ventilation initiated during IP infusion • Length of stay in intensive care unit and in hospital **after IP initiation.**	
Details for the pharmacokinetic analyses added to replace cross-reference to separate analysis plan.	Section 10.6
Additional grammatical, typographical errors and formatting revisions have been made in the document but are not identified here.	Throughout the document