Statistical Analysis Plan

1042-SE-3003

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

Investigational Product:	Ganaxolone
Reference Product:	Placebo
Indication:	Status Epilepticus (SE)
Phase：	3
Final：	Version 4.0, Amendment 3
Date:	June 4, 2024

Statistical Analysis Plan Approval

Author:

_____ _____
[redacted], Ph.D. Date (dd/mmm/yyyy)
[redacted]Biostatistics
Marinus Pharmaceuticals, Inc.

Review:

_____ _____
[redacted], M.D. Date (dd/mmmyyyy)
[redacted]
Marinus Pharmaceuticals, Inc.

Approval:

_____ _____
[redacted], Ph.D. Date (dd/mmmyyyy)
[redacted]Biometrics
Marinus Pharmaceuticals, Inc.

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ABBREVIATIONS

AE	Adverse Event
AED	Antiepileptic Drug
ATC	Anatomical-Therapeutic-Chemical
BMI	Body Mass Index
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
CI	Confidence Interval
CRF	Case Report Form
CSE	Convulsive Status Epilepticus
DMC	Data Monitoring Committee
ECG	Electrocardiogram
FDA	Food and Drug Administration
FOUR	Full Outline of UnResponsiveness Score
GCP	Good Clinical Practice
GNX	Ganaxolone
ICF	Informed Consent Form
ICH	International Council for Harmonization
ICU	Intensive Care Unit
IP	Investigational Product
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LAR	Legally Authorized Representative
MedDRA	Medical Dictionary for Regulatory Activities
ITT	Intent-to-Treat
mRS	Modified Rankin Scale
NCSE	Non-convulsive Status Epilepticus
PT	Preferred Term
PP	Per Protocol

RASS	Richmond Agitation and Sedation Scale
RSE	Refractory Status Epilepticus
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Status Epilepticus
SOC	System Organ Class
SRSE	Super Refractory Status Epilepticus
STESS	Status Epilepticus Severity Score
TEAE	Treatment-Emergent Adverse Event
WHO	World Health Organization

SUMMARY OF MAJOR CHANGES FROM PREVIOUS VERSION

SAP version 4.0 as an Amendment to SAP version 3.0	
Change	Rationale
Updated testing procedure	Requested by FDA

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide detailed descriptions and methods to be used for efficacy and safety analyses for Protocol 1042-SE-3003. This SAP is based on the Protocol 1042-SE-3003 amendment 5 (06May2024).

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA) and International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Guidance on Statistical Principles in Clinical Trials.[1] All work planned and reported for this SAP will follow internationally accepted guidelines for statistical practice published by the American Statistical Association.[2]

This is a double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of ganaxolone IV solution in status epilepticus (SE), with the option to transition the study to an open-label phase to obtain additional safety data. Unless stated otherwise, the analyses covered in this SAP apply to the double-blind phase of the study. The protocol contains additional details on study design, study conduct, and other operational aspects.

1.1 Study Objectives

1.1.1 Primary Objective

The primary objective of the study is to evaluate the efficacy and safety of intravenous (IV) ganaxolone (GNX) for the treatment of SE after failure of two or more antiseizure medications.

1.1.2 Secondary Objectives

The secondary objectives of the study are the following:

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

1.1.3 Exploratory Objectives

The exploratory objectives of the study are the following:

- Determine the effect of ganaxolone on healthcare resource utilization.
- Assess the effect of ganaxolone on doses of other antiseizure treatments and changes in seizure burden.

- Evaluate the effect of ganaxolone on quality of life, functional status, and level of responsiveness.

1.2 Study Endpoints

1.2.1 Primary Endpoints

The following co-primary endpoints are established to support the primary objective of the study:

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

1.2.2 Key Secondary Endpoints

The following key secondary endpoints will be analyzed:

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

1.2.3 Other Secondary Endpoints

The following additional secondary endpoints will be analyzed:

- Proportion of participants with any escalation of treatment in the first 24 hours following IP initiation, i.e., any medication other than IP for the acute treatment of SE in the first 24 hours.
- Time to treatment escalation following IP initiation (any other medication used for acute treatment of SE).
- Time to initiation of anesthesia for SE treatment through the final study follow-up visit/contact.
- Proportion of participants who develop Super Refractory SE (SRSE) through the final study follow-up visit/contact.
- Seizure burden through 72 hours following IP initiation.
- Level of responsiveness as assessed by the Full Outline of UnResponsiveness (FOUR) Score Scale.
- Level of sedation/agitation as assessed by the Richmond Agitation and Sedation Scale (RASS).
- Clinician Global Impression-Improvement (CGI-I).
- Level of functioning as assessed by the modified Rankin Scale (mRS).

- Level of functioning as assessed by the EuroQoL (EQ-5D-5L).
- Proportion of participants with mRS ≥ 3 at the time of hospital discharge.
- Proportion of participants whose treatment does not progress to IV anesthesia for 4 weeks following IP initiation.

1.2.4 Healthcare Utilization Endpoints

The following healthcare utilization endpoints will be analyzed:

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

1.2.5 Safety Endpoints

- Vital signs (height, weight, blood pressure [BP], pulse, respiratory rate [RR], body temperature, oxygen saturation).
- Electrocardiogram (ECGs).
- Clinical laboratory tests (hematology, chemistry and urinalysis, pregnancy and drug test).
- Physical exam findings.
- Use of concomitant medications.

  Adverse events.

1.2.6 Open-label Phase Endpoints

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

1.2.7 Pharmacokinetic Endpoints

- Maximum plasma concentration (Cmax).
- Time of maximum concentration (Tmax).
- Area under the concentration versus time curve from time 0 to t hours (AUC_{0-t}).
- Area under the concentration versus time curve from time 0 to infinity (AUC_{inf}).

- Clearance (CL). Calculated as dose/AUC_{inf}.

1.3 Study Design and Flow Chart

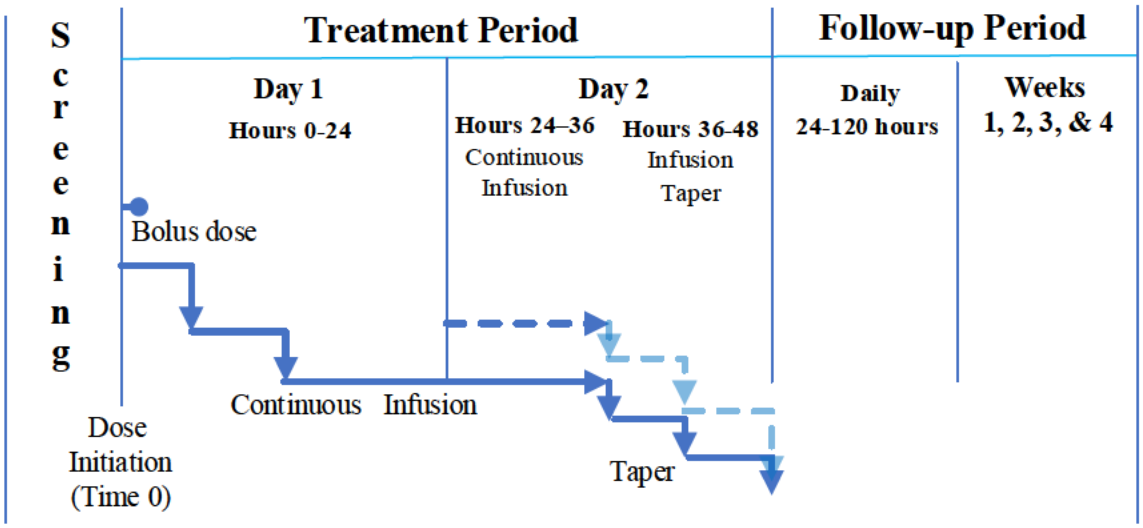
1.3.1 General Study Design and Plan

This is a double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of ganaxolone IV solution in SE, with the option to transition the study to an open-label phase to obtain additional safety data. Open-label enrollment would commence if there were a finding of efficacy from the double-blind phase at the interim analysis. Approximately 160 patients 12 years and older with SE will be screened to randomize approximately 124 participants. Randomized participants will receive ganaxolone IV solution or placebo, referred to as investigational product (IP), in a 1:1 ratio added to standard of care treatment.

After the IP has been discontinued, participants will enter the follow-up period where assessments/procedures will be collected every 24 hours through 120 hours (or until hospital discharge) and at the time of hospital discharge, followed by weekly visits/contacts at Week 1, 2, 3, and 4 following IP initiation.

The Week 1, 2, 3, and 4 visits can be conducted as inpatient visits if the participant is still in the hospital, or as telephone visits if the participant has been discharged. Attempts should be made to have discharged participants return for one of these visits in person. Each participant will be followed for approximately 4 weeks following IP initiation (Figure 1).

Figure 1: Study Design Flow Chart



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

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

Total participation is expected to be approximately 4 weeks.

An interim analysis will be conducted when two-thirds of the ITT population have completed the co-primary and key secondary efficacy assessments. Based upon the interim analysis results, DMC review and recommendation and sponsor agreement, the double-blind phase may discontinue enrollment due to a determination of efficacy. Alternatively, the DMC will recommend continuing the study without modification or provide another recommendation. If the DMC recommends that the study has met the efficacy objectives at the interim analysis and the Sponsor agrees, the study will transition to open label. All subsequently enrolled participants will receive open-label ganaxolone IV solution added to SE standard of care.

If study enrollment is proceeding at a rate such that the study would be complete or nearly complete by the time an interim analysis is accomplished, the Sponsor may elect not to conduct it.

1.3.2 Sample Size and Power

The double-blind phase will randomize and treat approximately 124 participants. The sample size is based on the assumption of at least a 75% response rate to ganaxolone treatment for each of the co-primary endpoints and no more than 45% response rate to placebo treatment with a 1:1 randomization ratio.

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

After receiving the DMC recommendation that the study may continue after the interim analysis, the sponsor made the decision to stop enrollment of the study, at which point about 100 participants have been randomized.

1.3.3 Randomization

The double-blind treatment for each participant will be determined by a predetermined randomization schedule. Participant identification numbers are assigned prior to dosing. Within each site (numbered uniquely within a protocol), participant identification numbers are assigned according to their sequence of presentation for study participation. Individual participant treatment is automatically assigned by the Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS).

1.3.4 Blinding and Treatment Assignment

The site pharmacy personnel who dispense are not required to be blinded and will not be involved in any study assessment. All participating staff involved in the evaluation and execution of the study will remain blinded to the participant's treatment assignment.

1.3.5 Unblinding the Treatment Assignment

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

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

2. STATISTICAL CONSIDERATIONS

2.1 General Considerations

- The treatment groups will be coded as "Ganaxolone" and "Placebo," and all summary tables will be provided by treatment group and overall. When applicable, treatment in open-label phase will be coded as "Openlabel Ganaxolone".
- In general, descriptive statistics (n, mean standard deviation [SD], median, 25^{th} and 75^{th} percentiles, minimum, and maximum) will be summarized by treatment group for continuous variables. Means and medians will be presented with one more decimal place than the precision of the data. Standard deviations will be presented with two more decimal

places than the precision of the data. Minimums and maximums will be presented with the same precision as the original data.

- Count and percentage of participants in each category will be provided for categorical variables. Unless stated otherwise, percentages are based on the number of participants in the treatment group of the analysis set. Percentages will be presented with one decimal place (xx.x), with the exception of 100%, which will be displayed without any decimal places, and the exception of 0%, which will not be displayed.
- All listings will be listed by treatment group, participant, test parameter, and time point (if applicable).
- Scheduled assessments will be included in summaries. Unscheduled assessments will only be included in the display sections that report abnormal laboratory results, vital signs, or ECG values. Data from all assessments (scheduled or unscheduled), will be included in the listings.
- Unless stated otherwise, baseline is defined as the last non-missing value prior to the first dose of study drug administration.
- P-values will be reported to 3 decimal places, with values less than 0.001 displayed as "<0.001."
- All outputs should have the following header at the upper left margin:

  Marinus Pharmaceuticals, Inc.
  Study 1042-SE-3003

  And the following header (right justified) at the upper right margin:

  Page n of N

  Tables/appendices/listing should be internally paginated (i.e., page numbers should appear sequentially within each table). All outputs should have SAS program name, source listing, and execution date and time included in the footnotes.

2.2 Analysis Populations

2.2.1 Safety Population

The Safety Population comprises all participants who received IP. Participants will be analyzed according to the intervention they received.

2.2.2 Intent to Treat (ITT) Population

The ITT Population comprises all randomized participants in the double-blind phase of the study who received IP and had at least one non-missing efficacy assessment. Participants will be analyzed according to the intervention to which they were randomized.

2.2.3 Per Protocol Population (PP)

The PP Population comprises of all participants in the ITT population without major protocol violations or deviations related to co-primary endpoint efficacy assessments. Participants will be analyzed according to the intervention they received.

2.2.4 Open-Label Population

All enrolled participants who receive open-label IP (should the study transition to open label).

2.2.5 Planned Analyses by Study Population

The planned analyses by population are listed in Table 1.

Table 1. Planned Analyses by Study Population

Planned Analysis	Analysis Population			
	Safety	ITT	PP	Open-Label
Demographic and Baseline Characteristics	√			√
Medical History	√			√
Prior and Concomitant Treatment	√			√
Protocol Deviation	√			√
IP Infusion Summary	√			√
Primary Efficacy		√	√	descriptive
Key Secondary Efficacy Analysis		√	√	descriptive
Other Secondary Efficacy Analysis		√		descriptive
Healthcare Utilization Endpoints		√		descriptive
Safety Analyses	√			√

2.3 Time Windows for Analyses

For by-visit safety or efficacy summaries, only scheduled visits will be analyzed. Data collected at unscheduled visits will be provided in listings.

2.4 Pooling of Centers

This multicenter study is to be conducted at approximately 100 sites in the United States, Canada, and Australia. Data from all centers will be pooled for analysis.

2.5 Handling of Missing Data

Unless stated otherwise, there will be no imputation of incomplete or missing data other than the dates mentioned below. Missing efficacy data will be imputed in a sensitivity analysis as described in Section 3.2.1.1.

The handling of partial start and stop dates for AEs are described in Table 2 below. Similar algorithms for handling missing and partial dates of concomitant medication usage are described in Table 3. In both cases, if a stop date is complete and an imputed start date is after the stop date, the start date will be set to the stop date.

Table 2: Adverse Event Start/Stop Date Imputation

Parameter	Missing	Additional Conditions	Imputation
Start date for AEs	D	M and Y same as M and Y of initiation of IP infusion	Date of initiation of IP infusion
		Y same but M prior to month of initiation of IP	Last day of month
		Y same but M after month of initiation of IP infusion	First day of month
		Y is prior to year of initiation of IP infusion	Last day of month
		Y is after year of initiation of IP infusion	First day of month
	M	Y is same as Y of initiation of IP infusion	Month of initiation of IP infusion
		Y is prior to year of initiation of IP infusion	M = December
		Y is after Y of initiation of IP infusion	M = January
	D and M	Y same as Y of initiation of IP infusion	Date of initiation of IP infusion
		Y prior to Y of initiation of IP infusion	M and D will be December 31
		Y after Y of initiation of IP infusion	M and D will be January 1
	Y, or M, D, Y	Y and/or start date missing	Date of initiation of IP infusion
Stop date for AEs	D	M and Y not missing	Use last day of month (i.e., D may take on values of 28, 29, 30, or 31, depending on month)
	M	Y not missing; if D also missing, impute D as described above	M = December
	Y, or M, D, Y	Y and/or stop date missing.	No imputation. Date left missing.

D=day, M=month, Y=year

Note: In all cases, if an estimated start date is after a complete stop date, the start date will be set to the AE stop date. Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.

Table 3: Imputation for Prior/Concomitant Medication Missing and Partial Dates

Parameter	Missing	Additional Conditions	Imputation
Start date for con meds	D only	M and Y are not missing or imputed.	Use 1st day of M.
	M only	D and Y are not missing or imputed.	M = January
	M and D	Y is not missing or imputed.	Use Jan 01 of Y
	M, D, and Y	None - date completely missing	No imputation but considered concomitant unless stop date is prior to first dose of IP.
Stop date for con meds	D only	M and Y are not missing or imputed.	Last day of month
	M only	D and Y are not missing or imputed.	M = December
	M and D	Y is not missing or imputed	Use Dec 31 of Y
	M, D, and Y	None - date completely missing and NOT ongoing	No imputation

Note: In all cases, if an estimated start date is after a complete stop date, the start date will be set to the end date of medication.

2.6 Analysis Software

All summaries and statistical analyses will be generated using SAS® version 9.4 or later.

2.7 Handling of Data after Interim Analysis

The interim analysis will be conducted based on data from approximately the first 82 participants in the ITT population who have completed assessments for the co-primary and key secondary endpoints. It is anticipated that data cleaning, data analysis, preparation of data and its review by the DMC will require approximately 8-12 weeks. During this time, double-blind randomization will continue.

If the decision is made based on the interim analysis results to discontinue the double-blind phase due to demonstration of efficacy, the analysis set for the primary and key secondary endpoints will consist of data provided to the DMC for review, i.e., approximately 82 participants in the ITT population. Co-primary and key secondary endpoint data for additional double-blind participants enrolled after the interim analysis data cutoff will be summarized in combination with data from the interim analysis using descriptive statistics. Interim efficacy analyses will only be performed for the primary and key secondary endpoints; the analyses of other efficacy endpoints will be performed in the full ITT population in the double-blind phase. Additionally, efficacy endpoint data from the open-label phase will be summarized using descriptive statistics.

If the decision is made at the interim analysis to continue the double-blind phase, safety and efficacy data collected after the interim analysis will be integrated with the interim data and will be included in the final analysis. Safety data from the double-blind and open-label phases will be summarized separately and in combination.

The interim analysis was conducted on the first 83 participants in the ITT population who have completed assessments for the co-primary and key secondary endpoints. The DMC recommended the study may continue without modification.

3. STATISTICAL ANALYSIS

3.1 Participant Information

3.1.1 Disposition of Study Participants

The number of participants screened for this study, the number of screen failures and the number of participants who received at least one dose of IP will be summarized using the Enrolled Population. Reasons for screen failure will be provided in the data listing.

Study completion and withdrawal from the double-blind phase will be summarized by treatment group for all enrolled participants. The summary table will include the numbers of participants included in each analysis set and those who completed or did not complete the study, along with the reasons for discontinuation (adverse events, protocol deviation, lost to follow-up, death, etc.) of study treatment and discontinuation from study will be summarized.

Reason for discontinuation from study will be provided in the data listing.

In addition, a summary of the number of participants included in each analysis set will be presented.

3.1.2 Protocol Deviations

Protocol deviations will be identified to measure adherence to key aspects of the protocol before the database freeze/lock for the relevant analysis. Specific data fields that will be examined to identify protocol deviation or violations include inclusion/exclusion criteria and deviations identified by the investigator. The protocol deviations will be summarized by deviation category based on the Safety Population. A data listing will also be provided.

3.1.3 Demographics and Baseline Characteristics

Descriptive summary statistics (n, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum) and/or frequency distributions (count and percentage), as appropriate, will be provided by treatment group for the Safety Population.

Demographic characteristics summarized will include:

- Age
- Age group (12 to < 18 yrs, ≥18 yrs)
- Sex (male, female)
- Race/ethinicity
- Height (cm)
- Weight (kg)
- Weight group (<40 kg, ≥40 kg)
- Body Mass Index (BMI; kg/m^2)

Baseline characteristics summarized will include:

- Etiology of SE (Cerebrovascular accidents, Anoxia or hypoxia, etc.)
- Pre-infusion duration of SE
- Number of failed AEDs
- Previous epilepsy history
- Status Epilepticus Severity Score (STESS)
- Richmond Agitation and Sedation Scale (RASS)
- Full Outline of UnResponsiveness (FOUR) Score
- Clinical Global Impression of Severity (CGI-S)

3.1.4 Medical History

Medical history will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) Terminology version 22.0 or higher. The number and percentage of participants with medical history will be summarized by System Organ Class (SOC) and Preferred Term (PT) based on the Safety Population.

3.1.5 Prior and Concomitant Medications

Prior medications are defined as medications that started prior to the initiation of IP. Concomitant medications are defined as medications that started after the initiation of IP or started before the administration of the study drug and ongoing after the IP initiation.

All investigator terms for prior and concomitant medications recorded on the Case Report Form (CRF) will be coded using the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) drug dictionary (WHO Drug Dictionary, March 1, 2021).

The number and percentage of participants with prior and concomitant medications will be summarized by ATC level 2 and PT based on the Safety Population, by treatment group and overall. Listings will also be provided for all prior and concomitant medications. Listing will identify treatments as either prior (before the initiation of IP) or concomitant (from initiation of IP to end of follow-up visit/contact).

In addition, benzodiazepines, AEDs, and anesthesia medications, as collected in a separated CRF, will be summarized in a similar fashion. A separate listing and summary table will be presented for Benzodiazepines, AEDs, and IV anesthesia.

3.1.6 Investigational Product Infusion Summary

Investigational product will be administered as a 48-hour continuous infusion, which includes an initial 3-minute bolus and ends with a 12-hour taper based on Table 4 and Table 5. The total administered dose (mg) for IP infusion and duration of IP infusion will be summarized based on the Safety Population.

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

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

IP = investigational product.

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

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

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

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

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

IP = investigational product.

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

3.2 Efficacy Analysis

Statistical hypotheses testing will be performed for the co-primary and key secondary endpoints for the double-blind phase. To control the family wise type I error, the testing will be performed sequentially (the coprimary endpoints will be tested simultaneously), in the order as listed. Subsequent testing will only be performed if the prior tests are significant.

3.2.1 Primary Efficacy Endpoints

3.2.1.1 Primary Analysis

The co-primary efficacy endpoints are:

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

*SE cessation will be determined by the investigator based on clinical and EEG features (details in the protocol).

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

The proportion of participants with SE cessation within 30 minutes and the proportion of participants with no progression to IV anesthesia for 36 hours following IP initiation will be summarized based on the ITT population. Descriptive statistics, count and percentage of participants will be summarized by treatment group.

An interim analysis will be performed when two thirds of the planned participants have completed assessment of the co-primary and key secondary efficacy endpoints. The overall type I error rate (i.e., alpha=0.05, two-sided) will be controlled using a power family alpha spending function $0.05t^{\log(2.5)/\log(2)}$, where an alpha of 0.0293 will be spent at the interim and the remaining alpha will be reserved for the final analysis. The statistical hypotheses will be tested for both co-primary endpoints at the same respective alpha level at interim or final analysis. The interim analysis was conducted on the first 83 participants in the ITT population who have completed assessments for the co-primary and key secondary endpoints. The study enrollment was stopped due to business reasons. More details can be found in Section 3.5. The final analysis will be conducted using the fixed weight combination test. The weights are based on the original amount of information before and after the interim analysis (i.e., 2/3 and 1/3) and the test is conducted using the original calculated final 2-sided alpha of 0.0343.

The interim analysis will be performed using the logistic regression method described below. Due to the limited amount of data, the data after the interim analysis will be analyzed using the Boschloo test. If the p-value (one-sided) of the interim analysis is p_1 and the p-value (one-sided) from after the interim analysis is p_2, and let Φ^{-1} be the inverse Normal function, a final Z score is calculated as

$$Z = \sqrt{\frac{2}{3}}\Phi^{-1}(1-p_1) + \sqrt{\frac{1}{3}}\Phi^{-1}(1-p_2)$$

The Z-test using the above Z score will be used as the final test.

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

The concerned estimand is defined by its attributes below:

- Population: the target study population comprises participants with status epilepticus who also meet the inclusion and exclusion criteria as specified in the study protocol. The analysis population is the Intent-to-Treat (ITT) population as defined in Section 2.
- Variable for the first co-primary: a binary response variable indicating a successful response which is defined as SE termination beginning within 30 minutes of IP initiation without use of medications for the acute treatment of SE.
- Variable for the second co-primary: a binary response variable indicating absence of IV anesthesia for 36 hours following IP initiation.
- Intercurrent events:
    - Discontinuation of study treatment due to any reason
    - Death
- Population-level summary: odds ratio between treatment groups.

The participants with any of the listed intercurrent events will be considered as a treatment non-responder. To deal with other intercurrent events, a treatment policy approach will be adopted. Due to the nature of the disease and short observational period, occurrence of intercurrent events is expected to be low.

3.2.1.2 Sensitivity Analysis

The primary efficacy analysis will be repeated in the PP population.

In addition to logistic regression, response rates for both primary endpoints will also be analyzed using the Boschloo test.

If missing data on the first or second co-primary endpoint exceeds 5%, a tipping point analysis will be performed for that endpoint. Assuming N_c participants have missing primary outcome data in the control group and N_t participants have missing primary outcome data in the treatment group, the primary analysis will be performed to assume 0 to N_c control participants achieved the primary outcome and 0 to N_t treatment group participants achieved the primary outcome. All $(N_c+1)(N_t+1)$ outcomes will be enumerated in a grid that shows the treatment effect and p-value and the 'tipping point' when the result would cease to be statistically significant. Model averaging will be used to account for multiple possible scenarios contributing to the same number of missing data values.

3.2.1.3 Subgroup Analysis

The primary efficacy analysis will be repeated for subgroups defined by the following baseline variables:

- Age group (12-18 yrs, ≥18 yrs)
- Sex (male, female)
- Weight group (<40, ≥ 40kg)

Subgroups could be collapsed if the number of participants in some subgroups is too small.

3.2.2 Key Secondary Efficacy Endpoints

3.2.2.1 Primary Analysis

The key secondary efficacy endpoints are:

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

Time to SE cessation will be assessed for the first 72 hours following IP initiation. Observations for cessation of SE that occurs at a time greater than 72 hours will be censored at 72 hours. Key secondary endpoints will be compared between GNX and placebo groups in the ITT population. The hypotheses for the key secondary endpoints will be tested only if both co-primary endpoints are statistically significant. The key secondary endpoints will be tested in the order listed, at the same alpha level of significance as the primary endpoints. More details can be found in Section 3.5.

For time to SE cessation following IP initiation, the comparison of the survival curves of time to SE cessation between treatment groups will be conducted by a log-rank test. The quartiles (1st [25% percentile], 2nd [median], 3rd [75% percentile]) and the associated 95% CI will be provided based on the Kaplan-Meier estimate of the survival curves. participants without SE cessation before 72 hours post dose initiation or at the time of discontinuation will be censored at 72 hours or the time of discontinuation, whichever is earlier; death before SE cessation will be censored at 72 hours.

The proportion of participants with no progression to IV anesthesia for 72 hours following IP initiation will be summarized based on the ITT population. Descriptive statistics, count and percentage of participants will be summarized. This key secondary efficacy endpoint will be analyzed using logistic regression, the same analysis method as for the co-primary endpoints.

3.2.2.2 Sensitivity Analysis

The Primary analysis method will be repeated in the PP population.

3.2.2.3 Subgroup Analysis

The primary analyses of the key secondary endpoints will be repeated for subgroups defined by the following baseline variables:

- Age group (12-18 yrs, ≥18 yrs)
- Sex (male, female)
- Weight group (<40, ≥ 40kg)

Subgroups could be collapsed if the number of participants in some subgroups is too small.

3.2.3 Other Secondary Efficacy Endpoints

All the other secondary endpoints analysis will be done in the ITT population. The secondary endpoints will be analyzed descriptively. No formal statistical comparisons are planned for these endpoints.

3.2.3.1 Proportion of Participants With Any Escalation of Treatment in the First 24 Hours Following IP Initiation

Proportion of participants with any escalation of treatment in the first 24 hours following IP initiation, i.e. any medication other than IP administered for the acute treatment of SE in the first 24 hours following IP initiation will be summarized by count and percentage of participants by treatment group. The 95% CIs will be also calcualted using Clopper Pearson method.

3.2.3.2 Time to Treatment Escalation Following IP Initiation

For time to treatment escalation following IP initiation (any mediation used for acute treatment of SE), the quartiles (1^{st} [25% percentile], 2^{nd} [median], 3^{rd} [75% percentile]) and the associated 95% CI will be provided based on the Kaplan-Meier estimate of the survival curves. For participants without treatment escalation, the time to treatment escalation will be censored at IP completion, or discontinuation from the study or death, whichever occurs earlier.

3.2.3.3 Time to Initiation of Anesthesia for SE Treatment Through the Final Study Follow-up Visit/Contact

For time to initiation of anesthesia for SE treatment through the final study follow-up visit/contact, the quartiles (1^{st} [25% percentile], 2^{nd} [median], 3^{rd} [75% percentile]) and the associated 95% CI will be provided based on the Kaplan-Meier estimate of the survival curves. For participants without initiation of anesthesia for SE treatment, the time to initiation of anesthesia will be censored at IP completion, discontinuation from the study or death, whichever occurs first.

3.2.3.4 Proportion of Participants Who Develop Super Refractory SE (SRSE) Through the Final Study Follow-up Visit/Contact

Count and percentage of participants who develop SRSE through the final study follow-up visit/contact will be provided for each treatment group.

3.2.3.5 Seizure Burden Through 72 Hours Following IP Initiation

The seizure burden through 72 hours following IP initiation is described as the percent of time during which there is electrographic seizure activity from IP initiation to 72 hours. Descriptive summary statistics (n, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum) of seizure burden will be provided by treatment group. The change from baseline of seizure burden will also be summarized using descriptive statistics by treatment group. The baseline seizure burden is defined for 30 minutes prior to IP initiation.

The number and percentage in each category of seizure burden (<20%, 20-50%, and >50%) will be also summarized by treatment group.

3.2.3.6 Level of Responsiveness as Assessed by the Full Outline of UnResponsiveness (FOUR) Score Scale

The FOUR Score is a tool designed to assess participants with impaired level of consciousness. It has a 17-point scale (with potential scores ranging from 0 to 16). The FOUR Score assesses four domains of neurological function: eye responses, motor responses, brainstem reflexes, and respiration. Each component is a 5-point scale, ranging from 0 to 4.

Descriptive summary statistics (n, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum) will be provided by treatment group and by scheduled visit for total FOUR Score.

Count and percentage of each scale for each component will also be provided by treatment group and by visit.

3.2.3.7 Level of Sedation as Assessed by the Richmond Agitation and Sedation Scale (RASS)

The RASS is a medical scale used to measure the agitation or sedation level. It is a 10-point scale, with four levels of anxiety or agitation (+1 [restless] to +4 [combative]), one level to denote a calm and alert state (0), and 5 levels of sedation (−1 [drowsy] to −5 [unarousable]).

Count and percentage of each scale for each component will be provided by treatment group and by visit.

3.2.3.8 Clinician Global Impression-Improvement (CGI-I)

The CGI-S and CGI-I assess overall health and functional status of a participant. Participant and

clinician rater versions indicate general worsening or improvement on a seven-point Likert-like scale.

The CGI-S contains a 7-point Likert scales for baseline overall severity of the participant's presentation (ranging from 1 = normal to 7 = very severe problem) and the CGI-I contains a 7-point Likert scale for overall global impression of change relative to baseline (ranging from 1 = very much improved to 7 = very much worse).

Descriptive summary statistics (n, mean, standard deviation, 25th and 75th percentiles, median, minimum, and maximum) will be provided for CGI-I score by treatment group and by schedule visit. Count and percentage of each scale for CGI-S and CGI-I will be summarized by treatment group and by visit.

3.2.3.9 Level of Functioning as Assessed by the Modified Rankin Scale (mRS)

The Modified Rankin Score (mRS) is a 6-point disability scale with possible scores ranging from 0 (no symptom at all) to 5 (severe disability). A separate category of 6 is usually added for participants who expire.

Descriptive summary statistics (n, mean, standard deviation, 25th and 75th percentiles, median, minimum, and maximum) will be provided for mRS score by treatment group and by schedule visit. Count and percentage of each scale will be summarized by treatment group and by visit.

3.2.3.10 Level of Functioning as Assessed by the EuroQoL (EQ-5D-5L)

The EuroQoL (EQ-5D-5L) is a standardized measure of health-related quality of life which comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems.

Descriptive summary statistics (n, mean, standard deviation, 25th and 75th percentiles, median, minimum, and maximum) will be provided for EQ-5D-5L index score by treatment group and by schedule visit. Count and percentage of each level for each dimension will be summarized by treatment group and by visit.

3.2.3.11 Proportion of Participants with mRS ⩾ 3 at the Time of Hospital Discharge

Count and percentage of participants with mRS ≥ 3 at the time of hospital discharge will be provided for each treatment group.

3.2.3.12 Proportion of Participants With No Progression to IV Anesthesia for 4 Weeks Following IP Initiation

The number and percentage of participants with no progression to IV anesthesia for 4 weeks

following IP initiation will be summarized by treatment group.

3.2.4 Healthcare Utilization Endpoints

All the healthcare utilization endpoints analysis will be conducted in the ITT population. Healthcare utilization endpoints will be summarized descriptively by treatment group. No formal statistical comparisons are planned for these endpoints.

3.2.4.1 Time on Positive Pressure Ventilation After IP Initiation

Time on positive pressure ventilation will be analyzed by a stratified log-rank test, where the time to event for each participant is defined as time from treatment initiation (or positive pressure ventilation initiation if the participant was not on ventilation at the start of treatment) to positive pressure ventilation being off, whether the participant was on ventilation at the start of treatment is used as the stratification factor. Participants who never needed positive pressure ventilation are defined to have 0 amount of time on positive pressure ventilation. Participants who died before getting off positive pressure ventilation will be censored at the latest possible assessment time. Participants who never got off positive pressure ventilation while on study will be censored at the last assessment time. The quartiles (1^{st} [25% percentile], 2^{nd} [median], 3^{rd} [75% percentile]) and the associated 95% CI will be provided based on the Kaplan-Meier estimate of the survival curves.

3.2.4.2 Proportion of Participants Requiring Positive Pressure Ventilation Initiated During IP Infusion

Proportion of participants requiring positive pressure ventilation initiated during IP infusion will be summarized by count and percentage by treatment group. The summary will be based on participants who were not on positive pressure ventilation at baseline.

3.2.4.3 Length of Stay in ICU and in Hospital

Post IP initiation Length of stay (hours) in ICU = Time of discharge from ICU – IP initiation time

Length of stay (hours) in hospital = Time of discharge from hospital – IP initiation time

Length of stay will be summarized with descriptive statistics (n, mean, standard deviation, median, 25^{th} and 75^{th} percentile, min and max) by treatment group.

3.2.4.4 Discharge Destination

Discharge destination is the location where the participant is living at the last follow-up assessment.

Count and percentage of each discharge destination will be summarized by treatment group.

3.2.5 Open-label Phase Efficacy Summary

Efficacy assessments for the open-label phase will be summarized using descriptive statistics.

3.3 Safety Analysis

All the safety summaries are based on the Safety Population. Baseline is defined as the last non-missing value prior to the first dose of study drug administration.

3.3.1 Adverse Events

Adverse events (AEs) will be coded by MedDRA® version 22.0 or higher and grouped by SOC and PT. The verbatim term will be included in the AE listings. Except where indicated, the summary tables will include only TEAEs. All AEs, treatment-emergent or otherwise, will be presented in participant data listings.

A treatment-emergent adverse event (TEAE) is defined as an AE that occurred or worsened at the time of or following IP initiation. To allow differentiation between the study period in which an AE occurred, two categories are defined based upon onset date. Adverse events that had onset dates prior to the IP initiation are considered “prior.” Adverse events with onset dates on or after IP initiation and up to the end of the follow-up period are considered "on-therapy" or equivalently “treatment emergent”. Adverse events with onset dates prior to the IP initiation but that worsen after IP starts will be considered treatment emergent.

An overview table, including number and percentage of participants with AEs, TEAEs, TEAEs by highest severity, serious TEAEs, study drug related TEAEs, TEAEs leading to IP discontinuation, and TEAEs leading to death will be provided.

In addition, the following summary tables will be provided:

- TEAE by SOC and PT
- TEAEs by PT
- TEAE by SOC, PT, and severity
- Study drug related TEAE by SOC and PT
- Serious TEAE by SOC and PT
- Serious and drug-related TEAE by SOC and PT
- TEAEs leading to study drug discontinuation by SOC and PT
- TEAEs leading to withdrawal

All AE tables will be sorted by SOC and PT in decreasing frequency of the number of participants in the GNX-treated group. If frequency ties, the sorting will be alphabetic.

A participant having the same AE more than once will be counted only once in the number and percentage of participants' calculation for that AE. Similarly, if a participant had more than one AE in a SOC, the participant will be counted only once in the number of participants with an AE for that SOC. If a participant has the same AE on multiple occasions, the highest severity (severe > moderate > mild) recorded for the event will be presented in the AEs by severity table.

Adverse event listing will be provided for all TEAE, serious TEAEs, TEAE related to IP, TEAE leading to study drug discontinuation, AEs leading to withdrawal, and participants who died during the study.

3.3.2 Vital Signs

Vital signs include weight (kg), height (cm), temperature (°C), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse rate (bpm), respiration rate (breaths per minute), and oxygen saturation (%). Descriptive statistics for vital signs and changes from baseline values at each time point will be provided for each parameter.

All vital signs data will be presented in the participant data listings.

3.3.3 Laboratory Evaluations

All laboratory parameters will be presented in Standard International (SI) units. Only scheduled lab parameters will be included in the lab summaries.

Laboratory data collected in this study include serum chemistry and hematology values, urinalysis results, pregnancy results, and drug of abuse results. The baseline laboratory value is defined as the last value observed prior to IP initiation. Any values collected after IP initiation are regarded as post-baseline. Change from baseline will be calculated as the post-baseline value minus the baseline value. Only the numeric part in laboratory values that contain non-numeric qualifiers, such as less than (<) a certain value or greater than (>) a certain value, will be used in the summary statistics.

Quantitative results (including actual value and change from baseline) will be summarized using descriptive statistics by baseline and post-baseline visit for each laboratory test based on the Safety Population. Shift tables cross-tabulating the baseline and post-baseline classifications (below [L], Normal [N], or above [H] the reference range), by visit, will be provided.

All laboratory data will be included in the listing, including whether the value was below (L), within (N), or above (H) the normal reference range (some urinalysis labs are assigned only normal and abnormal classifications).

Pregnancy results performed on selected participants will be listed.

Screening results for drugs of abuse, including alcohol, will be listed separately.

All blood gas results, including FiO2, PaQ2, and arterial pH, if available will be listed.

3.3.4 Electrocardiogram

Descriptive statistics for ECG parameters (PR interval, RR interval, QRS interval, QT interval, QTcF [QT interval corrected using Fridericia's method], QTcB [QT interval corrected using Bazett's method], heart rate) and changes from baseline values at each time point will be provided.

In addition, the number and percentage of participants in each category of the interpretation (normal, abnormal not clinically significant, abnormal clinically significant) will be summarized.

Select sites will participate in a substudy using a continuous 12 lead ECG recorder which should start approximately 60 minutes prior to IP initiation and should continue for 36 hours following IP initiation. The data from the substudy of cardiodynamic 12 Lead Electrographic (ECG) monitoring will be summarized in separate tables using the same approach as for the main study if the data is ready by the primary analysis.

All ECG data will be presented in the data listing.

3.3.5 Physical Examination

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

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

Physical examination results for each body system are interpreted as normal and abnormal. The number and percentage of participants in each category (normal, abnormal) and change from baseline (normal to abnormal or abnormal to abnormal) will be summarized for each body system by treatment group and by visit.

Listings for all the physical examinations will be provided.

3.4 Pharmacokinetic Analysis

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

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

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

3.5 Interim Analysis

An interim analysis is planned when two thirds of the ITT population have completed assessments for the primary and key secondary efficacy endpoints. If study enrollment is proceeding at a rate that the study would be nearly complete by the time an interim analysis is accomplished, the Sponsor may elect not to conduct it. If the interim analysis is conducted, an alpha of 0.0293 (details below) will be spent at the interim; if the interim is not conducted, no alpha will be spent. The interim analysis will be performed by an independent statistical organization and reviewed by an independent Data Monitoring Committee (DMC) who are not involved in the regular study operation and conduct.

The overall type I error rate (i.e., alpha=0.05, two-sided) will be controlled using a power family alpha spending function $0.05t^{\log(2.5)/\log(2)}$, with two-sided nominal alpha levels of 0.0293 and 0.0343 (with adjustment as needed) at the interim and the final analyses, respectively. At the interim analysis, the two co-primary endpoints will be tested first, both at the same nominal alpha level of 0.0293. If both endpoints are statistically significant, the key secondary endpoints will be tested sequentially (a test will only be performed if all the prior ones are significant) in the order as listed,

at the same nominal alpha level of 0.0293 as for the primary endpoints. If one or both primary efficacy endpoints fail to reach statistical significance at the interim analysis, the same testing process will be repeated at the final analysis at the nominal alpha level of 0.0343. The operational details of the interim analysis will be described in the Interim Analysis Plan.

An interim analysis was performed with 83 participants spending a two-sided alpha of 0.0293 as planned. The independent DMC recommended that the study could continue without modification. However, the sponsor made the decision to stop enrollment when 100 participants were randomized. The final analysis will be conducted using the fixed weight combination test. The weights are based on the amount of information that would have originally been available before and after the interim analysis (i.e., 2/3 and 1/3) and the test will be conducted using the original calculated final 2-sided alpha of 0.0343.

4. CHANGE TO ANALYSES SPECIFIED IN PROTOCOL

No changes.

5. PROGRAMMING SPECIFICATIONS

Detailed programming specifications will be documented and filed in the study file.

6. TABLES/LISTINGS/FIGURES TEMPLATES

Templates for planned tables, listings, and figures will be documented and filed in the study file.

7. REFERENCES

1. International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9).
2. American Statistical Association (ASA) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics.

8. APPENDICES

8.1 Schedule of Assessments

Details of schedule of assessment can be found in the protocol and protocol clarification memos

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

Details of schedule of assessment can be found in the protocol and protocol clarification memos

Periods/Day/ Duration	Screening[a] Day -1 to Day 1 Predose through screening	Dosing Day 1 IP initiation 0 through 24 hours following IP initiation				Dosing Day 2 24 hours through 36 hours following IP initiation		Taper Day 2 (12 hours) Starts at 36 hours following IP initiation	IP Discontinuation	IP Discontinuation Follow-up[b]							Early Termination
Visit	1	2				3			4	5	6	7	8	9	10	11 - 14	98
Timepoint		Minutes (m) /Hours (h) following IP initiation							With or without Taper	Hours following IP Discontinuation					Hospital Discharge	Weekly follow-up (Week 1, 2, 3, & 4)	ET
	-0	60 m	2 h	6 h	10 h	24 h	36 h	48 h	Collected prior to or as close to IP discontinuation as possible	24	48	72	96	120		6 ± 3, 14 ± 3, 21 ± 3, and 28 ± 3 days following IP discon	
Cardiodynamic 12 lead ECG monitoring (sub study only)[h]	←	—	—	—	—	—	—	→									
Biochemistry, hematology, and AEDs[i]	a								a	a					a	a	a
Urine chemistry (N-acetyl-β-D-glucosaminidase (NAG) and β2-microglobulin)[j]	a									a					a	a	a
Coagulation[k]	a									a					a		a
Routine Urinalysis[i]	a								a	a					a	a	a
Drugs of abuse, including alcohol[l]	a																
Pregnancy test (FCBP only)[l]	a																
EEG[m]	←	—	—	—	—	—	—	—	→								
Blood Gas[n]																	
CGI-S	a																
CGI-I[o]					a	a			a	a	a	a	a	a	a	a	a
Seizure Description Questionnaire-predose[p]	a																

Details of schedule of assessment can be found in the protocol and protocol clarification memos

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

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

a. The screening period is from the time participant/participant's parent/guardian/LAR consent is obtained (or deferred, if allowed by law) to immediately prior to IP initiation However, assessments collected prior to this timeframe that the investigator judges to be clinically relevant to the participant's current state can be utilized in the study and do not need to be repeated. For medically unstable participants, screening activities (e.g., labs or vital signs) should be collected as close to IP initiation as possible.

b. The planned duration for the follow-up period after IP is discontinued is approximately 4 weeks. Study assessments/procedures will be collected every 24 hours through 120 hours (or until hospital discharge) and at the time of hospital discharge followed by weekly follow-up visits at Week 1, 2, 3 and 4. Weeks 1, 2, 3 and 4 visits can be conducted as an inparticipant visit, if the participant is

still in the hospital, or as a telephone contact, if the participant has been discharged. Attempts should be made to have discharged participants return for one of these visits to be in person for clinical laboratory sample collection and RASS & FOUR Score assessments which can only be performed in person.

c. Demography, medical history, including seizures or SE etiology, and medication history will be collected prior to IP initiation but can be collected whenever feasible before the end of the taper.
d. Physical exam should be obtained from the participant's chart or completed predose (screening) or, if not available, collect within 2 hours following IP initiation, and at 36 hours, if clinically indicated, following IP initiation. Collect at the time of IP discontinuation (+/- 1 hour), either at the end of the taper or if the IP administration is stopped without a taper and 24 hours (+/- 1 hour) following IP discontinuation and at the time of hospital discharge. For participants who terminate early from the study, collect at the time of early termination (whenever possible). The investigator may conduct at any other time based on clinical judgment.
e. Vital signs including blood pressure, pulse, respiratory rate, temperature, and oxygen saturation should be collected predose (screening), 60 minutes (+/- 15 min), 2 (+/- 15 min), 6, 10, 24, and 36 hours (+/- 2 hour) following IP initiation. Collect at the time of IP discontinuation (+/- 1 hour), either at the end of the taper or if the IP administration is stopped without a taper and 24 hours (+/- 2hour) following IP discontinuation, and at the time of hospital discharge. For participants who terminate early from the study, collect at the time of early termination (whenever possible). The investigator may collect at any other time based on clinical judgment. Weight and height should be collected predose (screening) for calculation of BMI inclusion criterion, if feasible. If not collected predose (screening), collect prior to the end of the first 24 hours of the follow-up period.
f. RASS and FOUR score scales should be collected predose (screening),60 minutes (+/- 15-min), 2, 6, 10 (+/- 30 minutes), 24 and 36 hours (+/- 1 hour) following IP initiation. Collect at the time of IP discontinuation (+/- 1 hour), either at the end of the taper or if the IP administration is stopped without a taper. Collect 24 (+/- 1 hour), 48, 72, 96, and 120 hours (+/- 2 hours) following IP discontinuation and at the time of hospital discharge. Collect at the weekly follow-up visits (Week 1, 2, 3, or 4) for hospitalized participants and for participants who have been discharged (whenever possible). For participants who terminate early from the study (whenever possible), collect at the time of early termination.
g. ECG should be collected predose (screening) and 2 (+/- 30 min) following IP initiation. Collect at the time of IP discontinuation (+/- 1 hour), either at the end of the taper or if the IP administration is stopped without a taper and 24 hours (+/- 1 hour) following IP discontinuation and at the time of hospital discharge. For participants who terminate early from the study, collect at the time of early termination (whenever possible). The investigator may collect any other time based on clinical judgment.
h. Cardiodynamic 12 lead ECG monitoring. Select sites will participate in a sub study using a continuous 12 lead ECG recorder which should be started approximately 60 minutes prior to IP initiation and should continue for 36 hours following IP initiation. For more details refer to Appendix 5.
i. Clinical labs, hematology, serum chemistry (including creatinine, blood urea nitrogen, creatinine clearance calculation [if available], estimated glomerular filtration rate [eGFR] calculation [if available]), and concomitant AED levels (fosphenytoin/phenytoin, valproic acid, levetiracetam, lacosamide, phenobarbital, or brivaracetam, if collected per standard of care) and Routine Urinalysis (including urine protein, and microscopic examination, if any abnormal value is observed on the urine dipstick test) should be collected predose (screening), if unable to collect predose, collect within 2 hours following IP initiation. Collect at the time of IP discontinuation (+/- 1 hour), either at the end of the taper or if the IP administration is stopped without a taper and 24 hours (+/- 1 hour) following IP discontinuation and at the time of hospital discharge. Collect at the weekly follow-up visits (Week 1, 2, 3, or 4) for hospitalized participants and for participants who have been discharged (whenever possible). For participants who terminate early from the study, collect at the time of early termination (whenever possible). Collect in the event of an SAE. The investigator may collect at any other time based on clinical judgment.
j. Urine chemistry sample for N-acetyl-β-D-glucosaminidase (NAG) and β2-microglobulin should be collected predose (screening), if unable to collect predose, collect within 2 hours following IP initiation, 24 hours (+/- 1 hour) following IP discontinuation and at the time of hospital discharge. Collect at one of the weekly follow-up visits (Week 1, 2, 3, or 4) for hospitalized participants and when possible, for participants who have been discharged. For participants who terminate early from the study, collect at the time of early termination (whenever possible). Urine samples will be stored frozen unless otherwise dictated or revised in the Biospecimen Manual.
k. Clinical coagulation (including fibrinogen, activated partial thromboplastin time [APTT], prothrombin time [PT] and international normalize ratio [INR]) should be collected predose (screening), if unable to collect predose, collect within 2 hours following IP initiation, 24 hours (+/- 1 hour) following IP discontinuation and at the time of hospital discharge. For participants who terminate early from the study, collect at the time of early termination (whenever possible). The investigator may collect at any other time based on clinical judgment.
l. A urine or serum sample for drugs of abuse testing should be collected predose per the institution standard of care. A urine or serum sample for alcohol testing should be collected, if medically indicated. A urine or serum sample for pregnancy testing for females who are of childbearing potential, should be collected predose (screening). If unable to collect sample(s) at predose, collect as soon as possible following IP initiation. Enrollment is not contingent upon results. However, if a participant has a positive test result, it will be at the investigator's discretion to weigh the risks versus

benefits for enrollment or continued participation. If the investigator decides to discontinue the IP, refer to the taper directions in the Investigational Product, Dose and Mode of Administration section. If the institution requires the pregnancy test results be obtained prior to IP initiation, the institution guidelines will be followed. The investigator may collect at any other time based on clinical judgment.

m. EEG is required for confirmation of CSE and NCSE diagnosis. Continuous EEG recording should be utilized for all participants and should start at least 60 minutes before IP initiation and continue through the end of the first 24 hours of the follow-up period.
n. Blood gas, arterial or venous, if collected to manage the participant's care from the time of SE diagnosis through the first end of the first 24 hours of the follow-up period, the eCRF should be completed. If samples are not collected, a sample is not required. If a decision is made to intubate the participant between IP initiation through the end of the first 24 hours of the follow-up period, a blood gas sample should be collected. The sample should be collected immediately prior to or as close as possible to the time of intubation.
o. CGI-I should be collected 10 and 24 hours (+/- 1 hour) following IP initiation. Collect at time of IP discontinuation (+/- 1 hour), either at the end of the taper or if the IP administration is stopped without a taper. Collect 24 (+/- 1 hour), 48, 72, 96, and 120 hours (+/- 2 hours) following IP discontinuation and at the time of hospital discharge. Collect at Week 1, 2, 3, and 4 follow-up visits/contacts. For participants who terminate early from the study, collect at the time of early termination (whenever possible).
p. Seizure Description Questionnaire should be collected predose (screening) as close as possible prior to IP initiation.
q. Status Epilepticus Cessation Questionnaire should be collected as close as possible to 72 hours following IP initiation.
r. Super Refractory Status Epilepticus (SRSE) Questionnaire should be collected as close as possible to the diagnosis of SRSE and no later than the final study follow-up visit/contact.
s. EuroQoL (EQ-5D-5L) should be collected at 120 hours (+/- 2 hours) following IP discontinuation and at the time of hospital discharge. Collect at Week 2, 3, and 4 follow-up visit/contacts. For participants who terminate early from the study, collect at the time of early termination (whenever possible).
t. mRS should be collected 24 (+/- 1 hour), 48, 72, 96, and 120 hours (+/- 2 hours) following IP discontinuation and at the time of hospital discharge. Collect at Week 2, 3, and 4 follow-up visits/contacts. For participants who terminate early from the study, collect at the time of early termination (whenever possible).
u. AEs will be collected from the time of IP initiation until the final study follow-up visit/contact via non-direct questioning. Concomitant medications will be collected during the same time period. All AEs and associated concomitant medications will be collected through the final study follow-up visit/contact. For participants who terminate early from the study, prior to discontinuation as much information as is available should be recorded for ongoing AEs/SAEs, new AEs/SAEs, and their associated concomitant medications, especially those that may have led to the early termination. Each AED administered within 14 of IP initiation will be recorded and the reason for administration through the final study follow-up visit/contact.
v. Healthcare Utilization Questionnaires include the Hospitalization Questionnaire and the Positive Pressure Ventilation (PPV) and Intubation Questionnaire. The Hospitalization Questionnaire should be collected at hospital discharge or at final study visit/contact. The need for non-invasive or invasive ventilatory support within 24 hours prior to IP initiation and following IP initiation and within 48 hours following IP discontinuation should be collected as close as possible to the event.