PROTOCOL: 1042-SE-2001

TITLE:	A double-blind randomized, placebo-controlled study to evaluate the safety, tolerability, efficacy, and pharmacokinetics of intravenous ganaxolone as adjunctive therapy to treat subjects with status epilepticus
DRUG:	Ganaxolone
IND:	129,433
EUDRACT NO.:	TBD
SPONSOR:	Marinus Pharmaceuticals, Inc. 5 Radnor Corporate Center 100 Matsonford Road, Suite 500 Radnor, PA 19087 USA
PROTOCOL HISTORY:	Protocol Amendment 4: 07 August 2019, Version 5.0 Protocol Amendment 3: 24 January 2019, Version 4.0 Protocol Amendment 2: 10 May 2018, Version 3.0 Protocol Amendment 1: 26 January 2018, Version 2.0 Original Protocol: 29 September 2017, Version 1.0

PROTOCOL SIGNATURE PAGE

Sponsor's (Ma[redacted]ppr[redacted]

Signature:	**Date:** [redacted]
[redacted], M.D., Ph.[redacted] **Clinical Development**	

Investigator's Acknowledgement

I have read this protocol for Marinus Study 1042-SE-2001.

Title: A double-blind randomized, placebo-controlled study to evaluate the safety, tolerability, efficacy, and pharmacokinetics of intravenous ganaxolone as adjunctive therapy to treat subjects with 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 subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Conference on Harmonisation guidelines on Good Clinical Practice 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: (please hand print or type)	

Signature: _____ **Date:** _____

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **4**	**Amendment Date** **07 August 2019**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
Updated Marinus' office location and Marinus study team titles		Front page, Emergency Contact Information, Additional Contact Information
Added abbreviations		Abbreviations
Updated the estimated enrollment numbers		Synopsis and Section 3.1
Changed all protocol references of ganaxolone to ganaxolone IV solution; updated study drug formulation from the 3 mg/mL vials to 125 mL vials containing 100 mL of ganaxolone at a concentration of 1 mg/mL for the open-label group and study drug details for the double-blind group		Synopsis and Sections 3.1, 5.2.1, 6.1, 6.3.1, 6.3.2, 6.3.3, 8.2.1
Added qualifying text when referencing failure of first 2nd line IV AED therapy		Synopsis and Sections 2.2, 2.2.1, 3.1, 6.2.3, 7.1.2.1
Added need for IV anesthetic drugs as a secondary objective		Synopsis and Section 2.2.2
Added brivaracetam as a permitted IV AED and clarified that administering fosphenytoin and/or phenytoin will be counted as one (1) AED		Synopsis, Table 1 footnote h, and Sections 4.1, 5.2.2, 7.2.3.5
Updated study drug infusion doses (mg/hour and mg/kg/hour) and treatment duration (2 days which includes a 12-hour taper), and all references in the protocol that daily dose of ganaxolone is $\leq$ 830 mg/day, and that SE must be confirmed immediately prior to study drug bolus start		Synopsis, Table 1 and Sections 3.1, 6.2.3, Table 2 & 3, 7.1.2.1, 7.1.2.2
Revised the dosing regimen under the increased Captisol level with the caveat that the dose may be further adjusted based on safety and efficacy findings for the open-label group and communicated through a future Protocol Administrative Change Memo; deleted all references that "revisions will be incorporated into the next amendment of the Protocol"		Synopsis and Section 6.2.3
Updated the number of hours medical personnel must be present after start of study drug administration		Synopsis and Section 6.2.3
Added guidance for introducing new IV AEDs		Synopsis and Section 6.2.3
Added 2 scenarios for stopping study drug without a taper		Synopsis and Sections 6.2.3, 7.1.3
Added guidance regarding dose adjustments and interruptions and that the Marinus Medical Monitor must approve re-start of infusion for interruptions > 6 hours		Synopsis and Section 6.2.3
As there is no longer an option to extend the study drug treatment for four days, removed reference to EEG seizure burden calculation		Synopsis and Section 7.2.2.1
Updated the required and variable collection timepoints for safety and efficacy assessments/procedures; added Modified Ranking Scale (MRS), Full Outline of UnResponsiveness (FOUR) Scale and Intubation Question; added 2 questions to the Seizure and SE		Synopsis, Table 1, and Sections 7.2.2.1, 7.2.2.2, 7.2.2.3, 7.2.2.4, 7.2.2.5, 7.2.2.6,

Questionnaire. Removed collection timepoints from specific assessment/procedure text in Section 7	7.2.2.7, 7.2.3.3, 7.2.3.4, 7.2.3.6, 7.2.3.7, 7.2.3.8
Expanded collection requirements for Blood Gas	Synopsis, Table 1 footnote n, and Section 7.2.3.5
Added guidance on the collection locations for the pharmacokinetic and neurosteroid samples	Synopsis, Table 1 footnotes l and m, and Section 7.2.4.1, Table 4 and 5
Added collection requirements for cerebral spinal fluid, if a lumbar puncture is performed per investigator's discretion as part of their care, and if there is adequate volume for future analysis of ganaxolone	Synopsis, Table 1 footnote o, and Section 7.2.4.3.1, 9.9
Listed examples of IV anesthetics including ketamine	Synopsis, Table 1 footnote u, and Sections 4.2,5.2, 5.2.2,7.1.3
Added that "a 4th line treatment", "a 4th line treatment e.g., immunosuppressants, magnesium" is prohibited	Synopsis and Sections 5.2.2, 6.2.3, 7.1.3
Modified when AEs and concomitant medications will be collected and added specific AEs that need to be recorded during the weekly follow-up visits.	Synopsis, Table 1, and Sections 5.2, 8.1,
Modified exclusion criterion #8 to exclude subjects who are currently on dialysis but allow subjects to start dialysis during the study	Synopsis and Sections 4.2, 4.5.1
Modified secondary endpoints for level of responsiveness to include the Four Score Scale and RASS; for clinical outcome the Modified Ranking Scale will be used; for hospital metrics including length of stay, need for and duration of intubation and mechanical ventilation.	Synopsis and Sections 2.2, 9.7.2
Table 1 Visit/Timepoint or Duration updated to support revised study design; footnotes updated to support revised required and variable collection timepoints	Table 1
Updated the Study Flow Diagram to reflect the revised dosing regimen.	Figure 1
Added clarity for subjects who discontinue by separating subjects who discontinue from study drug and subjects who withdrawal from the study	Section 4.5
Removed duplicate text describing prior concomitant treatment; revised collection requirements for concomitant treatment	Section 5.1
Expanded the guidance on administration of background oral AEDs if their administration is interrupted during the study	Section 5.2.2
Added statement that the Investigator's Brochure has not been updated with the 1 mg/mL, ganaxolone IV solution formulation at this time but will be amended with the annual update	Section 8.2.1
Updated timeline for entering data into EDC	Section 9.1
Added exploratory endpoints to assess pressor administration and treatment of severe cardiovascular and respiratory events	Section 9.7.3
Added that APACHE or APACHE 2 score may be used as a prognostic tool in calculating mortality	Section 9.8

Updated the Study Decision Tree	Appendix 1
Added Summary of Changes Table from Protocol Amendment 3	Appendix 2
Revisions made in the document to standardize text throughout the protocol such as: study drug initiation for dose initiation and dose start; study drug discontinuation for study drug stop; 24-hour post taper to in-patient follow-up day; subject for participant	
Additional grammatical, typographical errors and formatting revisions have been made in the document but are not identified here	

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 Safety Department or delegate. A copy of this form must also be sent to the contract research organization (CRO)/Marinus Medical Monitor by e-mail using the details below.

Email: safetySE2001@marinuspharma.com

Fax: +1 484-679-2151

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

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

If unavailable**:**
[redacted] **M.Ed.**
[redacted] Clinical Development Operations
Marinus Pharmaceuticals, Inc.
Email: [redacted]
Office Telephone Number: [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 Trial Manager:

Marinus Program Manager:
[redacted] **M.Ed.**
[redacted] Clinical Development Operations
Marinus Pharmaceuticals, Inc.
Email: [redacted]
Office Telephone Number: [redacted]
Mobile Telephone Number: [redacted](primary contact method via text or call)

Marinus Trial Manager:
[redacted] **BSN**
[redacted]
Marinus Pharmaceuticals, Inc.
Email: [redacted]
Office Telephone Number: [redacted]
Mobile Telephone Number: [redacted](primary contact method via text or call)

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ABBREVIATIONS

AE	adverse event
AUC	area under the curve
ALT	alanine Aminotransferase
AST	aspartate Aminotransferase
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
C_{max}	peak plasma concentration
CRA	clinical research associate
CRO	contract research organization
CSE	convulsive status epilepticus
CSF	cerebral spinal fluid
DMC	data monitoring committee
EC	ethics committee
ECG	electrocardiography
eCRF	electronic case report form
EEG	electroencephalography
eGFR	estimated glomerular filtration rate
ESE	established status epilepticus
EU	European Union
FDA	Food and Drug Administration
FOUR	Full Outline of UnResponsiveness
G	gram
GABA	gamma-aminobutyric acid
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GCSE	generalized convulsive status epilepticus
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation

ILAE	International League Against Epilepsy
IM	intramuscular
IRB	Institutional Review Board
IV	intravenous
LAR	legally authorized representative
MG	milligram
MMSE	Mini Mental State Exam
MRS	Modified Rankin Scale
NCSE	Non-convulsive status epilepticus
PGCS	Pediatric Glasgow Coma Scale
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

STUDY SYNOPSIS

Protocol number: 1042-SE-2001	**Drug:** ganaxolone
Title of the study: A double-blind randomized, placebo-controlled study to evaluate the safety, tolerability, efficacy, and pharmacokinetics of intravenous ganaxolone as adjunctive therapy to treat subjects with status epilepticus	
Number of subjects (total and for each treatment arm): A total number of approximately 340 subjects will be screened to allow for up to approximately 272 subjects to receive study drug. Open-label pharmacokinetic group: This open-label pharmacokinetic group will enroll up to approximately 30 males and females, at least 12 years of age to confirm that the dose selected will achieve an approximate targeted plasma concentration of ganaxolone in the status epilepticus (SE) population who are on concomitant medications, and to obtain a preliminary assessment of safety, efficacy and feasibility of ganaxolone administration. Enrolled subjects will receive ganaxolone IV solution as adjunctive therapy to their standard of care. Subjects who early terminate for reasons other than lack of efficacy or adverse events related to ganaxolone (e.g., pump failure and other operational issues) may be replaced. Double-blind group: This double-blind, placebo-controlled group will screen a sufficient number of subjects to randomize 242 males and females, at least 12 years of age with SE. Randomized subjects will receive ganaxolone IV solution or placebo in a 1:1 ratio as adjunctive therapy to their standard of care.	
Investigator(s): Multicenter study	
Site(s) and Region: Multicenter study to be conducted globally at approximately 150 sites	
Study period (planned): June 2018 to May 2020	**Clinical phase:** 2
Objectives: **Primary:** • To establish that intravenous ganaxolone given concomitantly with 2nd line IV AED therapy is safe and effective in stopping status epilepticus that has already failed one 2nd line IV AED therapy that has been administered at an appropriate dose and duration to show efficacy and prevents escalation of treatment requiring an IV anesthetic drug (a 3rd line treatment) for seizure suppression **Secondary:** • To assess other secondary efficacy endpoints such as mortality and seizure cessation in SE subjects • To assess the pharmacokinetics of adjunctive IV ganaxolone in SE subjects • To assess the need for IV anesthetic drugs for treatment of current SE event in SE subjects	

Exploratory:

- [redacted]
- [redacted]

Rationale:

Status epilepticus (SE) is defined as a prolonged self-sustaining seizure or recurrent seizures without recovery of consciousness between seizures. [1] The International League of Against Epilepsy 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 abnormally, prolonged seizures (5 minutes for tonic-clonic SE and 10 minutes for focal SE with impaired consciousness) and which can have long-term consequences (after 30 minutes for tonic-clonic SE and >60 minutes for focal SE with impaired consciousness), including neuronal death and/or injury, and alteration of neuronal networks, depending on the type and duration of seizures.[1] SE is a neurological emergency that requires aggressive treatment to stop the seizures and prevent permanent neurological damage.[3] Mortality due to SE can range from 3% to 40% depending on etiology, age, SE type, and SE duration.[5] SE can be recognized clinically or using electroencephalograms (EEGs) by the presence of continuous ictal discharges.[3] Studies have shown that SE can cause neuronal death via excitotoxic mechanisms as a result of excessive neuronal firing.[6] Furthermore, convulsive SE is associated with many complications, including cardiac arrhythmias, rhabdomyolysis, pulmonary edema, electrolyte and glucose imbalance, and temperature disturbances. Approximately one third of subjects with refractory status epilepticus (RSE) and super refractory status epilepticus (SRSE) will die of their condition; one-third recover but with chronic neurologic or other deficits, and one third have been generally described as returning to baseline. The prognosis worsens the longer subjects are kept in a medically-induced coma. The primary goal of SE treatment is to gain control of the seizures rapidly and avoid complications, and treatment typically occurs in stages.[2] In general, the treatment of SE is very aggressive and particularly urgent for convulsive status epilepticus (CSE).

The current therapies for SE have inherent risks, which must be balanced against the benefit of rapid seizure control. Benzodiazepines are the agents of choice for first line treatment of SE but their use can cause respiratory depression and hypotension, requiring the use of supportive therapies.[2] Unfortunately, approximately 35-45% of patients are refractory to benzodiazepines. Second line therapy involves administration of an IV AED such as fosphenytoin, valproic acid, or levetiracetam for convulsive tonic-clonic status with the goal of stopping SE in patients who did not respond to first line treatment.[2] When a patient with SE fails to respond to a benzodiazepine and the initial 2nd line [AED] therapy they are classified as having RSE. RSE develops in 31-44% of patients with SE, with a mortality of 16-39%.[17,19] Additional therapeutic agents are required immediately; typically, anesthetics via continuous infusion.[2] Currently, the recommended anesthetic drugs include midazolam, propofol, thiopental, and pentobarbital. Anesthetics are associated with risks, especially if administered for a long time - propofol infusion syndrome and hypotension are two recognized adverse events associated with anesthetics for SE treatment. In addition, the need for assisted ventilation and the management of hypotension and cardiopulmonary depression have their own risks.[2]

Few therapies are approved for the treatment of SE and the urgent need for more efficacious therapies remains. Only two-thirds of patients in SE respond to first-line treatment.[3] Resistance to treatment has been partially attributed to the internalization of post-synaptic $GABA_A$-receptors and

externalization of glutamate receptors.[3] As prolonged epileptiform bursting results in a reduction of $GABA_A$-mediated synaptic inhibition, antiepileptic treatments which rely on enhancing intra-synaptic $GABA_A$ neurotransmission become less effective the longer SE continues.

Ganaxolone is a potent allosteric positive modulator of $GABA_A$ receptors in the brain at a site distinct from the site of action of benzodiazepine receptor agonists and barbiturates. γ-aminobutyric acid (GABA) is recognized as the principal inhibitory neurotransmitter in the cerebral cortex, and a disturbance in GABA-mediated functions results in the occurrence of epileptic seizures.[5] By enhancing the $GABA_A$ receptor function, ganaxolone provides an alternative mechanism in the treatment of seizures, and serves as effective therapy in the management of SE. Ganaxolone has been shown to stop SE in 2 distinct pre-clinical models of benzodiazepine-resistant SE.

Ganaxolone for this study is a proprietary IV formulation solubilized by Captisol® (betadex sulfobutyl ether sodium). The study targets plasma concentrations of ganaxolone that mimic concentrations associated with anticonvulsant effects in preclinical animal models of SE and that are expected to demonstrate anticonvulsant properties in humans.

The maximum level of Captisol® will not exceed 50 grams per day as agreed upon with the FDA.

Study drug, Dose, and Mode of Administration:

Once consent has been obtained, the study drug, ganaxolone IV solution for the open-label group and ganaxolone IV solution or placebo for the double-blind group, will be added to standard of care. The study drug will be added from the time that the first 2nd line IV AED, administered at an appropriate dose and duration to show efficacy, has failed and the second 2nd line IV AED is medically indicated.

To reduce variability in the population being assessed, the concurrent 2nd line IV AED therapy will be limited to fosphenytoin/phenytoin, valproic acid, levetiracetam, lacosamide, or brivaracetam. Taking any of these drugs alone or in combination is acceptable. Administering fosphenytoin and/or phenytoin will be counted as one (1) AED.

Ganaxolone IV solution for administration will be provided to the site as individual 125 mL vials containing 100 mL of 1 mg/mL of ganaxolone for the open-label group. Details of packaging, dose and administration of the ganaxolone IV solution and placebo for the double-blind group will be included in a future protocol amendment.

Study drug should be administered, preferably, through a dedicated (peripheral or central) IV line. The infusion parameters result in daily doses of ganaxolone of ≤ 830 mg/day and Captisol of ≤ 50 g/day as agreed upon with the FDA. Based on PK modeling, it is predicted that maximum concentrations of ganaxolone should remain within 1,000 ng/mL during infusion, but some variability is expected due to, for example, differences in subjects' weight. Note, at any time the infusion rate of the ongoing administration may be decreased for safety reasons.

Study drug will be administered as a 3-minute bolus, with a continuous infusion at the rate between 20-80 mg/hour for 36 hours, and a 12-hour study drug taper. The presence of SE must be confirmed immediately prior to the study drug bolus. Once study drug administration is started it should be delivered for 2 days (48 hours) which includes a 12-hour taper.

Subjects 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 (24-36 hours) the continuous infusion rate of 20 mg/hour will continue until the start of the study drug taper at 36 hours post study drug initiation. If needed, to manage seizure relapse or another medical reason, the infusion rate can be increased from 20 mg/hour up to a maximum rate of 45 mg/hour at any time during hours 24-36 of Day 2.
- To taper the study drug, the infusion rate at the 36-hour post study drug initiation timepoint will be reduced by 33.3% every 4 hours until the infusion 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, the second taper will be 33.3% from the first tapered infusion rate, and the final taper will be 33.3% from the previous tapered infusion rate. If, per the investigator's judgment, the study drug 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.
- At the time the study drug infusion is discontinued the subject will progress to the in-patient follow-up day assessments/procedures.

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

- A 0.43-mg/kg bolus dose (over ~3 minutes) will be administered with a continuous infusion at a dose of 1.14 mg/kg/hour for 2 hours followed by a continuous infusion dose of 0.57 mg/kg/hour for 10 hours, and 0.29 mg/kg/hour for the remaining 12 hours of Day 1.
- On Day 2 (24-36 hours) the continuous infusion dose of 0.29 mg/kg/hour will continue until the start of the study drug taper at 36 hours post study drug initiation. If needed, to manage seizure relapse or for another medical reason, the infusion dose can be increased from 0.29 mg/kg/hour up to a maximum of 0.64 mg/kg/hour at any time during hours 24-36 of Day 2.
- To taper the study drug, the infusion rate at the 36-hour post study drug initiation timepoint will be reduced by 33.3% every 4 hours until the infusion 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, the second taper will be 33.3% from the first tapered infusion rate, and the final taper will be 33.3% from the previous tapered infusion rate. If, per the investigator's judgment, the study drug taper needs to start at an earlier timepoint in the treatment period, the infusion rate at the start of the first taper will be decreased by 33.3% every 4 hours as described.
- At the time the study drug infusion is discontinued the subject will progress to the in-patient follow-up day assessments/procedures.

Medical oversight, new AED introduction, and additional dosing and study drug tapering details:

- Medical personnel must be present at all times during at least the first 3 hours after the start of the study drug administration. Then close monitoring of the subject by the study staff will continue as medically needed throughout the study.
- IV AED introduction:
    - For the first 10-hours of study drug administration, the decision to initiate new IV AEDs should be based on safety or efficacy and confirmed by relapsing clinical presentation or electrographic activity. Initiation of any new AEDs prophylactically (so called "transition/bridging") is not recommended, unless medically indicated.
    - In the event of safety or efficacy presentation, i.e. seizure relapse, that would prompt the investigator to make a treatment intervention, introduction of a new IV AED is recommended over immediate progression to a 3rd line agent, however all treatment decisions are at the investigator's discretion.
    - After the first 10-hours investigators are encouraged to initiate "transition/bridging" AEDs in anticipation of the study drug taper at 36-hours post study drug initiation on Day 2.

Study Drug Tapering:

- The scenarios for stopping the study drug without a taper include:
    - For subjects who receive study drug for less than 2 hours and/or
    - Study drug infusion is discontinued or interrupted, and the decision is made to not restart the infusion and/or
    - If at any time during study drug administration the subject progresses to an IV anesthetic drug (a 3rd line and/or 4th line treatment) for seizure suppression or
    - It is no longer safe to continue drug administration per the investigator's medical judgment.
- During the open-label group, based on the safety, efficacy, and pharmacokinetic data from the ongoing study, the infusion parameters in subsequent subjects may be adjusted to maximize the safety and efficacy of study subjects. If the infusion parameters are amended, the new infusion parameters will not exceed the daily limit of 50 g/day Captisol (≤ 830 mg/day ganaxolone) as agreed upon with the FDA. The revised infusion parameters will be communicated to Clinical Sites in a Protocol Administrative Change Memo and kept in the study and site files.
- Note, the infusion rate cannot be rounded-up for any subject regardless of weight; ≥ 40 kg or < 40 kg.
- For study drug dosing instructions reference the Pharmacy Manual.

Dose Adjustments and Interruptions:

As a general rule, dose (infusion rate) decreases and interruptions of the continuous infusion are discouraged at any time during study drug treatment. However, if there is an urgent medical need (e.g., severe hypotension, acidosis, severe sedation) or a subject's standard of care requires they undergo a procedure for which the infusion rate would need to be decreased or interrupted (e.g., an

MRI scan) it should be kept as short as possible but no longer than 6 hours. If > 6 hours the Marinus Medical Monitor must approve the re-start of the infusion.

Note:

- After the dose (infusion rate) decrease or infusion interruption, it will be per the investigator's judgment and assessment of risk/benefit if the subject should continue in the study or early discontinue.
- In cases when severe sedation is seen and early drug discontinuation is being considered, the Marinus Medical Monitor should be contacted prior to infusion termination, if feasible.
- If the decision is made for the subject to continue in the study, the infusion should be re-started at the rate matching the rate at the corresponding nominal time, counted from the start of the study drug infusion on Day 1. A study drug bolus or "catch-up" dose to deliver the study drug that was missed during the interruption should not be administered.
- Dose (infusion rate) increases above those specified in the protocol (or based on a future Protocol Administrative Change Memo) are not allowed at any time during infusion. This is to ensure daily Captisol and ganaxolone limits are kept ≤ 50 g/day and ≤ 830 mg/day, respectively.

Methodology:

This is a double-blind, randomized, placebo-controlled study to evaluate the safety, tolerability, efficacy of adjunctive ganaxolone IV solution in subjects with SE. This study will start with a small open-label group to confirm that the dose selected will achieve a potentially therapeutic exposure (bolus plus continuous infusion) to stop SE. The dose selected for Day 2 is designed to provide a stable plasma concentration to maintain status cessation. If needed, doses in the open-label group portion of the study may be adjusted based on the dosing and pharmacokinetic/safety profile from the subject's enrolled.

As previously described, the study drug will be added to the standard of care from the time that the first 2nd line IV AED, administered at an appropriate dose and duration to show efficacy, has failed and the second 2nd line IV AED is medically indicated during the treatment of SE. Study drug must be administered with the 2nd line IV AED treatment and should be initiated as close to the initiation of the second 2nd line IV AED as possible.

Potential subjects are anticipated to be identified in the emergency department and/or hospital in-patient or intensive care units.

Upon identification, subjects will be administered consent/assent and then screened for inclusion/exclusion criteria prior to receiving study drug as adjunctive therapy via continuous IV infusion, followed by a 12-hour study drug taper. As soon as the study drug administration is completed (with or without taper), subjects will have a 24-hour in-patient follow-up day and then follow-up visits/contacts at weeks 2, 3, and 4. For subjects who have the 12-hour study drug taper, the in-patient follow-up day starts as soon as the 12-hour study drug taper is complete. If the infusion rate becomes too low to sustain the infusion line, it can be discontinued at that point and the subject will progress into the in-patient follow-up day. For subjects where there is no study drug taper the in-patient follow-up day starts as soon as the study drug administration is discontinued. These subjects will continue with the week 2, 3, and 4 follow-up visits.

If the subject remains hospitalized, the week 2, 3, and 4 visits will be done in-person. If the subject has been discharged, these visits may be conducted via telephone call. However, it is recommended

that discharged subjects return so at least one of these visits will be conducted in-person. In total, each subject will be followed for approximately 4 weeks after the initiation of study drug.

Screening

Procedures specific to this protocol will not be performed until written informed consent/assent from the subject/parent/guardian/legally authorized representative (LAR) has been appropriately obtained per the investigator's hospital policy. As many of the subjects will not be able to provide consent/assent, the parent/guardian/LAR will provide consent on behalf of the subject to participate in the study. As soon as the subject is able, per the investigator's hospitals guidelines, consent/assent will be administered to them for continued participation. Consent/assent for subjects who are known to be at risk for SE may be obtained prior to an SE event.

Treatment and Follow-up

Study Drug Dosing

Up to approximately 30 subjects will be enrolled into the open-label group with ganaxolone and up to approximately 242 subjects will be randomized into the double-blind group. Subjects in the double-blind group will be randomized (1:1) to receive either ganaxolone IV solution or placebo with concurrent standard of care treatment. Study drug will be given as a bolus plus continuous infusion.

After study drug initiation, the standard duration of treatment is 2 days which includes a 12-hour study drug taper.

Safety and Assessments

Study drug will be given in addition to standard of care for SE and medical or surgical interventions deemed appropriate by the investigator. In addition to the medically indicated treatment, safety and tolerability will be monitored by but not limited to the following:

1. Physical examinations should be completed at:
    a. Pre-dose (screening) or, if not available, within 2 hours of study drug initiation, and at 36-hours (+/- 1-hour),
    b. Time of study drug discontinuation, either at the end of the study drug taper or if the study drug is stopped without a taper and
    c. 24-hours (+/- 1-hour) after study drug discontinuation.
    d. If possible, for subjects who early terminate, collect at the time early termination is being considered and as close as possible to the end of the study drug administration.
    e. Any time, if medically indicated, per investigator's judgment.
2. Status Epilepticus Severity Score (STESS) should be collected pre-dose (screening).
3. Vitals and the Glasgow Coma Scale (GCS) or Pediatric Glasgow Coma Scale (PGCS), Richmond Agitation and Sedation Scale (RASS), and the Full Outline of UnResponsiveness (FOUR) Score scales should be collected at:
    a. Pre-dose (screening), 60-minutes (+/- 15-min), 2- (+/- 15-min), 10-, 24-, and 36-hours (+/- 1 hour) after study drug initiation,
    b. Time of study drug discontinuation, either at the end of the study drug taper or if the study drug administration is stopped without a taper and
    c. 24-hours (+/- 1-hour) after study drug discontinuation.
    d. If possible, for subjects who early terminate from the study, collect at the time early termination is being considered and as close as possible to the end of the study drug administration.

e. Any time, if medically indicated, per investigator's judgment.

Weight and height should be collected pre-dose (screening) for calculation of the BMI inclusion criterion, if feasible. If not collected pre-dose (screening), collect prior to the end of the in-patient follow-up day.

4. Mini Mental State Examination (MMSE) should be performed at:
    a. The time consent/assent is administered to the subject for continued participation and then on the in-patient follow-up day.

    If the MMSE is not able to be assessed due to the subject's state, this should be recorded.
5. Electrocardiogram (ECG), the subject should have an ECG at:
    a. Pre-dose (screening), 2- (+/- 30-min) and 36-hours (+/- 1-hour) after study drug initiation,
    b. Time of study drug discontinuation; either at the end of the study drug taper or if the study drug administration is stopped without a taper and
    c. 24-hours (+/- 1-hour) after study drug discontinuation.
    d. If possible, for subjects who early terminate from the study, collect at the time early discontinuation is being considered and as close as possible to the end of the study drug administration.
    e. Any time, if medically indicated, per investigator's judgment.
6. Clinical laboratory measures, hematology, serum chemistry (including creatinine, blood urea nitrogen, and estimated glomerular filtration rate calculation), and concomitant AED levels (fosphenytoin/phenytoin, valproic acid, levetiracetam, lacosamide, or brivaracetam, if available), and Urinalysis (including urine protein, albumin and microscopic), should be collected at:
    a. Pre-dose (screening), if available, or within 2 hours of study drug initiation, at 24- and 36-hours (+/- 1-hour) after study drug initiation,
    b. Time of study drug discontinuation, either at the end of the study drug taper or if the study drug administration is stopped without a taper and
    c. 24-hours (+/- 1-hour) after study drug discontinuation.
    d. One of the weekly follow-up visits (week 2, 3, or 4) for subjects in-house and if possible, for subjects who have been discharged.
    e. If possible, for subjects who early terminate from the study, collect at the time early termination is being considered and as close as possible to the end of the study drug administration.

    Variable collections based on subject response:
    f. After the initial SE cessation, AED levels should be collected at time of first instance of seizure activity or SE relapse.

    Between study drug initiation and the in-patient follow-up day, where possible, collect a sample:
        i. If the decision is made to intubate the subject
        ii. At the time of a serious adverse event (related or not related)
    g. Any time, if medically indicated, per investigator's judgment.
7. Drugs of abuse (urine or serum), including alcohol testing and Pregnancy test (urine or serum) for women who are of childbearing potential, should be collected pre-dose (screening). If not possible to collect pre-dose, collect as soon as possible after start of study drug infusion. Enrollment is not contingent upon results. However, if a subject has a positive test result, it will be at the investigator's discretion to weigh the risks verses benefits for the

subject's continued participation. If the investigator decides to discontinue the study drug, refer to the study drug taper directions in the Study drug, Dose, and Mode of Administration section.

8. EEG is required for confirmation of non-convulsive status epilepticus (NCSE) diagnosis. Ideally, continuous EEG monitoring should start before study drug initiation and continue through the in-patient follow-up day. If continuous EEG is not possible or needed to diagnose (for convulsive SE) it should be instituted at the earliest possible time after study drug initiation (if a pre-dose EEG was not performed for the diagnosis of convulsive SE). Several study sites may be offered the use of a rapid EEG device to assist with pre-screening of subjects with NCSE. It will be at the investigator's discretion if they feel the device will benefit their site. More details can be found in Section 7.2.2.
9. Blood sampling for pharmacokinetic analysis (venous or arterial) of ganaxolone will be collected at the following times:
   Required collections:
   a. After the start of the study drug infusion: 60-minutes, then 2-, 4-, 8-, 10-, 24- and 36-hours,
   b. At the time of study drug discontinuation, either at the end of the study drug taper or if the study drug administration is stopped without a taper and
   c. 24-hours after study drug discontinuation.

   Variable collections based on subject response:
   d. After the initial SE cessation, collect a sample at the first instance of seizure activity or SE relapse and the subject does not progress to an IV anesthetic drug (a 3rd line treatment, e.g. midazolam, propofol, thiopental, pentobarbital, or ketamine)

   Between study drug initiation and the in-patient follow-up day, where possible, collect a sample:
   i. If the decision is made to intubate the subject
   ii. At the time of introduction of a new IV AED for safety/efficacy (not for AEDs given prophylactically for "transition/bridging")
   iii. At the time of any serious adverse event (related or not related)

   If study drug is administered via central access, the PK sample must not be collected from any central access ports. If study drug is administered via venous access, the PK sample must be collected via the contra-lateral arm of the study drug arm. The location of study drug access and location of PK sample collection should be documented in the subject's source. If the PK sample cannot be collected due to poor venous access and the study drug infusion site is the only viable option, the specimen should not be collected and the reason for non-collection documented in the subject's source.
10. Blood sampling for neurosteroid levels (venous or arterial) will be collected pre-dose (screening) and at 24-hours (+/- 1-hour) of study drug initiation. If study drug is discontinued during this 24 hours, the second sample should be collected prior to study drug discontinuation, if possible.
    The same collection rules as noted for pharmacokinetic sample collection apply for the neurosteroid sample collection.
11. Blood gas including FiO_2, PaO_2, and arterial pH, if collected per the investigator's discretion for subject's care, from the time of SE diagnosis through the of the in-patient follow-up day and recorded in the eCRF. If samples are not collected, a sample is not required.

However, if the decision is made to intubate the subject from study drug initiation through the end of the in-patient follow-up day, 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. During the study, it is expected that the total blood volume drawn from subjects for all safety, pharmacokinetic, and neurosteroid sampling at pediatric-only hospitals is approximately 62 to 88 mL of blood and at all other hospitals approximately 192.6 to 278.3 mL of blood, regardless of sex.

12. Cerebral Spinal fluid sample collection: If a subject has a lumbar puncture for the collection of cerebral spinal fluid (CSF) per investigator's discretion as part of their care and there is adequate volume, a sample will be aliquoted for future analysis of ganaxolone. If multiple lumbar punctures are performed, a sample from each puncture is requested. However, if not collected or not enough CSF is available to provide a sample for the study, a sample is not required.
13. Clinical Global Impression of Severity and Improvement (CGI-S and CGI-I, respectively)

CGI-S is collected at:

a. Pre-dose (screening) and 36-hours (+/- 1-hour) after study drug initiation,
b. Time of study drug discontinuation, either at the end of the study drug taper or if the study drug administration is stopped without a taper and
c. 24-hours (+/- 1-hour) after study drug discontinuation.
d. Week 2, 3, and 4 follow-up visits (in-person or via telephone call).
e. If possible, for subjects who early terminate from the study, collect at the time early termination is being considered and as close as possible to the end of the study drug administration.
f. Any time, if medically indicated, per investigator's judgment.

CGI-I is collected at:

a. Within the first 2 hours of study drug initiation and 36-hours (+/- 1-hour) after study drug initiation,
b. Time of study drug discontinuation, either at the end of the study drug taper or if the study drug administration is stopped without a taper and
c. 24-hours (+/- 1-hour) after study drug discontinuation.
d. Week 2, 3, and 4 follow-up visits (in-person or via telephone call).
e. If possible, for subjects who early terminate from the study, collect at the time early termination is being considered and as close as possible to the end of the study drug administration.
f. Any time, if medically indicated, per investigator's judgment.

14. Modified Rankin Scale (MRS) should be collected at:
    a. Time of study drug discontinuation, either at the end of the study drug taper or if the study drug administration is stopped without a taper and
    b. 24-hours (+/- 1-hour) after study drug discontinuation.
    c. Week 2, 3 and 4 follow-up visits (in-person or via telephone call).
    d. If possible, for subject's who early terminate from the study, collect at the time early termination is being considered and as close as possible to the end of the study drug administration.
    e. Any time, if medically indicated, per investigator's judgment.
15. Status Epilepticus and Seizure Questions should be collected at:

a. 15-minutes (+/- 5-min), 30-, 60-minutes (+/- 15-min), 2- , 4-, 6-, 8-,10-, 12-, 18- (+/- 30-min), and 24- and 36-hours (+/- 1 hour) after study drug initiation,
b. Time of study drug discontinuation, either at the end of the study drug taper or if the study drug administration is stopped without a taper and
c. 24-hours (+/- 1-hour) after study drug discontinuation.
d. Week 2, 3, and 4 follow-up visits (in-person or via telephone call).
e. If possible, for subjects who early terminate from the study, collect at the time early termination is being considered and as close as possible to the end of the study drug administration.

Assessment questions:

1. Is the subject in SE currently?
2. Was the subject in SE since the previous assessment?
   (Note: N/A for the 15-minute timepoint)
3. Is the subject having seizures currently?
4. Did the subject have seizures since the previous assessment?
   (Note: N/A for the 15-minute timepoint)
5. Have any new* AEDs been initiated since the last assessment?
   (Note: "New" refers to any AED that has not already been used to treat the current episode of SE)
6. If a new AED was initiated, was it to treat the current seizure/SE episode or initiated prophylactically (e.g., for transition/bridging), or other reason?
   (Note: "Prophylactic" refers to any elective/transitional/bridging AED therapy that is not indicated to treat seizure/EEG abnormal activity at this time or since the last assessment)
   Record any new AEDS on the concomitant eCRF page.

16. Intubation Question will be collected for subjects who are intubated either prior to study drug initiation or anytime through the end of the in-patient follow-up day:
    a. 18- (+/- 30-min), 24-, and 36-hours (+/- 1 hour) after study drug initiation,
    b. Time of study drug discontinuation, either at the end of the study drug taper or if the study drug administration is stopped without a taper and
    c. 24-hours (+/- 1-hour) after study drug discontinuation.

    Assessment point:

    1. Per your evaluation has the subject's medical condition improved enough to warrant considering extubation?

17. Adverse events (AEs) and Concomitant medications: AE's will be collected throughout the study via non-direct questioning. Concomitant medications will be collected during the same time period however, the collection requirements will differ depending on the subject's treatment progression as defined below.
    a. All adverse events and associated concomitant medications will be collected through the in-patient follow-up day.
    b. IV anesthetic agents (midazolam, propofol, thiopental, pentobarbital, or ketamine) administered during the study drug treatment period and the in-patient follow-up day should be followed through the week 4 visit/contact.
    c. During the weekly follow-up visits, only ongoing AEs and new AEs assessed by the investigator to be related to study drug will be recorded and the concomitant medications associated with these AEs.

d. In addition, during the weekly follow-up visits, AEs of urinary tract infection (UTI), hospital-acquired/ventilator-associated pneumonia, myocardial infarction (MI), sepsis from any source, critical illness myopathy/neuropathy, significant hypotension requiring support of vasopressors will be recorded regardless of relatedness. Associated concomitant medications for these AEs will not be recorded.
e. All SAEs regardless of relationship to study drug and their associated concomitant medications will be recorded from the time of study drug initiation through the last follow-up visit/contact.
f. For subjects who early terminate 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.

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

Study Follow-up and Discontinuation:
Subjects who discontinue study drug without a taper, e.g., takes study drug for less than 2 hours or progresses to an IV anesthetic drug (a 3rd line treatment) for seizure suppression or discontinues the study medication due to safety reasons will continue in the study and still have the in-patient follow-up and the week 2, 3, and 4 follow-up visits/contacts.

Subjects who early terminate from the study, e.g., due to consent withdrawn, should have the early termination procedures completed when early termination is being considered and as close as possible to the end of the study drug administration.
All subjects, except those who are early terminated from the study, will have the in-patient follow-up day and the follow-up visits/contacts at Weeks 2, 3, and 4. If the subject remains hospitalized these visits will be done in person but if the subject has been discharged these contacts will be conducted via telephone call. Even if a subject has been discharged, efforts will be made to have the subject return so at least one of the visits will be conducted in-person. These visits will be conducted weekly, starting approximately 7 ± 3 days after the in-patient follow-up day.

During these visits/calls, the site will follow-up on all serious adverse events (SAEs) and non-serious adverse events (AEs), AE resolution that occurs, and concomitant medications. In total, each subject will be followed for approximately 4 weeks.

Inclusion and Exclusion Criteria:

Inclusion Criteria:

1. Subject, subject's parent, guardian, or LAR must provide signature of informed consent, and, once capable (per the investigator's hospital guidelines), there must be documentation of consent/assent by the subject indicating the subject is aware of the investigational nature of the study, is able and willing to participate in the study, and is aware of the required restrictions and procedures
2. Male or female subjects 12 years of age and older at the time of the first dose of study drug
3. Clinical and/or electrographic seizures defined as:
    - Documented clinical seizures (convulsive SE): greater than 5 minutes' duration prior to treatment with study drug (per International League Against Epilepsy, ILAE)
      or

- Electrographic criteria (one must apply):
  - 10 minutes of continuous seizure activity on EEG (per ILAE)
  - Intermittent EEG seizure activity for more than 50% of the previous 60 minutes
  - If less than 60 minutes of EEG is available, then intermittent electrographic seizure activity must be present for greater than 50% of the available duration of the EEG AND the electrographic seizure activity must be at least 10 minutes when taken in aggregate

4. Subject on concurrent 2nd line IV AED therapy with fosphenytoin/phenytoin, valproic acid, levetiracetam, lacosamide, or brivaracetam for the management of the current episode of SE
5. BMI < 40 or, if not able to be calculated at screening, assessed by investigator as not morbidly obese

Exclusion Criteria:

1. Life expectancy of less than 24 hours
2. Anoxic brain injury as the primary cause of SE
3. Recent (< 24 hour) traumatic brain injury as the primary cause of SE
4. Administered anesthesia (3rd line treatment, e.g., midazolam, propofol, thiopental, pentobarbital, or ketamine) at adequate doses and duration for the treatment of the current episode of SE that required the subject to be hospitalized and 5 half-lives of the agent used has not elapsed
5. Subjects who are intubated for the administration of an IV anesthetic drug (a 3rd line treatment; e.g., midazolam, propofol, thiopental, pentobarbital, or ketamine) to treat SE; subjects who are intubated for airway protection are <u>not excluded</u>
6. Subjects known or suspected to be pregnant upon screening
7. To the best knowledge of the investigator, has allergy to progesterone or allopregnanolone medications/supplements or has previously received ganaxolone or exogenous allopregnanolone
8. If renal impairment is suspected (eGFR < 45 mL/min) or subject is currently on dialysis; if decision is made to start dialysis during study participation, subjects are not excluded
9. To the best knowledge of the investigator, subject has hepatic insufficiency at screening, for example alanine transferase or aspartate transferase level more than 5 times the upper limit of normal (ULN), or total bilirubin more than 2 times ULN at the screening visit
10. Subjects with a durable medical care agreement that would not allow hospital to administer their standard of care for treatment of SE
11. Subjects on an investigational drug that is not recommended by treatment guidelines are required to have a reasonable expectation that the investigational study drug has been cleared from their system, that is, that five half-lives have elapsed
12. Subjects who have a history or evidence of a medical condition that, in the investigator's judgment, would expose subject to an undue risk of a significant adverse event or interfere with assessments of safety or efficacy during the course of the study

Maximum Duration of Subject Involvement in the Study:

- Screening could be as short as a few minutes and as long as approximately 24 hours prior to the initiation of study drug. The screening period is from the time parent/guardian/LAR consent/assent is obtained to immediately prior to study drug initiation.
- The planned duration of adjunctive treatment is 2 days which includes a 12-hour study drug taper.
- There will be an in-patient follow-up period after the study drug administration is completed. The in-patient follow-up period starts at the time of study drug discontinuation; either at the end of the taper or if the study drug administration is stopped without a taper. The follow-up period consists of a 24 hour in-patient follow-up day and 3 weekly visits. These weekly visits can be performed as an in-person visit if the subject is still in the hospital, or as a telephone call if the subject has been discharged. However, it is recommended that discharged subjects return so at least one of these visits will be conducted in-person.
- In total, subjects will be followed for approximately 4 weeks.

Endpoints and Statistical Analysis:

Primary Endpoint:

- The number of subjects who didn't require an IV anesthetic drug (a 3rd line treatment) for SE treatment within the first 24 hours after study drug initiation

Secondary Endpoints:

- For subjects on concomitant second-line therapy: time to cessation of SE or next treatment decision (defined as the need for an IV anesthetic drug (a 3rd line treatment) when on ganaxolone)
- Level of responsiveness as assessed by the GCS, Four Score Scale, and RASS at 24 hours post study drug initiation
- The number of subjects who did not require additional 2nd line IV AED therapy for SE treatment in the 24-hours after study drug taper
- Safety and tolerability of IV ganaxolone as adjunctive SE therapy as assessed by neurologic, EEG, physical examinations, clinical laboratory tests, ECGs, vital signs, and AEs
- Number of subjects who maintained SE resolution 24 hours after study drug taper and at Week 4
- Number of subjects with seizure(s) following the cessation of SE through the in-patient follow-up day
- Seizure burden assessed as duration of electrographic seizure activity per hour of EEG recording collected
- Clinical outcome as assessed by MRS at the in-patient follow-up day and Week 4
- Characterization of the pharmacokinetic profile of ganaxolone IV solution in SE subjects
- Length of stay in intensive care unit and hospital, mortality, morbidity, need for and duration of intubation and mechanical ventilation, and seizure freedom

STUDY SCHEDULE(S)

Table 1: Schedule of Assessments

Periods	**Screening** [a]	**Treatment**				**Follow-up** [b]		**ET**
Visit/Timepoint or Duration	**Prior to study drug initiation**	**Dosing**		**Taper**	**Study Drug Discontinuation without Taper**	**In-patient Follow-up**	**Weekly follow-up (Week 2, 3, & 4)**	**Early Termination**
	Day -1 to Day 1 Pre-dose through screening	**Day 1** Study Drug Initiation 0 hours through 24 hours post study drug initiation	**Day 2** 24 hours through 36 hours post study drug initiation	**Day 2** 12-hours Starts at 36-hours post study drug initiation	Collected prior to or as close to study drug discontinuation as possible	**Day 3 Or** Starts as soon as study drug administration ends, lasts 24 hours	7 ±3, 14 ±3, and 21 ±3 days post last visit	Collected prior to or as close to study drug discontinuation as possible
Informed consent/assent	✔							
Inclusion/ exclusion criteria	✔							
Demography and medical/ medication history [c]	✔							
Physical exam [d]	✔		✔		✔	✔		✔
Status Epilepticus Severity Score (STESS)	✔							
Vital signs [e]	✔	✔	✔	✔	✔	✔		✔
Glasgow Coma Scale (GCS)/Pediatric GCS (PGCS) [e]	✔	✔	✔	✔	✔	✔		✔
Richmond Agitation and	✔	✔	✔	✔	✔	✔		✔

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	Day -1 to Day 1 Pre-dose through screening	**Day 1** Study Drug Initiation 0 hours through 24 hours post study drug initiation	**Day 2** 24 hours through 36 hours post study drug initiation	**Day 2** 12-hours Starts at 36-hours post study drug initiation	Collected prior to or as close to study drug discontinuation as possible	**Day 3 Or** Starts as soon as study drug administration ends, lasts 24 hours	7 ±3, 14 ±3, and 21 ±3 days post last visit	Collected prior to or as close to study drug discontinuation as possible
Severity Scale (RASS) [e]								
Full Outline of UnResponsivenes (FOUR) Score [e]	✔	✔	✔	✔	✔	✔		✔
Mini mental state exam (MMSE) [f]				✔		✔		
12-lead ECG [g]	✔	✔		✔	✔	✔		✔
Biochemistry, hematology, and antiepileptic drugs [h]	✔	✔	✔	✔	✔	✔	✔	✔
Urinalysis [h]	✔	✔	✔	✔	✔	✔	✔	✔
Drugs of abuse, including alcohol [i]	✔							
Pregnancy test (WCBP only) [i]	✔							
EEG [j]	✔	✔	✔	✔	✔	✔		✔

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Periods	**Screening** [a]	**Treatment**				**Follow-up** [b]		**ET**
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	Day -1 to Day 1 Pre-dose through screening	**Day 1** Study Drug Initiation 0 hours through 24 hours post study drug initiation	**Day 2** 24 hours through 36 hours post study drug initiation	**Day 2** 12-hours Starts at 36-hours post study drug initiation	Collected prior to or as close to study drug discontinuation as possible	**Day 3 Or** Starts as soon as study drug administration ends, lasts 24 hours	7 ±3, 14 ±3, and 21 ±3 days post last visit	Collected prior to or as close to study drug discontinuation as possible
Study Drug infusion [k]		✔	✔	✔				
Pharmacokinetic blood sampling [l]		✔	✔	✔	✔	✔		
Neurosteroid levels [m]	✔	✔						
Blood Gas [n]	✔							
Cerebral Spinal Fluid [o]	✔							
Clinical Global Impression of Severity (CGI-S) [p]	✔		✔	✔	✔	✔	✔	✔
Clinical Global Impression of Improvement (CGI-I) [q]		✔	✔	✔	✔	✔	✔	✔
SE & Seizure Questions [r]		✔	✔	✔	✔	✔	✔	✔
Intubation Question [s]		✔	✔	✔	✔	✔		
Modified Rankin Scale (MRS) [t]				✔	✔	✔	✔	✔

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Periods	**Screening** [a]	**Treatment**				**Follow-up** [b]		**ET**
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	Day -1 to Day 1 Pre-dose through screening	**Day 1** Study Drug Initiation 0 hours through 24 hours post study drug initiation	**Day 2** 24 hours through 36 hours post study drug initiation	**Day 2** 12-hours Starts at 36-hours post study drug initiation	Collected prior to or as close to study drug discontinuation as possible	**Day 3 Or** Starts as soon as study drug administration ends, lasts 24 hours	7 ±3, 14 ±3, and 21 ±3 days post last visit	Collected prior to or as close to study drug discontinuation as possible
AEs/SAEs [u]		✔	✔	✔	✔	✔	✔	✔
Concomitant medication [u]	✔	✔	✔	✔	✔	✔	✔	✔

ET, Early Termination; ECG, electrocardiogram; WCBP, women of childbearing potential; EEG, electroencephalograms; AE, adverse event; SAE, serious AE.

a. The screening period is from the time parent/guardian/LAR consent is obtained to immediately prior to study drug initiation.

b. The planned duration of follow-up will be 24 hours after study drug administration is stopped (called the in-patient follow-up day) and weekly for an additional 3 weeks. For Weeks 2, 3, and 4 the follow-up can be performed as an in-patient visit if the subject is still in the hospital or, if the subject has been discharged, as a telephone call. Attempts should be made to have discharged subjects return for one of the follow-up visits for clinical laboratory sample collection. The follow-up visit window is 7 ±3, 14 ±3, and 21 ±3 days.

c. Demography and medical history will ideally be collected prior to study drug initiation but can be collected whenever feasible before the end of study drug taper.

d. Physical exam should be obtained from the subject's chart or completed pre-dose (screening) or, if not available, collected within 2-hours of study drug initiation, and at 36-hours (+/- 1-hour). Collect at the time of study drug discontinuation, either at the end of the study drug taper or if the study drug administration is stopped without a taper and 24-hours (+/- 1-hour) after study drug discontinuation. If possible, for subjects who early terminate from the study, collect at the time of early termination is being considered and as close as possible to the end of the study drug administration. Collect any time, if medically indicated, per investigator's judgment.

e. Vital signs including blood pressure, pulse, respiratory rate, temperature, and oxygen saturation and the GCS/PGCS, RASS, and the FOUR scales should be collected pre-dose (screening), 60-minutes (+/- 15-min) and 2- (+/- 15-min), 10- ,24-, and 36-hours (+/- 1-hour) after study drug initiation. Collect at the time of study drug discontinuation, either at the end of the study drug taper or if the study drug administration is stopped without a taper and 24-hours (+/- 1-hour) after study drug discontinuation. If possible, for subjects who early terminate from the study, collect at the time early termination is being considered and as close as possible to the end of the study drug administration. Collect any time, if medically indicated, per investigator's judgment. Weight and height should be collected pre-dose (screening) for calculation of BMI inclusion criterion, if feasible. If not collected pre-dose (screening) collect prior to the end of the in-patient follow-up day.

f. MMSE should be performed at the time consent/assent is administered to the subject for continued participation and then on the in-patient follow-up day. If the MMSE is not able to be assessed due to the subject's state this should be recorded.

g. ECG should be collected pre-dose (screening), 2- (+/- 30-min) and 36-hours (+/- 1-hour) after study drug initiation. Collect at the time of study drug discontinuation, either at the end of the study drug taper or if the study drug administration is stopped without a taper and 24-hours (+/- 1-hour) after study drug discontinuation. If possible, for subjects

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Periods	**Screening** [a]	**Treatment**				**Follow-up** [b]		**ET**
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	Day -1 to Day 1 Pre-dose through screening	**Day 1** Study Drug Initiation 0 hours through 24 hours post study drug initiation	**Day 2** 24 hours through 36 hours post study drug initiation	**Day 2** 12-hours Starts at 36-hours post study drug initiation	Collected prior to or as close to study drug discontinuation as possible	**Day 3 Or** Starts as soon as study drug administration ends, lasts 24 hours	7 ±3, 14 ±3, and 21 ±3 days post last visit	Collected prior to or as close to study drug discontinuation as possible

who early terminate from the study, collect at the time early termination is being considered and as close as possible to the end of the study drug administration. Collect any time, if medically indicated, per investigator's judgment.

h. Clinical labs, hematology, serum chemistry (including creatinine, blood urea nitrogen, and estimated glomerular filtration rate calculation) and concomitant AED levels (fosphenytoin/phenytoin, valproic acid, levetiracetam, lacosamide, or brivaracetam, if available) and Urinalysis (including urine protein, albumin, and microscopic examination) should be collected pre-dose (screening), if available, or within 2 hours of study drug initiation, at 24- and 36- hours (+/- 1-hour) after study drug initiation. Collect at the time of study drug discontinuation, either at the end of the study drug taper or if the study drug administration is stopped without a taper and 24-hours (+/- 1-hour) after study drug discontinuation. Collect at one of the weekly follow-up visits (week 2, 3, or 4) for subjects in-house and if possible, for subjects who have been discharged. If possible, for subjects who early terminate from the study, collect at the time early termination is being considered and as close as possible to the end of the study drug administration. After the initial SE cessation, AED levels should be collected at time of first instance of seizure activity or SE relapse. Between study drug initiation and the in-patient follow-up day, where possible, collect AED levels if the decision is made to intubate the subject and for any serious adverse event (related or not related). Collect clinical labs, AEDs and urinalysis any time, if medically indicated, per investigator's judgment.

i. Drugs of abuse (urine or serum), including alcohol testing, and pregnancy test (urine or serum) for women who are of childbearing potential, should be collected pre-dose (screening). If not possible to collect pre-dose, collect as soon as possible after start of study drug infusion. Enrollment is not contingent upon results. However, if a subject has a positive test result, it will be at the investigator's discretion to weigh the risks verses benefits for the subject's continued participation. If the investigator decides to discontinue the study drug, refer to the study drug taper directions in the Study drug, Dose and Mode of Administration section.

j. EEG is required for confirmation of NCSE diagnosis. Continuous EEG recording ideally should start before study drug initiation and continue through the in-patient follow-up day. If continuous EEG is not possible or needed to diagnose (for convulsive SE) it should be instituted at the earliest possible time after study drug initiation (if a pre-dose EEG was not performed for the diagnosis of convulsive SE).

k. Subjects will receive a 30 mg bolus (over ~3 minutes) with a continuous infusion at a rate of 20-80 mg/hour for approximately 36 hours followed by 12-hour taper.

l. Blood sample collection for pharmacokinetic analysis (venous or arterial) will occur at 60-minutes then at 2-,4-,8-,10-, 24- and 36-hours after the start of study drug infusion. Collect at the time of study drug discontinuation, either at the end of the study drug taper or if the study drug administration is stopped without a taper and 24-hours after study drug discontinuation. After the initial SE cessation, collect a sample at the first instance of seizure activity or SE relapse and the subject does not progress to an IV anesthetic. Between study drug initiation and the in-patient follow-up day, where possible, collect a sample if the decision is made to intubate the subject; collect at the time of introduction of a new IV AED for safety/efficacy (not for AEDs given prophylactically for "transition/bridging"), and at the time of any serious adverse event (related or not related). PK samples cannot be collected from the study drug infusion line. The location of study drug access and location of PK sample collection should be documented in the subject's source.

Table 1: Schedule of Assessments

Periods	**Screening** [a]	**Treatment**				**Follow-up** [b]		**ET**
Visit/Timepoint or Duration	**Prior to study drug initiation**	**Dosing**		**Taper**	**Study Drug Discontinuation without Taper**	**In-patient Follow-up**	**Weekly follow-up (Week 2, 3, & 4)**	**Early Termination**
	Day -1 to Day 1 Pre-dose through screening	**Day 1** Study Drug Initiation 0 hours through 24 hours post study drug initiation	**Day 2** 24 hours through 36 hours post study drug initiation	**Day 2** 12-hours Starts at 36-hours post study drug initiation	Collected prior to or as close to study drug discontinuation as possible	**Day 3 Or** Starts as soon as study drug administration ends, lasts 24 hours	7 ±3, 14 ±3, and 21 ±3 days post last visit	Collected prior to or as close to study drug discontinuation as possible

m. Neurosteroid levels (venous or arterial) blood samples will be collected pre-dose (screening) and at 24-hours (+/- 1 hour) of study drug initiation. If study drug is discontinued during this 24 hours, the second sample should be collected prior to study drug discontinuation, if feasible. NS samples cannot be collected from the study drug infusion line. The location of study drug access and location of NS sample collection should be documented in the subject's source.

n. Blood gas including FiO_2, PaO_2, and Arterial pH, if collected per the investigator's discretion for subject's care, from the time of SE diagnosis through the in-patient follow-up day. If no samples are collected, a sample is not required. In addition, a blood gas sample should be collected when the decision is made to intubate the subject occurring after start of study drug infusion through the in-patient follow-up day. The sample should be collected immediately prior to or as close as possible to the time of intubation.

o. If a subject has a lumbar puncture for the collection of cerebral spinal fluid (CSF) per investigator's discretion as part of their care and there is adequate volume, a sample will be aliquoted for future analysis of ganaxolone. If multiple lumbar punctures are performed, a sample from each puncture is requested. If not collected or not enough CSF is collected to provide a sample for the study, a sample is not required.

p. CGI-S is collected pre-dose (screening) and 36-hours (+/- 1-hour) after study drug initiation. Collect at time of study drug discontinuation, either at the end of the study drug taper or if the study drug administration is stopped without a taper and 24-hours (+/- 1-hour) after study drug discontinuation. Collect at the week 2, 3, and 4 follow-up visits/contacts. If possible, for subjects who early terminate from the study, collect at the time early termination is being considered and as close as possible to the end of the study drug administration. Collect any time, if medically indicated, per investigator's judgment.

q. CGI-I is collected within 2 hours of study drug initiation and 36-hours (+/- 1-hour) after study drug initiation. Collect at time of study drug discontinuation, either at the end of the study drug taper or if the study drug administration is stopped without a taper and 24-hours (+/- 1-hour) after study drug discontinuation. Collect at the week 2, 3, and 4 follow-up visits/contacts. If possible, for subjects who early terminate from the study, collect at the time early termination is being considered and as close as possible to the end of the study drug administration. Collect any time, if medically indicated, per investigator's judgment.

r. Status Epilepticus and Seizure Questions should be collected at 15-minutes (+/- 5-min), 30-, 60-minutes (+/- 15-min), 2-, 4-, 6-, 8-, 10- 12- 18- (+/- 30-minutes) and 24- and 36- hours (+/- 1-hour) after study drug initiation. Collect at the time of study drug discontinuation, either at the end of the study drug taper or if the study drug is stopped without a taper and 24-hours (+/- 1-hour) after study drug discontinuation. Collect at the week 2, 3 and 4 follow-up visits/contacts. If possible, for subjects who early terminate from the study, collect at the time early termination is being considered and as close as possible to the end of the study drug administration.

s. Intubation Question should be collected at 18- (+/- 30-min), 24- and 36-hours (+/- 1 hours) after study drug initiation. Collect at time of study drug discontinuation, either at the end of the study drug taper or if the study drug administration is stopped without a taper and 24-hours (+/- 1-hour) after study drug discontinuation.

t. MRS is collected at the time of study drug discontinuation, either at the end of the study drug taper or if the study drug administration is stopped without a taper and 24-hours (+/- 1-hour) after study drug discontinuation. Collect at the week 2, 3, and 4 follow-up visits/contacts. If possible, for subjects who early terminate from the study, collect at the

Table 1: Schedule of Assessments

Periods	**Screening** [a]	**Treatment**				**Follow-up** [b]		**ET**
Visit/Timepoint or Duration	**Prior to study drug initiation**	**Dosing**		**Taper**	**Study Drug Discontinuation without Taper**	**In-patient Follow-up**	**Weekly follow-up (Week 2, 3, & 4)**	**Early Termination**
	Day -1 to Day 1 Pre-dose through screening	**Day 1** Study Drug Initiation 0 hours through 24 hours post study drug initiation	**Day 2** 24 hours through 36 hours post study drug initiation	**Day 2** 12-hours Starts at 36-hours post study drug initiation	Collected prior to or as close to study drug discontinuation as possible	**Day 3 Or** Starts as soon as study drug administration ends, lasts 24 hours	7 ±3, 14 ±3, and 21 ±3 days post last visit	Collected prior to or as close to study drug discontinuation as possible

time early termination is being considered and as close as possible to the end of the study drug administration. Collect any time if medically indicated, per investigator's judgment.

u. AEs and concomitant medications will be collected throughout the study; non-direct questioning will occur. The collection requirements will differ depending on the subject's treatment progression as follows: 1. All adverse events and associated concomitant medications will be collected through the in-patient follow-up day. 2. IV anesthetic agents (midazolam, propofol, thiopental, pentobarbital, or ketamine) administered during the study drug treatment period and the in-patient follow-up day should be followed through the week 4 visit/contact. 3. During the weekly follow-up visits, only ongoing AEs and new AEs assessed by the investigator to be related to study drug will be recorded and the concomitant medications associated with these AEs. 4. In addition, during the weekly follow-up visits, AEs of urinary tract infection (UTI), hospital-acquired/ventilator-associated pneumonia, myocardial infarction (MI), sepsis from any source, critical illness myopathy/neuropathy, significant hypotension requiring support of vasopressors will be recorded regardless of relatedness. Associated concomitant medications for these AEs will not be recorded. 5. All SAEs regardless of relationship to study drug and their associated concomitant medications will be recorded from the time of 1st dose through the last follow-up visit/contact. 6. For subjects who early terminate 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.

1. BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

Status epilepticus (SE) is a highly serious occurrence within the spectrum of epileptic disorders that is characterized by the manifestation of continuous or intermittent seizures lasting more than 5 minutes in duration without full recovery of consciousness or 10 minutes of continuous seizure activity on EEG, or intermittent paroxysmal activity for more than 50% of an hour.[1-4]

If SE is not treated immediately, prolonged seizure activity can result in permanent neuronal damage and contribute to the high morbidity and mortality associated with SE.[2,4,5] Paroxysmal hypersynchronous electrical discharges occur when there is too much excitation or too little inhibition in the area of the brain where the abnormal discharge starts.[6] Gamma-aminobutyric acid (GABA) is recognized as the principal inhibitory neurotransmitter in the cerebral cortex, and a disturbance in GABA-mediated functions results in the occurrence of epileptic seizures.[6] SE is often caused by pre-existing epilepsy, but it can also be caused by cerebral damage.[2] In subjects with chronic epilepsy, low blood concentrations of antiepileptic drugs (AEDs) can lead to SE.[1] Other recognized causes of SE include, but are not limited to, cerebrovascular accidents, anoxia or hypoxia, metabolic causes, and alcohol and drug withdrawal.[1,2]

A growing body of evidence from research and clinical observation supports the concept that SE becomes more difficult to control as its duration increases, and prolonged SE and refractoriness to treatment are associated with poor prognosis.[1] Resistance to treatment has been partially attributed to the internalization of postsynaptic $GABA_A$ receptors and externalization of glutamate receptors.[5] It has also been postulated that resistance may occur because of a mechanistic shift from inadequate GABAergic inhibitory receptor–mediated transmission to excessive N-methyl-D-aspartic acid excitatory receptor–mediated transmission.[7] Because prolonged epileptiform bursting results 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.

SE can be classified into three subtypes: generalized convulsive SE (GCSE), non-convulsive SE (NCSE), and refractory SE (RSE).[2,4] GCSE is characterized by convulsions that are associated with tonic-clonic movements of the extremities and mental status impairment, and may result in focal neurologic deficits lasting hours to days following an episode.[4] NCSE is defined as seizure activity seen on electroencephalography (EEG) without clinical symptoms; however, acutely ill subjects may present with impaired mental status following an NCSE episode.[4] RSE occurs in subjects who do not respond to the standard SE treatment regimen of a benzodiazepine and a secondary AED.[4]

SE is a neurologic emergency that requires aggressive treatment to stop the seizures and prevent permanent neuronal damage.[8] Mortality due to SE can range from 3% to 40% depending on etiology, age, status type, and status duration.[9] Previous studies have shown that seizures cause neuronal death via excitotoxic mechanisms as a result of excessive neuronal firing.[1] Furthermore, GCSE is associated with many complications, including cardiac arrhythmias, rhabdomyolysis, pulmonary edema, electrolyte and glucose imbalance, and temperature disturbances.[10]

The prognosis worsens and the mortality increases for subjects whose SE develops into RSE or super-refractory SE (SRSE).[11] Approximately one-third of subjects with RSE and SRSE will die of their condition; one-third recover but with chronic neurologic or other deficits, and one-third have been generally described as returning to baseline.[12,13] The longer subjects are kept in a long-term medically-induced coma to stop the seizures, the worse the prognosis.[14]

As SE is a medical emergency, the primary goal of treatment is to rapidly stop the seizures and avoid complications. Treatment typically occurs in stages: emergent initial therapy (first-line), urgent control therapy (second-line), and refractory therapy (third-line).[4] Therefore, continuous video-EEG monitoring is critical for monitoring sedation as well as SE outcome.[20]

The first-line standard-of-care treatment for early and established SE (ESE) is parenteral benzodiazepines.[7] A recent large-scale clinical study found that about 25% and 36% of subjects with SE did not respond to intramuscular (IM) midazolam and intravenous (IV) lorazepam, respectively.[15] Only two-thirds of subjects with SE respond to the first treatment, and evidence shows prolonged seizures can result in permanent neuronal damage and contribute to the high morbidity and mortality associated with SE.[6] Additionally, more than 20% of patients admitted for SE require intubation after benzodiazepine administration as first-line drug[29], solely for the sake of airway protection.

RSE is commonly defined as SE resistant to treatment with one first-line AED (benzodiazepines) and one second-line AED (phenytoin, phenobarbital, or valproate acid).[16,17] Because SE tends to become more refractory to conventional treatment over time and with the number of pharmacologic agents used[18] coma induction with an appropriate drug, such as barbiturates, propofol, or midazolam, is advocated after failure of second-line treatment.[19] The use of third-line agents such as pentobarbital, midazolam, propofol, and phenobarbital usually results in iatrogenic coma, which necessitates protection of the airways by intubation and mechanical ventilation.

As the goal of RSE treatment is to abolish all clinical and electrographic epileptic activity, continuous EEG monitoring is essential for this patient population. Without continuous EEG monitoring, the response to IV treatment could be difficult to interpret, because subclinical electrographic seizure activity can be detected in up to 48% of subjects after control of convulsive SE.[21] Burst suppression is often required in the intensive care phase of SE treatment, since RSE is associated with substantial mortality.

1.2 Product Background and Clinical Information

Ganaxolone is the 3β-methylated synthetic analogue of the neuroactive steroid allopregnanolone, but it is designed not to activate nuclear (classical) progesterone receptors. Ganaxolone differs from other GABA agents by interacting with both synaptic and extra-synaptic $GABA_A$ receptors and at binding sites distinct from benzodiazepines. Whereas benzodiazepines might lose their inhibitory action, ganaxolone does not because it selectively binds to $GABA_A$ receptors containing the α and δ subunits. By enhancing $GABA_A$ receptor function, ganaxolone provides an alternative mechanism in the treatment of seizures and could serve as effective therapy in the management of SE.

The therapeutic strategy for SE is always aggressive, and subjects in this condition often present with many comorbidities. The introduction of another medication to control SE must be balanced with the potential risks it brings, and most commonly used AEDs are associated with significant toxicities. Ganaxolone is an attractive potential therapy because of its current investigational safety profile, which is derived from a relatively large clinical database (> 1,500 subjects exposed) that contains both pediatric and adult populations. In clinical trials to date, it has shown anticonvulsant activity in subjects with seizure disorders. Marinus is investigating the approach of dosing ganaxolone to a level required to successfully control SE in this patient population.

Neuroactive steroids, which are positive allosteric modulators of both synaptic and extra-synaptic $GABA_A$ receptors,[22] have inhibitory properties to calm the overexcited brain (some have been used as anesthetics[23]) and might be effective in treating benzodiazepine-resistant SE.

As of 10 October 2018, approximately 1,557 unique subjects have received treatment with ganaxolone in ongoing and completed company-sponsored clinical trials ranging in duration from 1 day to more than 2 years, using doses from 50 to 2,000 mg/day.[24]

In addition, 175 subjects were enrolled in 2 post-partum depression studies and 41 subjects have been randomized in on-going phase 3 pediatric genetic epilepsy studies.

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

In the 20 completed Phase 2/3 clinical studies, 1238 unique subjects have received ganaxolone, including adult subjects with epilepsy, pediatric subjects with seizure disorders, pediatric subjects with fragile X syndrome, adult subjects with migraine, and subjects with post-traumatic stress disorder.

The overall frequency of treatment-emergent adverse events (TEAE) in company-sponsored placebo-controlled studies was 61.7% (613/993 subjects) in subjects who received GNX and 51.8% (330/637 subjects) in subjects who received placebo. The most frequently reported TEAEs in GNX-treated subjects were somnolence, dizziness, fatigue, and headache. All of these events, except for headache, occurred more frequently in GNX-treated subjects than placebo subjects. CNS-related evets appeared to be dose related, with the majority of these events occurring at doses ≥ 500 mg and were anticipated based on the mechanism of action of ganaxolone.

The majority of TEAEs were anticipated 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.

In the ganaxolone development program overall, 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 clinical laboratory measurements in clinical trials of ganaxolone. In the completed placebo-controlled Phase 1, 2, and 3 studies, 0.3% of subjects treated with ganaxolone 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 of Hy's law considered to be related to ganaxolone in the ganaxolone development program. In controlled clinical trials of ganaxolone, 1.1% of subjects receiving placebo and 1.7% of subjects receiving ganaxolone reported an AE of rash suggesting there is no obvious imbalance between drug and placebo in terms of frequency of this AE. However, in placebo-controlled studies rash led to discontinuation in GNX—treated subjects in 6 cases (0.6%) compared to no cases (0%) in placebo-treated subjects. Most rashes improved either while the drug was continued or following discontinuation. Two subjects participating in the Phase 2 study investigating ganaxolone in treatment of epilepsy developed an SAE of rash. Both events resolved after discontinuation of the study drug.

Preclinical studies and a study in 36 healthy volunteers assessing safety, pharmacokinetics, and pharmacodynamics of IV ganaxolone have been completed. Preclinical toxicity studies showed IV ganaxolone to be generally safe and adverse events to be consistent with expected dose-related sedation. In rats continuously dosed with IV ganaxolone for 14 days, no ganaxolone-related changes were noted in clinical pathology parameters or histopathology examination. There was no evidence of local irritation when ganaxolone was given IV or perivenously in preclinical studies. Furthermore, IV ganaxolone did not cause hemolysis and was compatible with human plasma.

The safety, pharmacokinetics, and pharmacodynamics of IV ganaxolone were investigated in 36 healthy volunteers in study 1042-0405, in which ganaxolone was administered as a bolus dosing (Stage 1) or as a bolus dose followed by a continuous infusion (Stage 2). Ten of the 36 subjects enrolled were women.

- Stage 1 enrolled and dosed subjects in four cohorts (A to D): 6 subjects in Cohort A (10 mg ganaxolone IV bolus in 3 subjects and 30 mg ganaxolone bolus in 3 subjects over 5 minutes), 8 subjects in Cohort B (20 mg ganaxolone bolus over 2 minutes), 8 subjects in Cohort C (30 mg ganaxolone bolus over 1 hour), and 8 subjects in Cohort D (10 mg ganaxolone bolus over 1 hour). Cohorts B, C, and D included 2 placebo subjects in each cohort.
- Stage 2 of the study dosed a total of 6 subjects with a 6 mg bolus followed by a 4-hour infusion at 20 mg/hour.

A total of 35 of the 36 subjects enrolled in Stages 1 and 2 completed the study as planned, while 1 subject withdrew their consent after completion of dosing but failed to come back for follow-up.

Six subjects reported treatment-emergent AEs in Stage 1 and 2. No single AE was seen twice. Only one event, headache, was considered by the investigator to be related to ganaxolone. None of the treatment-emergent AEs was serious, and all were of mild intensity. No clinically meaningful mean changes in laboratory test results, vital signs, or ECG parameters occurred in any cohort.

Pharmacokinetic data from study 1042-0405 showed that a bolus infusion of 30 mg ganaxolone over 5 minutes led to transient peak concentration levels (C_{max}) above 1,000 ng/mL with no safety concerns. Infusion of 30 mg/hour for 1 hour and 20 mg/hour for 4 hours led to

concentrations of 258 and 215 ng/mL, respectively, again without any safety concerns. This is consistent with findings from previous studies with the oral formulation of ganaxolone, in which C_{max} levels of up to 200 to 300 ng/mL were commonly observed and were not associated with major safety findings or toxicity (apart from sedation-related effects).

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

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

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

2. STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

Status epilepticus (SE) is defined as a prolonged self-sustaining seizure or recurrent seizures without recovery of consciousness between seizures.[1] The International League of Against Epilepsy 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 abnormally, prolonged seizures (5 minutes for tonic-clonic SE and 10 minutes for focal SE with impaired consciousness) and which can have long-term consequences (after 30 minutes for tonic-clonic SE and > 60 minutes for focal SE with impaired consciousness), including neuronal death and/or injury, and alteration of neuronal networks, depending on the type and duration of seizures.[1] SE is a neurological emergency that requires aggressive treatment to stop the seizures and prevent permanent neurological damage.[3] Mortality due to SE can range from 3% to 40% depending on etiology, age, SE type, and SE duration.[5] SE can be recognized clinically or using electroencephalograms (EEGs) by the presence of continuous ictal discharges.[3] Studies have shown that SE can cause neuronal death via excitotoxic mechanisms as a result of excessive neuronal firing.[6] Furthermore, convulsive SE is associated with many complications, including cardiac arrhythmias, rhabdomyolysis, pulmonary edema, electrolyte and glucose imbalance, and temperature disturbances. Approximately one third of subjects with refractory status epilepticus (RSE) and super refractory status epilepticus (SRSE) will die of their condition; one-third recover but with chronic neurologic or other deficits, and one third have been generally described as returning to baseline. The prognosis worsens the longer subjects are kept in a medically-induced coma. The primary goal of SE treatment is to gain control of the seizures rapidly and avoid complications, and treatment typically occurs in stages.[2] In general, the

treatment of SE is very aggressive and particularly urgent for convulsive status epilepticus (CSE).

The current therapies for SE have inherent risks, which must be balanced against the benefit of rapid seizure control. Benzodiazepines are the agents of choice for first line treatment of SE but their use can cause respiratory depression and hypotension, requiring the use of supportive therapies.[2] Unfortunately, approximately 35-45% of patients are refractory to benzodiazepines.[28] Second line therapy involves administration of an IVAED such as fosphenytoin, valproic acid, or levetiracetam for convulsive tonic-clonic status with the goal of stopping SE in patients who did not respond to first line treatment.[2] When a patient with SE fails to respond to a benzodiazepine and the initial 2nd line therapy they are classified as having RSE. RSE develops in 31-44% of patients with SE, with a mortality of 16-39%.[29] Additional therapeutic agents are required immediately; typically, anesthetics via continuous infusion.[2] Currently, the recommended anesthetic drugs include midazolam, propofol, thiopental, and pentobarbital. Anesthetics are associated with risks, especially if administered for a long time – propofol infusion syndrome and hypotension are two recognized adverse events associated with anesthetics for SE treatment. In addition, the need for assisted ventilation and the management of hypotension and cardiopulmonary depression have their own risks.[2]

Few therapies are approved for the treatment of SE and the urgent need for more efficacious therapies remains. Only two-thirds of patients in SE respond to first-line treatment.[3] Resistance to treatment has been partially attributed to the internalization of post-synaptic $GABA_A$-receptors and externalization of glutamate receptors.[3] As prolonged epileptiform bursting results in a reduction of $GABA_A$-mediated synaptic inhibition, antiepileptic treatments which rely on enhancing intra-synaptic $GABA_A$ neurotransmission become less effective the longer SE continues.

Ganaxolone is a potent allosteric positive modulator of $GABA_A$ receptors in the brain at a site distinct from the site of action of benzodiazepine receptor agonists and barbiturates. Γ-aminobutyric acid (GABA) is recognized as the principal inhibitory neurotransmitter in the cerebral cortex, and a disturbance in GABA-mediated functions results in the occurrence of epileptic seizures.[5] By enhancing the $GABA_A$ receptor function, ganaxolone provides an alternative mechanism in the treatment of seizures, and serves as effective therapy in the management of SE. Ganaxolone has been shown to stop SE in 2 distinct pre-clinical models of benzodiazepine-resistant SE.

Ganaxolone for this study is a proprietary IV formulation solubilized by Captisol® (betadex sulfobutyl ether sodium). The study targets plasma concentrations of ganaxolone that mimic concentrations associated with anticonvulsant effects in preclinical animal models of SE and that are expected to demonstrate anticonvulsant properties in humans. On December 21, 2016 (Serial No. 0014), Marinus submitted a Request for FDA Feedback on the draft Phase 2 Study 1042-SE-2001 protocol and provided specific questions. One question was related to the proposed maximum daily dosing limit of Captisol exposure in this study of approximately 35 grams/day. On February 13, 2017, the FDA responded and indicated that the proposed maximum daily dosing limit of Captisol 35 grams/day, is acceptable in adults and pediatric patients > 12 years of age.

On November 15, 2018 (Serial No. 0034), Marinus submitted a Request for FDA Feedback with data from the currently enrolled subjects to request an increase in the daily Captisol limit from 35 g/day to 50 g/day. On December 13, 2018, the FDA provided their agreement citing, "Balancing the potential benefit of ganaxolone against the potential risk of a high Captisol exposure, we can allow you to exceed your current Captisol limit of 35 g/day but not to exceed 50 g/day in Study 1042-SE-2001." Therefore, the maximum level of Captisol® in this study will not exceed 50 g/day.

The FDA indicated that if Marinus wanted to further increase the total daily dose of Captisol beyond 50 g/day, a new request for FDA feedback would need to be submitted based on a summary of the clinical experience from a sufficient number of subjects in Study 1042-SE-2001 who achieved Captisol exposures between 35 and 50 g/day. The FDA would review this data and respond accordingly.

2.2 Study Objectives

2.2.1 Primary Objective

To establish that intravenous ganaxolone given concomitantly with 2nd line IV AED therapy is safe and effective in stopping status epilepticus that has already failed one 2nd line IV AED therapy administered at an appropriate dose and duration to show efficacy and prevents escalation of treatment requiring an IV anesthetic drug (a 3rd line treatment) for seizure suppression.

2.2.2 Secondary Objectives

To assess other secondary efficacy endpoints such as mortality and seizure cessation in SE subjects

To assess the pharmacokinetics of adjunctive ganaxolone IV solution in SE subjects

To assess the need for IV anesthetic drugs for treatment of current SE event in SE subjects

2.2.3 Exploratory Objectives

[redacted]

3. STUDY DESIGN

3.1 Study Design and Flow Chart

This is double-blind, randomized, placebo-controlled study to evaluate the safety, tolerability, efficacy of adjunctive ganaxolone IV solution in subjects with SE. This study will start with a small open-label group to confirm the dose selected will achieve an approximate targeted plasma concentration of ganaxolone in the SE population who are on concomitant medications, and to obtain a preliminary assessment of safety, efficacy and feasibility of ganaxolone administration.

The dose selected for Day 2 is designed to provide a stable plasma concentration to maintain status cessation. If needed, doses in the open-label group may be adjusted based on the dosing and pharmacokinetic/safety profile from the subject's enrolled.

A total number of approximately 340 subjects will be screened to allow for up to approximately 272 subjects to receive study drug in the open-label and the double-blind groups. Subjects who early terminate for reasons other than lack of efficacy or adverse events related to ganaxolone (e.g., pump failure and other operational issues) may be replaced. In the double-blind group, randomized subjects will receive ganaxolone IV solution or placebo in a 1:1 ratio.

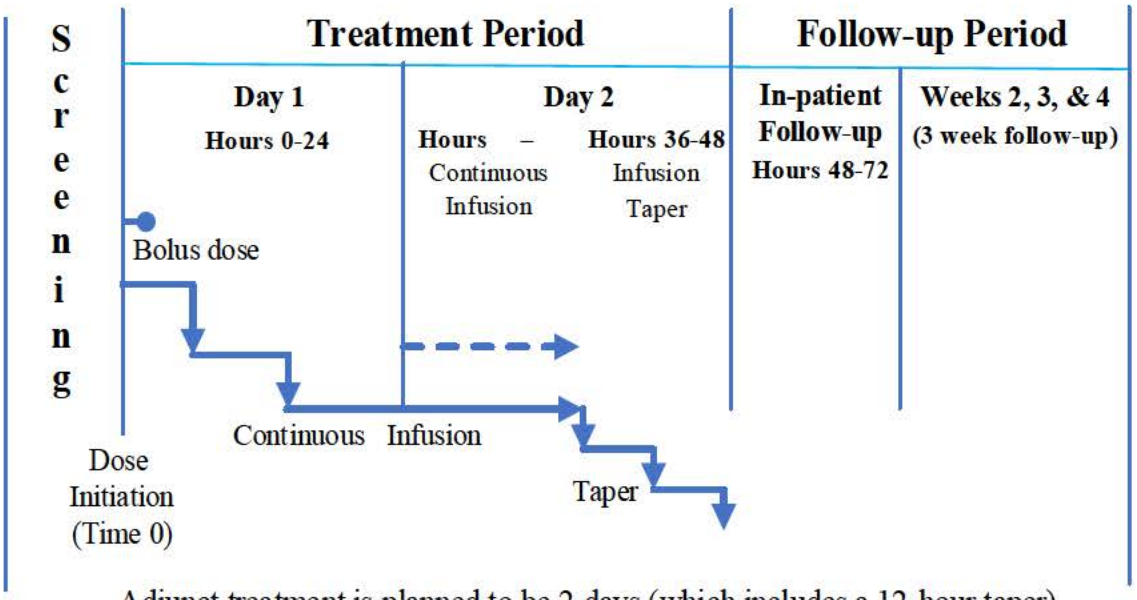
Study drug will be added to the standard of care at the time that the first 2nd line IV AED, administered at an appropriate dose and duration to show efficacy, has failed and the second 2nd line IV AED is medically indicated during the treatment of SE. Study drug must be administered with 2nd line IV AED as close to the dose initiation of the second 2nd line IV AED as possible.

Potential subjects are anticipated to be identified in the emergency department and/or hospital in-patient or intensive care units.

Upon identification, subjects will be administered consent/assent and then screened for inclusion/exclusion criteria prior to receiving study drug as adjunctive therapy via continuous IV infusion, followed by a 12-hour study drug taper. As soon as the study drug administration is completed (with or without taper), subjects will have a 24-hour in-patient follow-up day and then follow-up visits/contacts at weeks 2, 3, and 4. For subjects who have the 12-hour study drug taper, the in-patient follow-up day starts as soon as the 12-hour study drug taper is complete. If the infusion rate becomes too low to sustain the infusion line, it can be discontinued at that point and the subject will progress into the in-patient follow-up day. For subjects where there is no study drug taper the in-patient follow-up day starts as soon as the study drug administration is discontinued. These subjects will continue with the week 2, 3, and 4 follow-up visits.

If the subject remains hospitalized, the week 2, 3, and 4 visits will be done in-person. If the subject has been discharged, these visits may be conducted via telephone call. However, it is recommended that discharged subjects return so at least one of these visits will be conducted in-person.

Figure 1: Study Design Flow Chart



Adjunct treatment is planned to be 2-days (which includes a 12-hour taper).

Hours 24-36 should start with an infusion rate of 20mg/hr with dose adjustments allowed up to 45mg/hr.

Total subject participation is expected to be approximately 4 weeks.

3.2 Duration and Study Completion Definition

The subject's maximum duration of participation is expected to be approximately 4 weeks. It is anticipated the study will take 24 months to complete including approximately 18 months of subject enrollment.

The study completion date is defined as the date the final subject, across all sites, completes their final protocol-defined assessment. Please note that 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.

3.3 Sites and Regions

This multicenter study is to be conducted globally, with approximately 150 sites planned to participate.

4. STUDY POPULATION

Each subject/parent/guardian/legally authorized representative (LAR) must participate in the informed consent process and provide written informed consent/assent before any procedures specified in the protocol are performed. Consent/assent will be administered per the hospital's 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. Consent/assent for subjects who are known to be at risk for SE may be obtained prior to a SE event. The period of time the pre-consent/assent is valid will be determined by each hospital's IRB/EC. However, reconsenting will be needed should the consent/assent be updated at any point during the study.

4.1 Inclusion Criteria

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

1. Subject, subject's parent, guardian, or LAR must provide signature of informed consent, and, once capable (per the investigator's hospital guidelines), there must be documentation of consent/assent by the subject indicating the subject is aware of the investigational nature of the study, is able and willing to participate in the study, and is aware of the required restrictions and procedures
2. Male or female subjects 12 years of age and older at the time of the first dose of study drug
3. Clinical and/or electrographic seizures defined as:
    - Documented clinical seizures (convulsive SE): greater than 5 minutes' duration prior to treatment with study drug (per ILAE)

      or

    - Electrographic criteria (one must apply):
        - 10 minutes of continuous seizure activity on EEG (per ILAE)
        - Intermittent electrographic seizure activity for more than 50% of the previous 60 minutes
        - If less than 60 minutes of EEG is available, then intermittent electrographic seizure activity must be present for greater than 50% of the available duration of the EEG AND the electrographic seizure activity must be at least 10 minutes when taken in aggregate
4. Subject on concurrent 2nd line IV AED therapy with fosphenytoin/phenytoin, valproic acid, levetiracetam, lacosamide, or brivaracetam for the management of the current episode of SE
5. BMI < 40 or, if not able to be calculated at screening, assessed by investigator as not morbidly obese

4.2 Exclusion Criteria

Subjects 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 as the primary cause of SE
3. Recent (< 24 hour) traumatic brain injury as the primary cause of SE

4. Administered anesthesia (3rd line treatment; e.g., midazolam, propofol, thiopental, pentobarbital, or ketamine) at adequate doses and duration for the treatment of the current episode of SE that required the subject to be hospitalized and 5 half-lives of the agent used has not elapsed
5. Subjects who are intubated for the administration of an IV anesthetic drug (a 3rd line treatment; e.g., midazolam, propofol, thiopental, pentobarbital, or ketamine) to treat SE; subjects who are intubated for airway protection are not excluded
6. Subjects known or suspected to be pregnant upon screening
7. To the best knowledge of the investigator, has allergy to progesterone or allopregnanolone medications/supplements or has previously received ganaxolone or exogenous allopregnanolone
8. If renal impairment is suspected (eGFR $\leq$ 45 mL/min) or subject is currently on dialysis; if decision is made to start dialysis during study participation, subject is not excluded.
9. To the best knowledge of the investigator, subject has hepatic insufficiency at screening, for example alanine transferase or aspartate transferase level more than 5 times the upper limit of normal (ULN), or total bilirubin more than 2 times ULN at the screening visit
10. Subjects with a durable medical care agreement that would not allow hospital to administer their standard of care for treatment of SE
11. Subjects on an investigational drug that is not recommended by treatment guidelines are required to have a reasonable expectation that the investigational study drug has been cleared from their system, that is, that five half-lives have elapsed
12. Subjects who have a history or evidence of a medical condition that, in the investigator's judgment, would expose subject to an undue risk of a significant adverse event or interfere with assessments of safety or efficacy during the course of the study

4.3 Restrictions

Subjects must abstain from the use of alcohol and from consuming grapefruit, Seville oranges, starfruit, or citrus-derived products until completion of the study.

Females who are breastfeeding will be encouraged to "pump and dump" for the duration of study participation and for 45 days after the last dose of study drug.

4.4 Reproductive Potential

4.4.1 Female Contraception

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

Female subjects 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 specimens collected prior to study drug initiation. If not possible then, collected as soon as possible after study drug initiation. Enrollment is not contingent upon results. However, if a subject has a positive test result, it will be at the investigators discretion to weigh the risks verses benefits for the subjects continued participation.

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 subject 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.

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 3 months after the last dose of study drug. Medically acceptable contraceptives include surgical sterilization (such as a vasectomy) and a condom used with a spermicidal gel or foam. Contraceptive measures such as Plan B™, sold for emergency use after unprotected sex, are not acceptable methods for routine use.

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

4.5 Discontinuation of Subjects

A subject may withdraw, or their parent, guardian, or LAR may withdraw the subject, from the study drug administration and/or the study at any time for any reason without prejudice to their future medical care by the physician or at the hospital. The investigator or sponsor may withdraw the subject at any time (e.g., in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject from study drug with the Medical Monitor when possible unless due to progression to an IV anesthetic drug (a 3rd line treatment) for seizure suppression.

Study drug discontinuation

Subjects who discontinue study drug without a taper, e.g., takes study drug for less than 2 hours or progresses to an IV anesthetic (a 3rd line treatment) for seizure suppression or discontinues the study medication due to safety reasons will continue in the study and still have the in-patient follow-up day and the week 2, 3 and 4 follow-up visits/contacts.

Study withdrawal

Subjects who early terminate from the study, e.g. due to consent withdrawn, any outstanding screening procedures and the evaluations listed for the Early Termination Visit in Table 1 should be completed when early termination is being considered and as close as possible to the end of the study drug administration.

4.5.1 Subject Withdrawal Criteria

All subjects reserve the right to withdraw from the clinical study at any time, as stated in the informed consent form. The investigator may also discontinue subjects from the clinical study for any of the following reasons:

1. The subject has persistent ventilatory depression that results in a SpO2 < 90% or ETCO2 > 50 mmHg (measured using nasal cannula monitor) despite the use of airway maneuvers including assisted ventilation. Standard airway maneuvers to treat sedation-induced upper airway obstruction (jaw thrust, chin lift, or supraglottic device such as a laryngeal mask airway) or hypoventilation (ventilation assisted with a mask or supraglottic device) would be instituted at the discretion of the physician monitoring the patient in order to maintain SpO2 > 90% and ETCO2 < 51 mmHg. If the subject does not respond to these methods, the subject would be discontinued
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 ≤ 45 mL/min and subject 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 subject's best interest to continue to receive study drug
5. Rash that is clinically significant and considered to be related to the study drug (e.g., morbilliform, urticarial, papular)
6. Subject experiences an SAE considered to be related to the study drug

Decisions to discontinue the study will be made at each participating site by the principal investigator. If feasible, the reason for discontinuation should be discussed with the Medical Monitor prior to subject discontinuation unless due to the progression to an IV anesthetic drug (a 3rd line treatment) for seizure suppression.

4.5.2 Reasons for Discontinuation

The reason for discontinuation must be determined by the investigator and recorded in the subject's medical record and in the eCRF. If a subject 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:

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

4.5.3 Subjects Lost to Follow-up Prior to Last Scheduled Visit

A minimum of three documented attempts must be made to contact any subject 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 subject'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 subject should be classified as Lost to Follow-up in the eCRF. However, if contact is made but the subject 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 received within 30 days prior to the first dose of study drug (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.

5.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between the date of the first dose of study drug and the end of the follow-up period, inclusive. However, the collection requirements will differ depending on the subject's treatment progression as defined below.

- All concomitant medications will be collected through the in-patient follow-up day

- During the weekly follow-up visits, only concomitant medications associated with ongoing AEs and new AEs assessed by the investigator to be related to study drug will be recorded

- All concomitant medications associated with SAEs regardless of relationship to study drug will be recorded from the time of study drug initiation through the last follow-up visit/contact

- In addition, for subjects who stop study drug administration without a taper but continue with the follow-up visits, any IV anesthetic agents (midazolam, propofol, thiopental, pentobarbital, or ketamine) that were started on the in-patient follow-up day should be followed through the last follow-up visit/contact

- At the time that early termination from the study is being considered, prior to discontinuation as much information as is available should be recorded on the concomitant medications associated with ongoing AEs/SAEs and new AEs/SAEs, especially those that may have led to the early termination

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

Ganaxolone IV solution will be administered as adjunctive therapy to the hospital's standard of care. Any medication classified by the hospital as per the standard of care will be acceptable. Anything outside of the standard of care should be discussed with the Medical Monitor.

5.2.2 Prohibited Treatment

As per the exclusion criterion in Section 4.2, the only allowable concurrent 2nd line IV AED therapies to treat the current episode of SE are fosphenytoin/phenytoin, valproic acid, levetiracetam, lacosamide, or brivaracetam. Administering fosphenytoin and/or phenytoin will be counted as one (1) AED. These drugs can be used alone or in combination with each other. If the subject is receiving oral AED therapy to manage a subject's chronic medical condition, for example, epilepsy, migraine, or neuropathic pain, that therapy is acceptable and should continue unchanged, if feasible and medically justified. This prophylactic treatment does not count towards the SE treatment failures required to qualify for this study. If any of these oral AED medications had to be interrupted around the time of the current SE episode, it is recommended that they would be re-started 10 hours after study drug initiation, if medically acceptable. Also, subjects who have been enrolled in another clinical study for SE are required to have a reasonable expectation that the other investigational drug has been cleared from their system, that is, that five half-lives have elapsed. Subjects on IV AEDs that are standard of care can be enrolled in the study. Subjects who have taken exogenous allopregnanolone or ganaxolone previously are not eligible for the study.

If a subject progresses at any time during the study to an IV anesthetic drug (a 3rd line treatment; e.g. midazolam, propofol, thiopental, pentobarbital, or ketamine and/or 4th line treatment; e.g., immunosuppressants, magnesium) for seizure suppression, study drug administration will be discontinued, however the subject will continue with the in-patient follow-up day and the week 2, 3, and 4 follow-up visits.

6. STUDY DRUG

6.1 Identity of Study drug

The test product is ganaxolone IV solution, which will be provided in glass vials/bottles.

For the Open-Label Group, ganaxolone IV solution, 1 mg/mL – 100 mL/vial is a sterile solution containing 1 mg of the active ingredient ganaxolone per 1 mL solution. Ganaxolone IV Solution, 1 mg/mL – 100 mL/vial is packaged as a 100 mL dose in 125 mL glass vials. Details of packaging, dose and administration of the ganaxolone IV solution and placebo for the double-blind group will be included in a future amendment.

The formulation consists of a sterile solution of ganaxolone drug substance that has been solubilized by complexation with Captisol® (Betadex Sulfobutyl Ether Sodium). In addition to Captisol, the formulation consists of water for injection (diluent), buffering agents (potassium phosphate, sodium phosphate) and sodium chloride (tonicity modifier). The drug product is terminally heat sterilized.

The composition of the Ganaxolone IV Solution, 1 mg/mL – 100 mL/vial is provided below.

Quantitative Composition of Ganaxolone IV Solution, 1 mg/mL – 100 mL/Vial

Component	Reference to Standards	Content per mL (mg/mL)	Concentration (%w/w)	Function
Ganaxolone	Marinus	1.00	0.097	Active ingredient
Betadex sulfobutyl ether sodium (Captisol)	NF	59.74	5.817	Solubilizing agent
Potassium phosphate, monobasic (KH_2PO_4)	NF	2.46	0.239	Buffer agent[a]
Sodium phosphate, dibasic heptahydrate ($Na_2HPO_4.7H_2O$)	USP	2.78	0.271	Buffer agent[a]
Sodium chloride	USP	2.00	0.195	Tonicity modifying agent
Water for injection	USP	q.s. 1 mL	93.381	Diluent

NF = National Formulary; USP = United States Pharmacopeia; w/w = weight by weight.

[a] Formulation pH = 6.4

Drug Product Name: Ganaxolone IV Solution, 1 mg/mL – 100 mL/vial

Manufacturer: Alliance Contract Pharma, LLC., Harleysville, PA 19438 USA

Strength for Open-Label Group: ready-to-infuse 1-mg/mL sterile solution in a glass vial

Packaging: Ganaxolone IV Solution, 1 mg/mL – 100 mL/vial will be provided to the site as individual vials containing 1 mg/mL of Ganaxolone.

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

Storage: The investigator has the overall responsibility for ensuring that study drug is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. Study drugs are distributed by the pharmacy or by a nominated member of the study team.

Ganaxolone IV solution, 1 mg/mL – 100 mL/vial has on-going stability and to date has been found stable if stored at 15°-25°C (59°-77°F) until use. Excursions up to 30°C (86°C) that are experienced in pharmacies, hospitals, and warehouses, and during shipping are allowed.

6.1.1 Blinding the Treatment Assignment

For the double-blind group, the site pharmacy personnel who dispenses the study drug is not required to be blinded and will not be involved in any study assessments. All other participating staff involved in the evaluation and execution of the study will remain blinded to subject's study drug treatment.

6.2 Administration of Study drug(s)

6.2.1 Interactive Response Technology for Study Drug Management

For the double-blind group an Interactive Voice/Web Response System (IVRS/IWRS) will be utilized for the following study drug tasks:

- Randomization
- Supply management
- Inventory management and supply ordering
- Expiration date tracking
- Returns
- Emergency unblinding

Details on the name and address of the system and use will be detailed in the Investigator files at each site.

6.2.2 Allocation of Subjects to Treatment

This is a double-blind study with an initial open-label group. The actual treatment given to individual subjects in the double-blind group is determined by a randomization schedule. For both groups, subject identification numbers are assigned to all subjects prior to dosing. Within each site (numbered uniquely within a protocol), subject numbers are assigned per the sequence of subject presentation for study participation.

The randomization number represents a unique number corresponding to study drug allocated to the subject, once eligibility has been determined.

Individual subject treatment for the double-blind is automatically assigned by the IVRS/IWRS.

Subjects participating in the open-label portion of the study will be dispensed ganaxolone IV solution. The study drug will be identified as ganaxolone IV solution and any vial identified as such can be dispensed. Sites will be responsible for logging and tracking the open-label supplies via study accountability logs and entered into the eCRF. All open-label supplies will have a unique vial number for tracking purposes.

6.2.3 Dosing

Total adjunctive ganaxolone IV solution therapy infusion treatment is planned to be 2 days which includes a 12-hour study drug taper. All subjects will have an ~3-minute bolus dose with a continuous infusion at the rate of 20-80 mg/hour, and a 12-hour study drug taper (see Table 2 and 3 for details). Once study drug administration is started it should be delivered for 2 days (48 hours) which includes a 12-hour taper.

Study drug should be administered, ideally, through a dedicated (peripheral or central) IV line. These infusion parameters result in daily doses of ganaxolone of ≤ 830 mg/day and Captisol of ≤ 50 g/day as agreed upon with the FDA. Based on PK modeling, it is predicted that maximum concentrations of ganaxolone should remain within 1,000 ng/mL during infusion, but some variability is expected due to, for example, differences in subjects' weight. Note, at any time, the infusion rate of the ongoing administration may be decreased for safety reasons, see Dose Adjustments and Interruptions section below for more information.

Note, pharmacokinetic data from study 1042-0405 in healthy volunteers showed that a bolus infusion of 30 mg ganaxolone over 5 minutes led to transient peak concentration levels (C_{max}) above 1,000 ng/mL (maximal observed C_{max} was 1,850 ng/mL) with no safety concerns. Infusion of 30 mg/hour for 1 hour and 20 mg/hour for 4 hours led to concentrations of 258 and 215 ng/mL, respectively, again without any safety concerns (see Section 1.2 Product Background and Clinical Information).

During the open-label group, based on the safety, efficacy, and pharmacokinetic data from the ongoing study, the infusion parameters in subsequent subjects may be adjusted to maximize the safety and efficacy of study subjects. If the infusion parameters are amended, the new infusion parameters will not exceed the daily limit of 50 g/day Captisol (≤ 830 mg/day ganaxolone) as agreed upon with the FDA. The revised infusion parameters will be communicated to Clinical Sites in a Protocol Administrative Change Memo and kept in the study and site files.

Potential subjects must have failed one 2nd line IV AED therapy, administered at an appropriate dose and duration to show efficacy. Ganaxolone IV solution (open-label group) or ganaxolone IV solution or placebo (double-blind group) will be administered in combination with standard of care at the time that the first 2nd line IV AED has failed and the second 2nd line AED is medically indicated during the treatment of SE. Study drug must be administered with 2nd line IV AED treatment and should be initiated as close to the dose initiation of the second 2nd line IV AED as possible.

Upon administration of study drug, subjects will be monitored for improvement or resolution of SE (clinical or EEG response).

Note, the infusion rate cannot be rounded-up regardless whether dosing is in subjects ≥ 40 kg or < 40 kg.

Subjects 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 (24-36 hours) the continuous infusion rate of 20 mg/hour will continue until the start of the study drug taper at 36 hours post study drug initiation. If needed, to manage seizure relapse or another medical reason, the infusion rate can be increased from 20 mg/hour up to a maximum rate of 45 mg/hour at any time during hours 24-36 of Day 2.

- To taper the study drug, the infusion rate at the 36-hour post study drug initiation timepoint will be reduced by 33.3% every 4 hours until the infusion 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, the second taper will be 33.3% from the first tapered infusion rate, and the final taper will be 33.3% from the previous tapered infusion rate. If, per the investigator's judgment, the study drug 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.

- At the time the study drug infusion is discontinued the subject will progress to the in-patient follow-up day assessments/procedures.

Table 2: Dosing for Subjects ≥ 40 kg (on an mg/hour basis)

Days	Start Time from Study Drug Initiation	Study Drug Dose (mg/hour)	Study Drug Infusion Rate (mL/hour)	Duration
Day 1	0 hours: bolus dose via syringe or infusion pump	30	30	3 minutes
Day 1	0 hours through 2 hours post study drug initiation: continuous infusion, started with bolus	80	80	2 hours
Day 1	2 hours through 12 hours post study drug initiation	40	40	10 hours
Day 1	12 hours through 24 hours post study drug initiation	20	20	12 hours
Day 2[a]	24 hours through 36 hours post study drug initiation	20 - 45	20 - 45	12 hours
	Study Drug Taper			
Day 2[b]	36 through 48 hours post study drug initiation (12-hour taper)	13.34 - 30.02	13.34 - 30.02	4 hours
		8.90 - 20.02	8.90 - 20.02	4 hours
		5.93 - 13.35	5.93 - 13.35	4 hours

a. On Day 2 (24-36 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.

b. To taper the study drug, the infusion rate at the 36-hour post study drug 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, the second taper will be 33.3% from the first tapered infusion rate, and the final taper will be 33.3% from the previous tapered infusion rate. If, per the investigator's judgment, the study drug 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.

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

- A 0.43-mg/kg bolus dose (over ~3 minutes) will be administered with a continuous infusion at a dose of 1.14 mg/kg/hour for 2 hours followed by a continuous infusion rate of 0.57 mg/kg/hour for 10 hours, and 0.29 mg/kg/hour for the remaining 12 hours of Day 1.

- On Day 2 (24-36 hours) the continuous infusion dose of 0.29 mg/kg/hour will continue until the start of the study drug taper at 36 hours post study drug initiation. If needed, to manage seizure relapse or for another medical reason, the infusion dose can be increased from 0.29 mg/kg/hour up to a maximum of 0.64 mg/kg/hour at any time during hours 24-36 of Day 2.

- To taper the study drug, the infusion rate at the 36-hour post study drug initiation timepoint will be reduced by 33.3% every 4 hours until the infusion 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, the second taper will be 33.3% from the first tapered infusion rate, and the final taper will be 33.3% from the previous tapered infusion rate. If, per the investigator's judgment, the study drug 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.

- At the time the study drug infusion is discontinued the subject will progress to the in-patient follow-up day assessments/procedures.

Table 3: Dosing for Subjects < 40 kg (on an mg/kg/hour basis)

Days	Start Time from Study Drug Initiation	Study Drug Dose (mg/kg/hr)	Study Drug Infusion Rate (mL/hr)[a]	Duration
Day 1	0 hours: bolus dose via syringe or infusion pump	0.43	Variable depending on subject's weight	3 minutes
Day 1	0 hours through 2 hours post study drug initiation dose: continuous infusion, started with bolus	1.14	Variable	2 hours
Day 1	2 hours through 12 hours post study drug initiation	0.57	Variable	10 hours
Day 1	12 hours through 24 hours post study drug initiation	0.29	Variable	12 hours
Day 2[b]	24 hours through 36 hours post study drug initiation	0.29 - 0.64	Variable	12 hours
	Study Drug Taper			
Day 2[c]	36 through 48 hours post study drug initiation (12-hour taper)	0.19 - 0.43	Variable	4 hours
		0.13 - 0.29	Variable	4 hours
		0.08 - 0.19	Variable	4 hours

a. Reference the Pharmacy Manual for study drug infusion rates based on mg/kg/hour dosing.

b. On Day 2 (24-36 hours), the continuous infusion dose can be increased from 0.29 mg/kg/hour to a maximum dose of 0.64 mg/kg/hour at any time, if needed, to manage seizure relapse or other medical reason.

c. To taper the study drug, the infusion rate at the 36-hour post study drug 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, the second taper will be 33.3% from the first tapered infusion rate, and the final taper will be 33.3% from the previous tapered infusion rate. If, per the investigator's judgment, the study drug 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.

Medical Oversight:

Medical personnel must be present at all times during at least the first 3 hours after the start of the study drug infusion. Then close monitoring of the subject by the study staff will continue as medically needed throughout the study.

New AED Introduction:

- For the first 10-hours of study drug administration the decision to initiate new IV AEDs should be based on safety or efficacy and confirmed by relapsing clinical presentation or electrographic activity. Initiation of any new AEDs prophylactically (so called "transition/bridging") is not recommended, unless medically indicated.

- In the event of safety or efficacy presentation, i.e. seizure relapse that would prompt the investigator to make a treatment intervention, introduction of a new IV AED is recommended over immediate progression to a 3rd line agent, however all treatment decisions are at the investigator's discretion.

- After the first 10-hours investigators are encouraged to initiate prophylactic AEDs in anticipation of the study drug taper at 36 hours post study drug initiation on Day 2.

Scenarios for stopping the study drug without a taper include:

- For subjects who receive study drug for less than 2 hours and/or
- Study drug infusion is discontinued or interrupted, and the decision is made to not restart the infusion and/or
- If at any time during study drug administration the subject progresses to an IV anesthetic drug (a 3rd line and/or 4th line treatment) for seizure suppression or
- It is no longer safe to continue drug administration per the investigator's medical judgment.

Dose Optimization:

During the open-label group, based on the safety, efficacy, and pharmacokinetic data from the ongoing study, the infusion parameters in subsequent subjects may be adjusted to maximize the safety and efficacy of study subjects. If the infusion parameters are amended, the new infusion parameters will not exceed the daily limit of 50 g/day Captisol ($\leq$ 830 mg/day ganaxolone) as agreed upon with the FDA. The revised infusion parameters will be communicated to Clinical Sites in a Protocol Administrative Change Memo and kept in the study and site files.

For study drug dosing instructions reference the Pharmacy Manual.

Dose Adjustments and Interruptions:

Dose (infusion rate) decreases and interruptions of the continuous infusion are discouraged at any time during study drug treatment. However, if there is an urgent medical need (e.g., severe hypotension, acidosis, severe sedation) or a subject's standard of care requires they undergo a

procedure for which the infusion would need to be decreased or interrupted (e.g., an MRI scan) it should be kept as short as possible but no longer than 6 hours. If > 6 hours the Marinus Medical Monitor must approve the re-start of the infusion.
Note:

- After the dose (infusion rate) decrease or infusion interruption, it will be per the investigator's judgment and assessment of risk/benefit if the subject should continue in the study or early discontinue.
- In cases when severe sedation is seen and early drug discontinuation is being considered, the Marinus Medical Monitor should be contacted prior to infusion termination, if feasible.
- If the decision is made for the subject to continue in the study, the infusion should be re-started at the rate matching the rate at the corresponding nominal time, counted from the beginning of the study drug infusion on Day 1. A study drug bolus or "catch-up" dose to deliver the study drug that was missed during the interruption should not be administered.
- Dose (infusion rate) increases above those specified in the protocol (or based on a future Protocol Administrative Change Memo) are not allowed at any time during infusion. This is to ensure daily Captisol and ganaxolone limits are kept ≤ 50 g/day and ≤ 830 mg/day, respectively.

6.2.4 Unblinding the Treatment Assignment

During the double-blind group, the treatment assignment must not be broken except in emergency situations in which the identification of the study drug is required for further treatment of the subject. The investigator should contact the Medical Monitor before unblinding, if possible. 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 un-blinded the subject.

In the event that 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 subject is withdrawn from the study, but should be followed up for safety purposes. Any code-breaks that occur must be reported to the Contract Research Organization (CRO) and sponsor.

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling

Labels containing study information and vial identification are applied to the study drug containers.

Each 125 mL vial contains 100 mL of ganaxolone at a concentration of 1 mg/mL (open-label group). Details of packaging, dose and administration of the ganaxolone IV solution and placebo for the double-blind group will be added in a future amendment. A label is applied to each vial/bottle with information on strength, manufacturing batch or job number, expiry or manufacturing date, storage conditions, and name of the manufacturer, as well as a warning that the drug is intended for research only.

The study drug will be dispensed to qualified staff members who will administer the study drug to the subject.

All study drug is labeled with a minimum of the following: protocol number, unique vial/bottle number, dosage form (including product name and quantity in pack), directions for use, storage conditions, batch number and/or packaging reference, the statements "For investigational use only" and/or "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 study drug intended for the double-blind portion of the study.

Additional labels (e.g., those used when dispensing marketed product) may, on a case-by-case basis, be applied to the study drug in order to satisfy local or hospital requirements, but must not:

- Contradict the clinical study label
- Obscure the clinical study label
- Identify the study subject by name, without consultation with the sponsor (only applicable to the vial or bottle). Additional labels may not be added without the sponsor's prior full agreement.

Open-label Group:
Ganaxolone IV Solution Vial Label (1 mg/mL):
Protocol 1042-SE-2001 Vial Number: XXX
Contents: Ganaxolone IV Solution, 1mg/mL Quantity: 100 mL/vial
[redacted] Fill volume: 100 mL
Date of Manufacture: DDMMYYYY
Dose according to Pharmacy Manual Instructions
Store at 15°C to 25°C (*59°F to 77°F)*
Intravenous use only. Keep out of reach of children.
Caution: New Drug—Limited by Federal (US) Law to Investigational Use
Manufactured by ACP, Harleysville, PA 19438 USA for Marinus Pharmaceuticals, Inc., Radnor, PA 19087 USA Telephone: (484) 801-4670

Double-blind Group:
Details of the label for Ganaxolone IV solution and placebo for the double-blind group will be added in a future amendment.

6.3.2 Packaging

Ganaxolone IV solution for administration will be provided to the site as individual vials or bottles containing 1 mg/mL (open-label group) or 1 mg/mL or placebo (double-blind group).

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 study drug is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. Study drugs are distributed by the pharmacy or by a nominated member of the study team. The 1 mg/mL ganaxolone IV solution vials 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 experienced in pharmacies, hospitals, and warehouses, and during shipping are allowed. Details on how to store the study drug can be found in the Pharmacy Manual. Prior to administration inspect the study drug for particulate matter, cloudiness, and discoloration. If any of these is present, do not use and notify the sponsor.

Study drug must be stored in accordance with labeled storage conditions. Temperature monitoring of the study drug is required at the storage location to ensure that the study drug 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 study drug and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects 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 study drug that could affect the integrity of the product(s), such as fumigation of a storage room.

6.4 Drug Accountability

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

The investigator has the overall responsibility for administering/dispensing study drug. Where permissible, tasks may be delegated to a qualified designee (e.g., a pharmacist) who is adequately trained in the protocol and who works under the direct 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 study drug administration orders and confirm that the study drug is only dispensed to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the study drug carrying their treatment assignment. All administered, and/or dispensed medication will be documented in the eCRFs and/or other study drug record.

No study drug 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 and subject-administered study drug is either to be sent to a nominated contractor on behalf of the sponsor for destruction or are to be destroyed by the site. Study drug 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 supplied 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 study drug must be packed in a tamper-evident manner to ensure product integrity. Contact the sponsor for authorization to return any study drug prior to shipment. Shipment of all returned study drug must comply with local, state, and national laws.

With the written agreement of the sponsor, unused stock and subject-administered study drug 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 study drug must be in accordance with local, state, and national laws.

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

6.5 Subject Compliance

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

7. STUDY PROCEDURES

7.1 Study Schedule

See Table 1 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 and Neurosteroid sample collection
4. Clinical laboratory tests
5. Physical examination

NOTE: Blood sampling for pharmacokinetic evaluation must 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 subjects are anticipated to be identified in emergency departments and/or hospital in-patient units. Upon identification, subjects will be screened for inclusion/exclusion criteria prior to receiving ganaxolone IV solution as adjunctive therapy.

Procedures specific to this protocol and not otherwise considered standard of care, will not be performed until written informed consent from the subject/parent/guardian/LAR has been appropriately obtained. Consent for subjects who are at risk for SE may be obtained prior to an SE event, this is also referred to as pre-consenting. Additional details on consent can be found in Section 10.3.1.

A screen failure is a subject who has given informed consent and failed to meet the inclusion criteria and/or met at least one of the exclusion criteria and has not been administered the study drug. Subjects cannot be rescreened once they have been designated as a screen failure per incidence of SE. Subjects who fail the screening but are not treated with ganaxolone IV solution may be rescreened if they face a new SE event.

7.1.2 Treatment Period

7.1.2.1 Study Drug Initiation Through In-patient Follow-up Day (Day 1 to Day 3)

Eligible SE subjects receiving standard of care (potential subjects must have failed one 2nd line IV AED, administered at an appropriate dose and duration to show efficacy, will be given adjunctive ganaxolone IV solution. Ganaxolone IV solution will be given as an IV bolus with a continuous infusion at a rate of 20-80 mg/hour including a 12-hour study drug taper. The presence of SE must be confirmed immediately prior to the study drug bolus. Subjects will receive the ganaxolone IV solution as described in Section 6.

7.1.3 Follow-up Period

The follow-up period for this protocol is approximately 4 weeks.

Subjects will have an in-patient follow-up day after the study drug taper is completed as noted in the previous section. The in-patient follow-up day starts as soon as the 12-hour study drug taper is completed. If the infusion rate becomes too low to sustain the infusion line, it can be discontinued at that point and the subject will progress into the in-patient follow-up assessments. For subjects where there is no study drug taper, the in-patient follow-up assessments start as soon

as the study drug administration is discontinued. These subjects will continue with the week 2, 3, and 4 follow-up visits.

If, however, a subject takes study drug for less than 2 hours and/or progresses at any time during the study to an IV anesthetic drug (a 3rd line treatment and/or 4th line treatment e.g., immunosuppressants, magnesium) for seizure suppression they will be discontinued from the study drug without study drug taper. Any outstanding screening assessments should be completed, and Table 1 lists the assessments/procedures that should be collected when the decision to stop study drug administration is made and as close as possible to the end of the study drug administration. These subjects will progress to the in-patient follow-up day and the week 2, 3, and 4 follow-up visits.

Once dosing is completed, the planned duration of follow-up will be weekly for an additional 3 weeks. These weekly visits can be performed as an in-patient visit if the subject is still in the hospital, or as a telephone call if the subject has been discharged. However, it is recommended that efforts be made to have discharged subjects return so at least one of these visits will be conducted in-person. The subject/parent/guardian/LAR, as appropriate, will receive a follow-up contact weekly approximately 7 ± 3, 14 ± 3, and 21 ± 3 days following the in-patient follow-up day.

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

A subject who discontinues or early terminates from the study (e.g., due to consent withdrawn) should have the early termination procedures completed when early termination is being considered and as close as possible to the end of the study drug administration. A list of early termination assessments can be found in Table 1.

7.1.4 Additional Care of Subjects After the Study

No aftercare is planned for this study. Subjects should return to their physician's care.

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 EEG

EEG is required for confirmation of NCSE diagnosis. Ideally, continuous EEG monitoring should start before study drug initiation to get a baseline assessment and continue through the in-patient follow-up day. If continuous EEG is not possible or needed to diagnose (for convulsive SE) it should be instituted at the earliest possible time after study drug initiation (if a pre-dose EEG was not performed for the diagnosis of convulsive SE).

Several study sites may be offered the use of a portable EEG device to assist with pre-screening of subjects with NCSE. 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)

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

7.2.2.3 Glasgow Coma Scale (GCS) and Pediatric Glasgow Coma Scale (PGCS)

The GCS is a neurological scale which aims to give a reliable and objective way of recording the state of a person's consciousness for initial as well as subsequent assessments. The PGCS is the equivalent of the GCS and is used to assess the mental state of child patients. For specific collection timepoints reference Table 1.

7.2.2.4 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 subject. Subject and clinician rater versions indicate general worsening or improvement on a seven-point Likert-like scale. For specific collection timepoints reference Table 1.

7.2.2.5 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.

7.2.2.6 Status Epilepticus and Seizure Questions

All subjects will be assessed for the presence of seizures and SE after the administration of the study drug. For specific collection timepoints reference Table 1.

All assessment points:

1. Is the subject in SE currently? Yes or No
2. Was the subject in SE since the previous assessment? Yes or No
   (Note: N/A for the 15-minute timepoint)
3. Is the subject having seizures currently? Yes or No
4. Did the subject have seizures since the previous assessment Yes or No
   (Note: N/A for the 15-minute timepoint)
5. Have any new AEDs been initiation since the last assessment? Yes or No
   (Note: "New" refers to any AED that has not already been used to treat the current episode of SE)
6. If a new AED was initiated, was it to treat the current seizure/SE episode or initiated prophylactically (e.g., for transition/bridging), or other reason?
   (Note: "Prophylactic" refers to any elective/transitional/bridging AED therapy that is not indicated to treat seizure/EEG abnormal activity at this time or since the last assessment)
   Record any new AEDs on the concomitant eCRF page.

7.2.2.7 Intubation Question

All intubated subjects will be assessed for possible extubation based on medical improvement. For specific collection timepoints reference Table 1.

Assessment Point:

1. Per your evaluation has the subject's medical condition improved enough to warrant considering extubation? Yes or No

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 and Medication History

Medical history will include the following:

- Previous and concomitant illnesses, surgeries, and medications
- Family history
- History of drug and alcohol abuse
- History of seizures and/or SE events

7.2.3.2 Physical and Neurologic 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 full 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 study drug initiation will be documented in the subject's source documents and in the medical history eCRF. Conversely, abnormalities identified at this first PE that are thought to develop after study drug 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.

Neurologic examinations should be performed at the time consent/assent is administered to the subject for continued participation and then on the in-patient follow-up day using the Mini Mental State Examination (MMSE) as stated in Table 1.

7.2.3.3 Adverse Event Collection

Subjects 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 are collected from the time of first dose of study drug through the last 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 until the in-patient follow-up day is completed. If not continuously monitored, vitals should be assessed as stated in Table 1 including collection for subjects who stop study drug without a taper or early terminate the study.

Noninvasive blood pressure (systolic and diastolic) and pulse rate will be measured by an automated blood pressure device after the subject 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 screening vital signs that are deemed clinically significant in the opinion of the investigator are to be recorded as AEs.

Weight and height should be collected at screening for calculation of the BMI inclusion criterion, if feasible. If not collected at screening they will need to be collected at any timepoint prior to the end of the in-patient follow-up day.

7.2.3.5 Clinical Laboratory Evaluations

All clinical laboratory assays will be performed per the hospitals laboratory's normal procedures. 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 subject's clinical condition may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

For drugs of abuse, including alcohol testing, enrollment is not contingent upon results. However, if a subject tests positive, it will be at the investigator's discretion to weigh the risks verses benefits for the subject's continued participation. If the investigator decides to discontinue the study drug, please refer to Section 4.5.

The following clinical laboratory assessments will be performed as part of the protocol:

Hematology & Coagulation	Biochemistry	Urinalysis
Hemoglobin (Hb) Hematocrit 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 % Basophils % Eosinophils % Lymphocytes % Monocytes % Neutrophils Basophil count Eosinophil count Lymphocyte count Monocyte count Neutrophil count Fibrinogen Activated partial thromboplastin time (aPTT) Prothrombin time International normalized ratio (INR)	Sodium Potassium Calcium Glucose Total protein Albumin Creatinine Blood urea nitrogen (BUN) Bilirubin Alkaline phosphatase (ALP) Aspartate transaminase (AST) Alanine transaminase (ALT) Gamma-glutamyl transferase (GGT) Total cholesterol Antiepileptic drug levels (AEDs): fosphenytoin/ phenytoin, valproic acid, levetiracetam, lacosamide, and/or brivaracetam	pH Protein Blood Ketones Glucose Bilirubin Specific gravity Albumin If ***<u>any abnormal value</u>*** is observed on the urine dipstick test, the sample should be further analyzed with urine microscopy: WBC RBC Cellular casts Granular casts Hyaline casts **<u>Urine or Serum Drug Screen</u>** Phencyclidine Opiates metabolite THC methamphetamines/amphetamine Barbiturates Benzodiazepines Cocaine Methadone Oxycodone Alcohol

All blood gas samples, including FiO_2, PaO_2, and Arterial pH, if collected per the investigator's discretion for subject's care, from the time of SE diagnosis through the in-patient follow-up day, should be recorded in the eCRF. If no samples are collected, a sample will not be required.

In addition, a blood gas sample should be collected when the decision is made to intubate the subject. The sample should be collected immediately prior to or as close as possible to the time of intubation.

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 study drug initiation, and if pregnancy is suspected. If not possible to collect pre-dose, then collect as soon as possible after study drug initiation. It is at the sites' discretion whether to perform a urine or serum pregnancy test. Enrollment is not contingent upon results. However, if a subject has a positive test result, it will be at the investigators discretion to weigh the risks verses benefits for the subjects continued participation. If the investigator decides to discontinue the study drug, please refer to Section 4.5.

7.2.3.6 Electrocardiography

ECG should be collected after the subject 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.

ECGs should be collected at the timepoints noted in Table 1.

7.2.3.7 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.

7.2.3.8 Full Outline of UnResponsiveness (FOUR) Score

The FOUR Score is a clinical grading scale in the assessment of patients with impaired level of consciousness. The FOUR Score is a 17-point scale (with potential scores ranging from 0-16). Decreasing FOUR Score is associated with worsening levels of consciousness. The FOUR Score assesses four domains of neurological function: eye responses, motor responses, brain stem reflexes, and breathing pattern. The FOUR Score should be collected at the timepoints noted in Table 1.

7.2.4 Others

7.2.4.1 Clinical Pharmacology Blood Sample Collection and Handling Procedures

Blood samples will be collected at the times specified in Table 1. The sponsor's expectation is that the investigator will ensure that every effort is made to collect all pharmacokinetic 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 from samples drawn within 4 hours post study drug initiation or by more than ±60 minutes for samples

drawn beyond 4 hours post study drug 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 K2EDTA 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, must 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.

If study drug is administered via central access, the PK sample cannot be collected from any central access ports. If study drug is administered via venous access, the PK sample must be collected via the contra-lateral arm of the study drug arm. The location of study drug access and location of PK sample collection should be documented in the subject's source. If the PK sample cannot be collected due to poor venous access and the study drug infusion site is the only viable option, the specimen should not be collected and the reason for non-collection documented in the subject'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 Quest Pharmaceutical Services for analysis. The study monitor 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 subjects complete the in-patient follow-up day, the site will ship the primary plasma samples to QPS. Upon notification of receipt of the primary samples by QPS, the backup samples will be shipped to the bioanalytical laboratory. Refer to the Biospecimen Manual for details regarding specimen 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.

7.2.4.3.1 Cerebral Spinal Fluid (CSF)

If a subject has a lumbar puncture for the collection of CSF per investigator's discretion as part of their care and there is adequate volume, a sample will be aliquoted for future analysis of ganaxolone. If multiple lumbar punctures are performed, a sample from each puncture is requested. If not collected or not enough CSF is collected to provide a sample for the study, a sample will not be required.

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

7.2.4.4 Neurosteroid Blood Sample Collection and Handling Procedures

Blood samples will be collected at the times specified in Table 1. Venous blood samples (2.5–6.0 mL) will be drawn 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, must be documented as a concomitant medication.

If study drug is administered via central access, the neurosteroid sample cannot be collected from any central access ports. If study drug is administered via venous access, the neurosteroid sample must be collected via the contra-lateral arm of the study drug arm. The location of study drug access and location of neurosteroid sample collection should be documented in the subject's source. If the neurosteroid sample cannot be collected due to poor venous access and the study drug infusion site is the only viable option, the specimen should not be collected and the reason for non-collection documented in the subject's source.

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.

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

Specific collection times can be found in Table 1.

Table 4: Volume of Blood to Be Drawn from Each Subject

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	6	2	51-68
	Hematology	4.0	6	2	24-32
	Coagulation	5.1	6	2	30.6-40.8
	IV AEDs	7.5	6	5	45-82.5
Pharmacokinetic samples (with indwelling catheter) [c]		3.0	9	4	27-39
Neurosteroid samples (with indwelling catheter) [c]		7.5	2	0	15
Arterial blood gas (for intubation only) [b]		1.0	0	1	1
Total mL					192.6-278.3

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, pharmacokinetic, and neurosteroid 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 a full sample collection list. There are required collection timepoints for all subjects 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 subject.

c. Blood samples for pharmacokinetic and neurosteroid analysis will be collected as noted in Table 1. Venous or arterial samples are acceptable.

Table 5: Volume of Blood to Be Drawn from Each Subject (Pediatric Hospital 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	6	2	12-16
	Hematology	1.0	6	2	6-8
	Coagulation	1.0	6	2	6-8
	IV AEDs	1.0	6	5	6-11
Pharmacokinetic samples (with indwelling catheter) [c]		3.0	9	4	27-39
Neurosteroid samples (with indwelling catheter) [c]		2.5	2	0	5
Arterial blood gas (for intubation only) [b]		1.0	0	1	1
Total mL					62–88

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, pharmacokinetic, and neurosteroid 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 a full sample collection list. There are required collection timepoints for all subjects 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 subject.

c. Blood samples for pharmacokinetic and neurosteroid analysis will be collected as noted in Table 1. Venous or arterial samples are acceptable.

During this study, it is expected that some sites (e.g., children's hospitals) will collect smaller volumes of blood from subjects per their local laboratory standards. The ranges in Table 4 and Table 5 reflect the possible range for adult and child verses a child-only hospital. The total blood volume could be as low as approximately 62 mL for pediatric-only verses 192.6 mL for other hospitals and up to approximately 88 mL for pediatric-only and 278.3 mL for other hospitals.

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 option collections have been included in Table 4 and Table 5.

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 tube, the assessments may be combined.

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 subject 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 a medicinal (investigational) product, whether or not related to the medicinal (investigational) product[28].

As this study allows for pre-consenting of subjects, all AEs will be collected from the time of first dose of study drug until the defined follow-up period stated in Section 7.1.3. 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 appropriate AE pages in the eCRF and in source documents. In addition to untoward AEs, unexpected benefits outside the study drug 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 subjects who:

a. Have 2 days of treatment which includes a 12-hour study drug taper, all adverse events will be collected through the in-patient follow-up day. During the weekly follow-up visits only, ongoing AEs and new AEs assessed by the investigator to be related to study drug will be recorded. All SAEs regardless of relationship to study drug will be recorded from the time of 1st dose through the last follow-up visit/contact.
b. Stop study drug administration without a study drug taper but continue with the follow-up visits, all adverse events will be collected through the in-patient follow-up day. During the weekly follow-up visits, only ongoing AEs and new AEs assessed by the investigator to be related to study drug will be recorded. All SAEs regardless of relationship to study drug will be recorded from the time of 1st dose through the last follow-up visit/contact. Additionally, AEs of UTI, hospital-acquired/ventilator-associated pneumonia, MI, sepsis from any source, critical illness myopathy/neuropathy and significant hypotension requiring vasopressor support will be recorded as AEs regardless of relatedness.
c. Early terminate from the study, prior to discontinuation as much information as is available should be recorded on any on-going AEs/SAEs and AEs/SAEs 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 study drug, 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 subject.

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 relationship between the study drug 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 study drug. 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 study drug 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 subject's medical condition, other therapies, or accident.
Not related	The event can be readily explained by other factors, such as the subject'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 course of 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 subject 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 study drug, 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 after the end of treatment with the study drug), and the range of variation of the respective parameter within its reference range must be taken into consideration.

For subjects who complete the study and don't progress to an IV anesthetic drug (a 3rd line treatment) for seizure suppression, if, at the end of the treatment phase, there are abnormal clinical laboratory, vital sign, or ECG values that were not present in the pretreatment findings observed closest to the start of study drug 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 subject, 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 subjects, all pregnancies are to be reported from the time of first dose of study drug until the defined follow-up period stated in Section 7.1.3.

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 Safety Department or its delegate

using the Pregnancy Report Form. A copy of the Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the CRO/Marinus Medical Monitor using the details specified in the emergency contact information section at the beginning of the protocol. If a subject has a positive test result, it will be at the investigator's discretion to weigh the risks verses benefits for the subjects 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 electronic Case Report Form 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 Safety Department or delegate 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 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor per the SAE reporting procedure whether or not it results in an AE/SAE as described in Section 8.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than one category.

- Abuse: Persistent or sporadic intentional intake of a study drug for a nonmedical purpose (e.g., to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society.

- Misuse: Intentional use of a study drug other than as directed or indicated at any dose. (Note: This includes a situation in which the study drug is not used as directed at the dose prescribed by the protocol.)

- Overdose: Intentional or unintentional intake of a dose of a study drug exceeding a prespecified total daily dose of the product.

- Medication error: An error made in prescribing, dispensing, administering, and/or use of a study drug. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the study drug are not considered reportable as medication errors.

Medication errors should be collected and reported for all products under investigation.

The administration and/or use of an expired study drug should be considered as a reportable medication error.

All study drug 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 for safety information for this study is the Ganaxolone Investigator's Brochure, which the sponsor has provided under separate cover to all investigators. However, the Investigator's Brochure has not been updated with the details of the 1 mg/mL ganaxolone IV solution. The formulation details have been added to Section 6 and will be added to the Investigator's Brochure at the annual update.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Marinus Safety Department or its delegate and the CRO/Marinus Medical Monitor within 24-hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.7) unless they result 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 e-mail the form to the Marinus Safety Department or its delegate. A copy of the Marinus SAE Fax Cover Letter (and any applicable follow-up reports) must also be sent to the CRO/Marinus 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 study drug 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 subject 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 in-patient 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 SAEs 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 or convulsions that do not result in in-patient 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 subjects, all SAEs (regardless of relationship to study) are collected from the time of first dose of study drug until the defined follow-up period stated in Section 7.1.3 and must be reported to the Marinus Safety Department and the CRO/Marinus Medical Monitor within 24-hours of the first awareness of the event.

In addition, any SAE considered "related" to the study drug and discovered by the investigator at any interval after the study has completed must be reported to the Marinus Safety Department 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 subject after study drug 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 subject'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 subject's death, the outcome should be considered not resolved, without a resolution date recorded.

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

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 institutional review boards (IRBs), local ethics committee (EC), or the relevant local regulatory authority of all SAEs that occur at their site as required.

9. DATA MANAGEMENT AND STATISTICAL METHODS

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 at the site initiation visit and/or at the investigator's meeting. Once a subject is enrolled, the site should initiate data entry within 5 business days of study drug initiation with the goal of having all data entered within 4-weeks of study drug initiation.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the CRO Data Management Plan and 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 Statistical Analysis Process

The study will be analyzed by the sponsor or its agent.

The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information, such as subject disposition, demographics, and baseline characteristics, study drug exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused, and spurious data will be addressed.

To preserve the integrity of the statistical analysis and study conclusions, the SAP will be finalized prior to database lock and the sponsor being unblinded to treatment assignments.

All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC 27513). R (R Foundation for Statistical Computing) may be used for the predictive probability calculations used in the interim analyses.

9.4 Sample Size, Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

Data from the open-label group will be summarized using descriptive statistics and not included in double-blind efficacy analysis.

In the double-blind group, the response rates in the treatment and control groups will be compared using a 1-sided hypothesis test. An O'Brien-Fleming error spending function will be used with two predefined interim analyses. The two interim analyses will occur after approximately 156 and 200 subjects have completed 24-hours of study drug administration. Prior to initiating these pre-planned analyses, the data for these subjects will have a minimum of their critical fields cleaned.

Using a total one-sided Type I error of 2.5%, critical values for the two interim and one final analysis are noted in Table 6.

Table 6: Interim Analysis Variables

Analysis	# Subjects who completed the study anytime within 24 hours of study drug administration	One-sided Critical Value	Error Spend	Cumulative Error Spend
Interim 1	156 subjects	0.0073	0.0073	0.0073
Interim 2	200 subjects	0.0135	0.0083	0.0156
Final	242 subjects	0.0200	0.00935	0.025

In the double-blind group a Data Monitoring Committee (DMC) will be assembled to review the safety and efficacy data at various intervals of the study. Only the unblinded DMC will be privy to these interim analyses and may recommend the trial stop for early success or safety findings.

Likewise, at each interim analysis, Bayesian predictive probabilities for success at the maximum (N=242) sample size will be calculated. If the predictive probability of success is < 5%, then the DMC may recommend the trial stops for futility. These are non-binding futility analyses, e.g., the Type I error = 2.5% even without these futility analyses. The Bayesian predictive probabilities will use non-informative Beta (1/2, 1/2) priors for both unknown response rates and be conducted using the methodology described in Saville et al., 2014 (Clinical Trials).

9.5 Sample Size Calculation and Power Considerations

The double-blind sample size was constructed to offer at least 85% power with a 20% effect.

Table 7 shows the power for a control group response rates ranging from 30% to 70% and assuming a 20% improvement in the treatment group.

Table 7: O'Brien-Fleming Power and Sample Size Power Calculation

Control Response %	Treatment Response %	Probability of Stopping at 156 Subjects	Probability of Stopping at 200 Subjects	Probability of Stopping at 242 Subjects	Total Power	Expected N
0.3	0.5	0.48	0.19	0.19	0.86	193
0.4	0.6	0.44	0.22	0.19	0.85	195
0.5	0.7	0.48	0.19	0.19	0.86	193
0.6	0.8	0.56	0.18	0.16	0.90	187
0.7	0.9	0.70	0.16	0.10	0.97	175

Two-hundred and forty-two subjects with the described O'Brien-Fleming stopping rules ensures 85% power in the scenario of 60% vs. 40% and increases for other scenarios with 20% effect sizes.

Using the futility rules based upon predicted probabilities, when control and treatment group response rates are equal, the probability of early stopping is 88% and expected sample size is 171.

9.6 Study Population

The **Screened Set** will consist of all subjects who have signed an informed consent.

The **Safety Set** will consist of all subjects who have received ganaxolone IV solution.

The **Modified Intent-to-Treat (mITT) Set** includes all subjects who received at least one dose of the study drug and who provided any post study drug initiation seizure/status outcome data.

The **Per-Protocol Set** will consist of all subjects in the mITT population without major protocol violations. The Per Protocol population is for supportive efficacy analysis. Major protocol violations will be defined prior to database lock.

The **Completer Set** will consist of all subjects in the mITT who have completed the final scheduled primary assessment for the study.

The **Pharmacokinetic Set** will consist of all subjects in the Safety Set for whom the primary pharmacokinetic data is considered sufficient and interpretable.

9.7 Efficacy Analyses

9.7.1 Primary Efficacy Endpoint

The primary efficacy endpoint is defined as the number of subjects who did not require an IV anesthetic drug (a 3rd line treatment) for SE treatment within the first 24 hours after study drug initiation.

The primary efficacy analysis will be conducted over the mITT Set. The primary efficacy analysis will be conducted by using a logistic model that includes treatment group as a factor along with factors controlling for age, GCS, and history of epilepsy. One-sided tests will be performed and compared to the critical values shown in Section 9.4, thus ensuring overall 1-sided Type I error ≤ 0.025.

9.7.2 Secondary Endpoints

- For subjects on concomitant second-line therapy: time to cessation of SE or next treatment decision (defined as the need for an IV anesthetic drug (a 3rd line treatment) when on ganaxolone)
- Level of responsiveness as assessed by the GCS, Four Score Scale, and RASS at 24 hours post study drug initiation
- The number of subjects who did not require additional 2nd line IV AED therapy for SE treatment in the 24-hours after taper
- Safety and tolerability of ganaxolone IV solution as adjunctive SE therapy as assessed by neurologic, EEG, and physical examinations, clinical laboratory tests, ECGs, vital signs, and spontaneously reported AEs
- Number of subjects who maintained SE resolution 24 hours after study drug taper and at Week 4
- Number of subjects with seizure(s) following cessation of SE through the in-patient follow-up day
- Level of responsiveness as assessed by the GCS if SE is continuing, on the in-patient follow-up day
- Seizure burden assessed as duration of electrographic seizure activity per hour of EEG recording collected
- Clinical outcome as assessed by MRS at the in-patient follow-up day and Week 4
- Characterization of the pharmacokinetic profile of ganaxolone IV solution in SE subjects
- Length of stay in intensive care unit and hospital, mortality, morbidity, need for and duration of intubation and mechanical ventilation, and seizure freedom

9.7.3 Exploratory Endpoints

9.8 Safety Analyses

AEs 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. Treatment-emergent AEs will be further summarized by severity and relationship to study drug. AEs related to study drug, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized and listed.

Clinical laboratory tests, vital signs, ECG findings, MRS, and FOUR Score will be summarized by treatment group and visit. Potentially clinically important findings will also be summarized or listed. Where applicable, the estimated subject mortality will be calculated using APACHE or APACHE 2 score.

The study team physician and the clinical operations lead will monitor emerging safety data from each subject periodically throughout the duration of the study. This data will be blinded for the double-blind group.

9.9 Other Analyses

EEGs will be monitored and assessed by the site for the following:

- EEG pattern consistent with SE
- EEG pattern consistent with cessation of SE
- Seizure burden
- Burst suppression (if achieved)

A central EEG reader will verify site-marked EEG patterns to confirm consistency of SE and seizure identification and cessation.

Blood samples for neurosteroid levels will be analyzed by a bioanalytical laboratory. Details of the data analysis and presentation will be detailed in the statistical analysis plan.

Cerebral spinal fluid, if collected per the investigator's discretion and adequate volume is available, will be stored for future analysis.

9.9.1 Pharmacokinetic Analyses

The pharmacokinetic population includes all subjects who have received at least 1 dose of study drug and who have sufficiently complete concentration-time data (at least 5 data points with a quantifiable plasma ganaxolone concentration value).

The following ganaxolone plasma pharmacokinetic parameters will be calculated as data allows and as appropriate using noncompartmental approaches. Pharmacokinetic variables will be computed using WinNonlin Professional, version 5.2 or similar software. Actual elapsed sampling times relative to ganaxolone administration will be used for the estimation of pharmacokinetic metrics. The following pharmacokinetic parameters of ganaxolone in plasma will be calculated. Additional parameters may be calculated on discretion of the pharmacokinicist, pending review of the data.

- 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_{infN}

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, International Conference on Harmonisation (ICH), European Union (EU) Directive 2001/20/EC 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.

10.1 Sponsor's Responsibilities

10.1.1 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 applicable industry regulations, ICH GCP Guideline E6 (1996), and EU Directive 2001/20/EC, 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, subjects' 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 study drug for shipment to the site.

10.1.2 Public Posting of Study Information

The sponsor, or their designee, is responsible for posting appropriate study information on applicable websites such as ClinicalTrials.gov. Information included in clinical study registries may include participating investigator's names and contact information.

10.1.3 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.

10.1.4 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.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, 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 a potential for recruiting the required number of suitable subjects 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 subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject'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).

10.2.2 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 subjects 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 all study drug, containers, and other study materials to the sponsor. 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.

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

eCRFs are supplied by the CRO and should be handled in accordance with 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. eCRFs 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 per 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.

10.2.3.2 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 subject's medical file and original clinical laboratory reports.

All key data must be recorded in the subject'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 subject 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., subject'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 regulatory agency (e.g., the US Food and Drug Administration [FDA], European Medicines Agency [EMA], UK Medicines and Healthcare Products Regulatory Agency) or an auditor.

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

10.2.3.3 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 US FDA (as well as other US national and local regulatory authorities), the EMA, the UK Medicines and Healthcare Products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.3.4 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 study drug; and any significant equity interest in the sponsor or subsidiaries as defined in 21 Code of Federal Regulations 54 2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent and assent, where applicable, from all study subjects prior to any study-related procedures, including screening

assessments. As the disease under consideration is a life-threatening condition for which subjects 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 subject for study participation. Consent /assent will be administered per the institutions 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 subject directly. Alternatively, consent and assent for subjects 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 hospitals IRB/EC. However, reconsenting will be needed 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 subject, subject's parent, guardian, or the LAR, as applicable, is requested to sign and date the subject's informed consent form or a certified translation, if applicable, after the subject parent, guardian, or LAR has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent and assent documentation (i.e, a complete set of subject information sheets and fully executed signature pages) must be given to the subject, subject's parent, guardian, or the LAR, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The principal 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 principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2 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 document (approved by the sponsor or their designee), relevant supporting information, and all types of subject 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 documents and amendments to the protocol unless there is a subject safety issue.

Study drug 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.

10.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with Health Insurance Portability and Accountability Act (HIPAA) of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the CRO/sponsor.

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

After subjects, 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 subjects' identities.

Subjects 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 subject).

The results of studies containing subjects' 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.

10.5 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 hospital 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.

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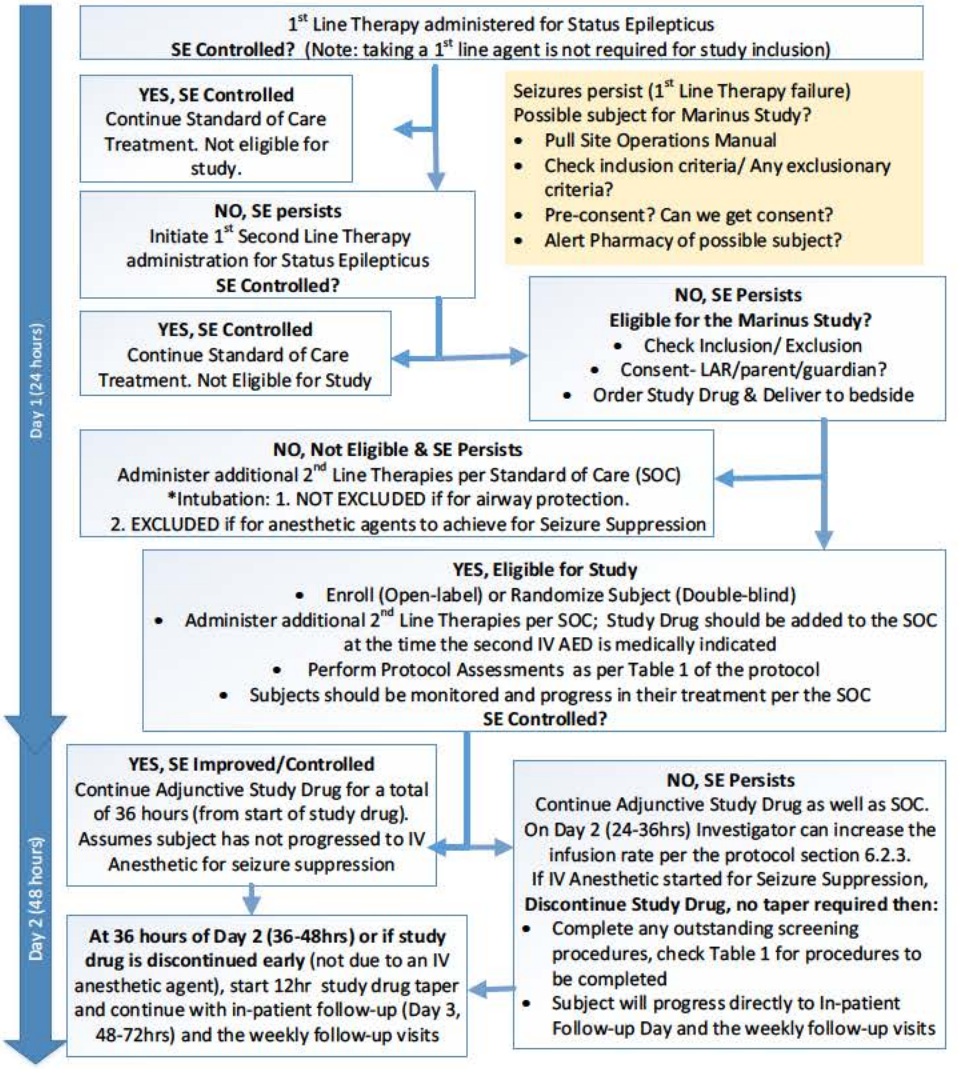
12. APPENDICES

Appendix 1: Study Decision Tree



Note: Regardless of the Day the Study drug is discontinued (with or without taper), continue standard of care and study assessments/procedures through the in-patient follow-up visit. Follow-up contact/visits will be conducted at Weeks 2, 3, and 4

Note: For subjects who receive study drug for less than 2 hrs, have their infusion interrupted/discontinued and not restarted, and/or if at any time during study drug administration the subject progresses to an IV anesthetic (a 3rd line treatment) for seizure suppression no study drug taper is required

Appendix 2: Summary of Changes Table from Previous Protocol Amendments

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **26 January 2018**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
Clarified the total number of subjects expected to be screened and enrolled in the study.		Synopsis, Section 3.1
In the Primary Objective, Primary Endpoint, and Secondary Endpoint, removed the wording ''additional IV AEDs", "Additional 2nd line therapy", and "subsequent AEDs" to simplify the study and target the key next medication (IV anesthetics) that physicians would see benefit in avoiding.		Synopsis, Sections 2.2.1, 9.7.1, and 9.7.2
To provide consistency across sites, specified that the study drug should be added to the standard of care at the time that the second AED is medically indicated and ideally given via its own dedicated line.		Synopsis, Sections 3.1 and 6.2.3
Updated the two options for stopping study drug. Added to the first option that the 24hour taper is for subjects who have taken drug for >2hours and do not progress to IV anesthetics for seizure suppression and the second option, immediately stopping study drug without tapering is for subjects who have taken study drug for less than 2 hours or who are progressing to an IV anesthetic drug (a 3rd line treatment) for seizure suppression. In this second scenario no taper is needed as the subject will be receiving increasing doses of an anesthetic agent.		Synopsis, Sections 6.2.3 and 7.1.3
Provided additional guidance that any subject who progresses to an IV anesthetic drug (a 3rd line treatment) for seizure suppression should immediately have the study drug stopped and be discontinued from the study. As possible, any outstanding screening procedures and early termination procedures should be completed. No additional procedures will be conducted other than following up on any ongoing AE/SAEs and the associated concomitant medications related to these AE/SAEs.		Synopsis, Sections 4.5, 5.2.2, 6.2.3, and 7.1.3
Added clarification that if the partial seizure burden improvement is between 33-50% the investigator can contact the Medical Monitor to discuss if study drug treatment beyond the initial 2 days is medically indicated and that the seizure burden calculation should encompass the entire first 2 days of dosing.		Synopsis, Sections 6.2.3 and 7.2.2
Added the collection of neurosteroids samples, clarified that the pharmacokinetic samples can be venous or arterial, updated the sample collection volumes, corrected a math error in the total possible blood volume being collected, and removed the detailed vendor and pharmacokinetic sample shipping information.		Synopsis, Section 7.2.5 and 9.9
Clarified the four blocks of time when seizure burden should be calculated.		Synopsis and Section 7.2.2
Clarified that if a subject discontinues the study on the same day that an assessment has already been collected, that the assessment doesn't need to be repeated for the early termination procedures unless there is a change since the previous assessment collection.		Synopsis and Section 7.1.3
Pregnancy testing, added wording to confirm that it is at the sites discretion where to perform a urine or a serum pregnancy test.		Synopsis and Section 7.2.3.6

Added the Status Epilepticus and Seizure Questions should also be collected on the 24hour post-dose taper day. This would capture answers to the 2 questions for subjects who are discontinued from the study.	Synopsis and Section 7.2.2
Adverse Events and Concomitant Medications, added text to clarify the collection of information for subjects who discontinue the study.	Synopsis and Section 7.1.3
Inclusion criteria #4 has been revised to remove the "and" of the "and/or". New wording is as follows: "Subject on concurrent 2nd line therapy with fosphenytoin/ phenytoin, valproic acid, levetiracetam, or lacosamide".	Synopsis and Section 4.1
Combined the Key Secondary and Secondary Endpoints under the Secondary Endpoints header as this is a phase 2 study.	Synopsis and Section 9.7.2
Section 1.2 Product Background and Clinical Information has been updated to reflect the language in the most current Investigators Brochure and harmonize the language concerning breast feeding across the ganaxolone development program.	Sections 1.2 and 4.3
Subject Withdrawal Criteria has been updated to clarify that subjects with impaired kidney function (eGFR is 45 mL/min or below) can start dialysis while on the study.	Section 4.5.1
Confirmed that the Medical Monitor does not need to be contacted if a subject is being discontinued because they are progressing to an IV anesthetic drug (a 3rd line treatment) for seizure suppression.	Section 4.5.1
As the study allows for pre-consenting of subjects the wording was updated to reflect that subject numbers will be assigned prior to dosing instead of as they consent to take part in the study and that adverse events, serious adverse events and pregnancy will be collected from the time of study drug initiation and not from the site of consent signature.	Sections 6.2.2, 7.2.3.3, 8.1, 8.1.6, and 8.2.4
Clarified that during the study drug taper if the infusion rate becomes too low to sustain the infusion line that it can be discontinued at that point.	Section 6.2.3
Investigator's Brochure entry was updated to reflect the current version information.	References
Study flow chart was updated to reflect the dosing timepoint clarification and the opportunity to consult the Medical Monitor if the seizure burden reduction is between 33-50%.	Appendix
Additional grammatical, typographical errors and formatting revisions have been made in the document but are not identified here.	

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2**	**Amendment Date** **10 May 2018**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
Updated the [redacted] to [redacted] MD, PhD.		Protocol Signature Page and Emergency Contact

Increased the potential sample size of the open-label group and the study overall. Further defined the open-label group objectives and clarified that subjects who terminate early for reasons other than lack of efficacy or AEs related to ganaxolone can be replaced.	Synopsis and Section 3.1
Updated the open-label group dosing regimen including justification for the revision and correction that the daily dose of ganaxolone will not exceed 35 grams/day Captisol (approximately 500 mg/day ganaxolone) as agreed upon by the FDA.	Synopsis and Sections 3.1 and 6.2.3
To provide consistency across sites the wording describing when the study drug should be started with respect to the SE standard of care was expanded upon, "…study drug will be added to the standard of care from the time that the first 2nd line IV AED has failed and the second 2nd line IV AED is medically indicated during the treatment of SE. Study drug must be administered concomitantly with second 2nd line IV AED as close to the dose initiation of the second 2nd line IV AED as possible."	Synopsis and Sections 3.1 and 6.2.3
The study drug is tapered over 18-hours. The length of the taper period has been updated from 24-hours to an 18-hour taper period to match. Also added language that the 24-hour post-taper follow-up day should start immediately upon the completion of the study drug taper.	Synopsis including Table 1 and Sections 3.1, 6.2.3 including Table 2 & 3, 7.1.3, and 7.2.5
Clarified that the 24-hour in-patient follow-up period has been updated to "24-hour post-taper follow-up day".	Synopsis, Sections 3.1, and 7.1.3,
Clarified the definition and calculation of seizure burden.	Synopsis and Sections 6.2.3 and 7.2.2
Clarified that in addition to the pharmacokinetic samples already noted in the protocol, if subject terminates the study early or if a subject has SE relapse while the subject receives ganaxolone and is not being considered for early termination due to lack of efficacy, a pharmacokinetic sample should be collected. Two additional blood samples for pharmacokinetic analysis have been added to the total blood volume calculation.	Synopsis and Section 7.2.5 Tables 4 & 5
The inclusion criteria were modified to add BMI and clarify the protocol required clinical and electrographic seizure criteria.	Synopsis and Sections 4.1 and 7.2.3.4
The capture of EEG was clarified to explicitly state it is required for diagnosis of NCSE and continuous monitoring should begin as soon as possible.	Synopsis and Section 7.2.2
Clarified that if study drug is discontinued during this 24-hours, the second neurosteroid sample should be collected prior to study drug termination, if possible.	Synopsis and Section 7.2.5 Tables 4 & 5
Clarified that the Status Epilepticus and Seizure Questions should be collected on the 24-hour post-taper follow-up day or at the time of early termination.	Synopsis and Section 7.2.2
Two exclusion criteria were added to further refine the possible patient population; the definition of traumatic brain injury was included and a general statement about the suitability of a subject based on their history and investigators judgment.	Synopsis and Section 4.1
Updated the enrollment numbers for the ongoing post-partum depression study and add the details of when the FDA confirmed the maximum dose of Captisol (35grams) allowed for this protocol.	Section 1.2
Updated the Study Flow Diagram to reflect the revised dosing regimen.	Section 3.1, Figure 1

Added subject withdrawal criteria around respiratory depression and other adverse events or safety issues.	Section 4.5.1
The reason for discontinuation was changed from Withdrawal by subject to Consent Withdrawn to align with the study population and that a subject or their parent, guardian, or LAR may withdraw the subject from the study.	Section 4.5.2
Specified that if a subject is receiving prophylactic oral AED therapy to manage a subject's chronic medical condition, for example, epilepsy, migraine, or neuropathic pain, that therapy is acceptable and should continue unchanged if feasible and medically justified. And that this prophylactic treatment does not count toward the SE treatment failures required to qualify for this study.	Section 5.2.2
As the study allows for pre-consenting of subjects the wording was revised in Protocol Amendment 1 that adverse events, serious adverse events and pregnancy will be collected from the time of study drug initiation and not from the site of consent signature. Two wording changes that were previously missed have been updated.	Sections 7.2.3.3 and 8.2.5
Added detail on the data review the data monitoring committee will perform during the double-blind group and that the study team will perform while the open-label group is on-going.	Sections 9.4 and 9.8
Correct the Day 2 assessment of seizure burden percentages box in the Study Decision Tree where a call to the Medical Monitor is needed.	Appendix 1
Added Summary of Changes Table from Protocol Amendment 1.	Appendix 2
Additional grammatical, typographical errors and formatting revisions have been made in the document but are not identified here.	

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **3**	**Amendment Date** **24 January 2019**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
Updated the Marinus Emergency and Additional Contact Information		Emergency Contact and Additional Contact Information
Updated all protocol references to the maximum level of Captisol allowed in the protocol to be 50 grams per day and 714 mg/day of Ganaxolone as agreed upon by the FDA on 13Dec2018.		Synopsis and Sections 2.1 and 6.2.3
Revised the dosing regimen under the increased Captisol level with the caveat that the dose may be further adjusted based on safety and efficacy findings for the open-label group and communicated through a Protocol Administrative Change Memo. However, the new infusion parameters will not exceed the daily limits of 50 grams/day Captisol (approximately 714 mg/day ganaxolone) as agreed upon with the FDA. Removed reference to Loading and Maintenance Dosing. Refined the description of when study drug tapering is not required.		Synopsis and Sections 3.1, 6.2.3 (including Tables 2 and 3), 7.1.2.1

Revised the follow-up visit criteria to require efforts be made to have at least one of the visits be in-person. During that in-patient visit clinical laboratory samples will be collected for safety assessment.	Synopsis and Sections 3.1 and 7.1.3
Revised that for at least the first 2 hours after the start of study drug administration medical personnel must be present at all times.	Synopsis and Section 6.2.3
Removed the Day 2 requirement for the investigator to contact the Medical Monitor to discuss if continued treatment beyond 2 days is medically indicated.	Synopsis and Sections 6.2.3 and 7.2.2
Revised the procedures to be followed and assessment collected for subjects who discontinue study drug and continue to the follow-up visit as well as the procedures (either with 18-hour taper or without a taper) and assessment for subject who early terminate from the study e.g, due to withdraw of consent. This include the timeframe of when the in-patient follow-up visit (24-hour post-taper follow-up day) starts.	Synopsis and Sections 3.1, 4.5, 5.2, 5.2.2, 6.2.3, 7.1.3, 7.2.3.2, 7.2.3.3, 7.2.3.4, 7.2.3.7
Based on the new dosing regimen, one 10-hour post-dose initiation pharmacokinetic sample collection has been added. The total blood volume has been updated to include the additional pharmacokinetic sample as well as additional chemistry, AED, and hematology samples at the in-patient follow-up visit.	Synopsis and Table 4 and 5 in Section 7.2.4.4
Removed the brief physical exam and made all collections a full physical exam.	Synopsis and Section 7.2.3.2
Clarified that the Glasgow Coma Scale should be collected at any time there is a change in the subject's state **(both improvement and worsening)** that the investigator thinks is clinically significant.	Synopsis and Section 7.2.2
Added language that several sites will be offered the use of a Rapid EEG machine for study pre-screening activities.	Synopsis and Section 7.2.2
Refine the exclusion criteria: Clarified that anesthesia administered for the treatment of the current episode of SE is exclusionary unless 5 half-lives have passed since its administration. Delete exclusion criterion #7 about pressor use as the exclusion of subject who have progressed to IV anesthetics makes this requirement obsolete Clarified that if a subject has previously received ganaxolone or exogenous allopregnanolone they are excluded	Synopsis and Sections 4.2 and 5.2.2
Table 1, Schedule of Assessments has been updated: Changed the Table header to be Visit/Time Point or Duration to better characterize the study days Combined the Dose Initiation and Day 1 columns as these are the same day. Changed the taper day to be Day 3 OR Day 5 and added the 18-hour duration. Specified that the Post-taper follow visit should start immediately after study drug administration is stopped i.e. 18-hour taper is completed or study drug is stopped without a taper. Added a Study Drug Discontinuation without Taper column and the associated assessments. Separated the 24-hour post-taper follow-up visit and the Early Termination visit into two columns.	Synopsis

Added a biochemistry and hematology sample at one of the Week 2, 3, or 4 follow-up visits. Removed the check mark for AE/SAE collection prior to dose initiation. Updated the footnotes for the follow-up visit requirements, the assessments for subjects who stop study drug without a taper and those who early terminate the study, clinical laboratory sample collection, study drug dosing, and pharmacokinetic sample collection.	
Updated the enrollment numbers from the most recent Ganaxolone IB and for the ongoing Marinus studies.	Section 1.2
Added the communication details of when the FDA approved the Captisol daily limit increase (≤50g/day) allowed for this protocol.	Section 2.1
Updated the Study Flow Diagram to reflect the revised dosing regimen.	Section 3.1, Figure 1
Clarified the classification requirements for Lost to Follow-up subjects.	Section 4.5.3
Added language around dose adjustment and clarified the dose interruption restrictions.	Section 6.2.3
Removed the compounded study drug storage parameters and directed sites to refer to the Pharmacy Manual for details.	Section 6.3.3
Revised the text to specify that a PI/sub-I is ordering drug and specifying the administration orders in their system and appropriately trained site staff will administer the study drug.	Sections 6.4 and 6.5
Removed the pharmacokinetic and neurosteroid sample processing requirements and directed study staff to refer to the Biospecimen Manual for instructions.	Sections 7.2.4.1 and 7.2.4.4
Updated the blood volume table and footnotes to reflect the new pharmacokinetic sample, and the follow-up for subject who stop study drug without a taper and the early termination assessments. Revised the blood volumes to account for the chemistry, hematology, coagulation, and AED levels being drawn at the same timepoints so only one of the samples needs the extra 1mL of waste as well as the revised vacutainer tubing being used by some of the sites.	Section 7.2.5, Table 4 and 5
Updated the Study Decision Tree	Appendix 1
Added Summary of Changes Table from Protocol Amendment 2.	Appendix 2
Additional grammatical, typographical errors and formatting revisions have been made in the document but are not identified here.	