STATISTICAL ANALYSIS PLAN

Protocol: 1042-SE-2001

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

Sponsor:	Marinus Pharmaceuticals, Inc.
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STATISTICAL ANALYSIS PLAN APPROVAL

Prepared by:

_____ Date: _____
[redacted]

Approved by:

_____ Date: _____
[redacted] Biostatistics
Marinus Pharmaceuticals, Inc.

_____ Date: _____
[redacted] MD, MS.HP
[redacted]
Marinus Pharmaceuticals, Inc.

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1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide detailed descriptions of predefined methods to be used for efficacy and safety analyses for Protocol 1042-SE-2001. The latest version of the protocol at the time of the writing of this statistical analysis plan is Final Protocol (Amendment 3, 24 January 2019, Version 4.0).

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) 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 international accepted guidelines published by the American Statistical Association2 for statistical practice.

The following documents were also considered in preparation for writing this SAP:

- International Conference on Harmonization (ICH) E3 Guideline: Structure and Content of Clinical Study Reports[3]
- ICH E6 Guideline on Good Clinical Practice[4]
- ICH E8 General Considerations for Clinical Trials[5]
- ICH E9 Statistical Principles for Clinical Trials[6]

The SAP is a supplement to the study protocol, which should be referred to for additional details on study design, study conduct, and other operational aspects of the study.

The original protocol included a double-blind phase which was planned after an open-label lead-in to confirm the dose selected achieved an approximately targeted plasma concentration of ganaxolone in the target population and to collect safety, efficacy, and feasibility of ganaxolone administration This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different. This SAP covers analysis of data collected from the open-label. The double-blind phase will now be conducted as a separate phase 3 study. Therefore, some of the analyses described in the study protocol will not be conducted. Key efficacy, safety, and pharmacokinetic data are summarized, and no formal statistical tests are performed for inference. Subjects are categorized in to three cohorts based upon target dose of study medication. Cohorts are:

- Cohort 1: High (Target dose of 713 mg/day)
- Cohort 2: Medium (Target dose of 650 mg/day)
- Cohort 3: Low (Target dose of 500 mg/day)

2 STUDY OBJECTIVES

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 and prevents escalation of treatment requiring an IV anesthetic drug (a 3rd line treatment) for seizure suppression.

2.2 Secondary Objectives

- To assess other secondary efficacy endpoints such as mortality, seizure cessation in SE subjects
- To assess the pharmacokinetics of adjunctive IV ganaxolone in SE subjects

2.3 Exploratory Objectives

[redacted]

3 STUDY DESIGN

For detail study design, as was originally planned, please refer to study protocol (Amendment 3, Version 4.0, 24 January 2019).

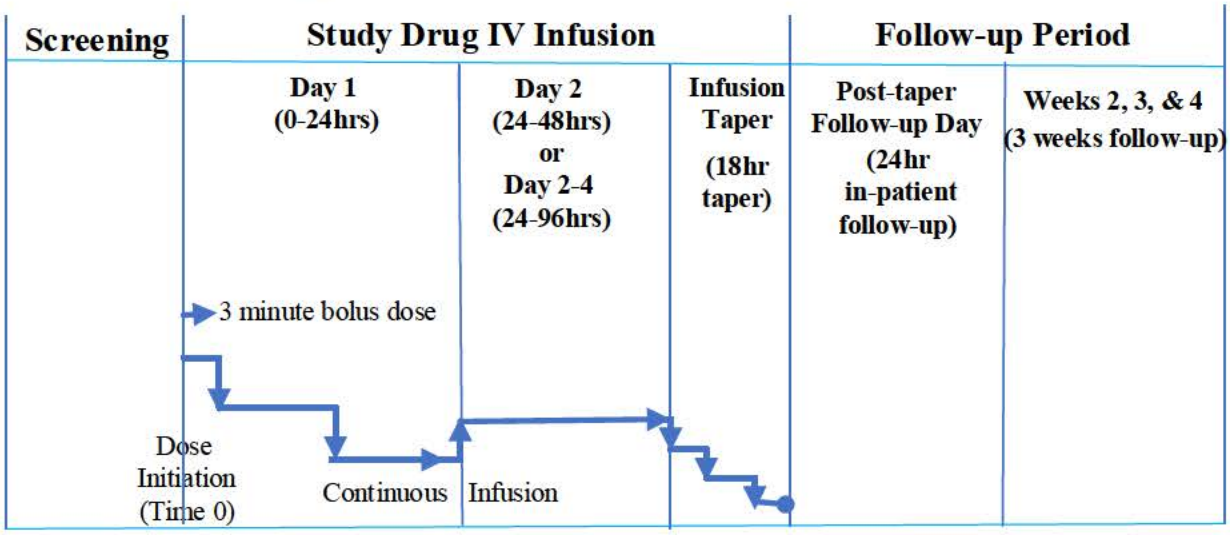
3.1 Study Design and Flow Chart

This is double-blind, randomized, placebo-controlled study to evaluate the safety, tolerability, efficacy of adjunctive IV ganaxolone 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 status epilepticus (SE) population who are on concomitant medications, and to obtain a preliminary assessment of safety, efficacy and feasibility of ganaxolone administration.

As indicated in Section 1, the double-blind phase was not conducted as part of this study. The double-blind phase will be conducted as a separate phase 3 study.

Figure 1 below shows originally planned study design.

Figure 1: Study Design Flow Chart



Adjunct treatment is planned to be 3- or 5-days (including an 18-hour taper).

Total subject participation is expect to be approximately 4 weeks.

3.2 Duration and Study Completion Definition

The original study was expected to be completed in 24 months.

3.3 Sites and Regions

This study was originally planned to be conducted globally, with approximately 150 sites planned to participate.

3.4 Study Population

Male or female subjects 12 years of age and older at the time of the first dose are eligible to participate in this study. Potential subjects are anticipated to be identified in the emergency department and/or hospital inpatient or intensive care units.

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 for subjects who are known to be at risk for SE may be gained prior to a SE event.

3.5 Study Evaluation

The trial schedule of events is provided in Table 1 in Appendix 1.

3.6 Blinding and Treatment Assignment

Not applicable. Only lead-in open-label phase was conducted in this study.

3.7 Allocation of Subjects to Treatment

Not applicable. Only lead-in open label phase was conducted hence there was no allocation of subjects to treatment.

3.8 Sample Size and Power

Original sample size (completed subjects = 242) was computed to provide 85% power assuming a 20% effect size. Three-hundred and twenty-eight subjects were to be screened to enroll 262 subjects, to allow for drop-out.

4 STATISTICAL METHODS

4.1 Analysis Populations

The Study populations will be defined as follows:

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

The **Safety Population** will consist of all subjects who have received at least one dose of IV ganaxolone.

The **Pharmacokinetic Population** will consist of all subjects in the **Safety Population** for whom the primary pharmacokinetic data is available.

4.2 Endpoints

4.2.1 Primary Efficacy Endpoints

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.

4.2.2 Secondary Endpoints

The following are 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 within 24 hours of SE stopping

- 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, 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 24-hour post-taper follow-up day
- Level of responsiveness as assessed by the GCS if SE is continuing, on the 24-hour post-taper follow-up day
- Seizure burden assessed as duration of electrographic seizure activity per hour of EEG recording collected
- Clinical outcome at the 24-hour post-taper follow-up day and Week 4
- Characterization of the pharmacokinetic profile of IV ganaxolone in SE subjects
- Length of stay in intensive care unit and hospital, mortality, and seizure freedom

4.2.3 Exploratory Endpoints

[redacted]

4.2.4 Safety Endpoints

The following are safety endpoints:

- Adverse Events (AEs)
- Clinical Laboratory Tests
- Vital Signs
- ECG
- Concomitant Medications

4.2.5 Pharmacokinetic Endpoints

The following are pharmacokinetic endpoints:

- Ganaxolone plasma concentration
- 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}

4.3 Planned Analyses and Analysis Population

	Analysis Population			
Planned Analysis	**Screened Population**	**Safety Population**	**Pharmacokinetic Population**	**Comments**
Subject Disposition	√			
Demographic Characteristics		√		
Baseline Characteristics		√		
Prior and Concomitant Treatment		√		
Protocol Violation		√		
Efficacy Analyses		√		
Safety Analyses		√		
Pharmacokinetic Analyses			√	

4.4 General Analysis and Reporting Convention

Since data from only open-label phase are analyzed, there will be only one treatment group. For efficacy and safety summaries, where applicable, subjects will be categorized into three cohorts (Cohort 1: High, Cohort 2: Medium, and Cohort 3: Low) based upon target dose of study medication. An overall group will also be reported representing all subjects.

General Convention:

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

- Continuous study measurements will be summarized by treatment group (Open-Label Group or Cohorts and Open-Label Group) and time point (as applicable) using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Means and medians will be presented with one more decimal place than the precision of the data. Standard deviations will be presented with two more decimal places than the precision of the data. Minimums and maximums will be presented with the same precision as the original data.

- Categorical study assessments will be summarized by treatment group (Open-Label Group or Cohorts and Open-Label Group) and time point (as applicable) using frequency counts and percentages. Unless stated otherwise, percentages are based on the number of subjects 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.
- Descriptive summaries based on the modified ITT (mITT) analysis set and per-protocol (PP) analysis set will be displayed by randomized treatment.
- Descriptive summaries based on the safety analysis set will be displayed by actual treatment received.
- All listings will be listed by cohort, subject, 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, vitals, or ECG values. Data from all assessments (scheduled and unscheduled), will be included in listings.
- All statistical tests will be performed at a significance level of 0.05 (two-tailed). Where applicable, two-sided 95% confidence intervals will be reported. For tables.
- p-values will be reported to 3 decimal places, with values less than 0.001 displayed as '<0.001'. Unless otherwise noted, no adjustments for multiple comparisons will be made.
- No preliminary rounding will be performed; rounding should only occur after analysis. To round, consider the digit to the right of last significant digit: if <5 then round down, if ≥5 then round up.
- Unless stated otherwise, the baseline will be calculated as the last observed assessment (including scheduled and unscheduled assessments) before the initiation of dose. Change from baseline values will be calculated as the post-baseline value minus the respective baseline value.
- For the safety analysis set, prior medications are those that started and ended before the initiation of IV. Concomitant medications are those that started before initiation of IV and continued into blinded treatment or those that started after the initiation of IV of blinded treatment.
- Unless stated otherwise, available data from screen failures will be excluded from all tables and figures, but will be presented in any applicable data listings where data was collected for screen failure subjects.

Safety and Other Rules:

For adverse events with partially missing onset dates, an onset date is imputed as detailed in "Programming Specifications".

Missing or partially missing prior and/or concomitant start dates are imputed using the same rules for AE onset dates. If the stop date is missing the medication is considered to have been received during all periods after that determined by the start date (but see also rules for stop-date imputation).

Programming Specifications

a) All output should have the following header at the upper left margin:

Marinus Pharmaceuticals, Inc.
Study 1042-SE-2001

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

Page n of N
ddMMMyyyy

Tables/appendices/listings should be internally paginated (i.e., page numbers should appear sequentially within each table). All output should have SAS program name in the lower right, the data source(s) used to generate the output in the lower left.

b) In general, data listings should be sorted by cohort, subject number and time point/start dates, unless specific instructions to do otherwise.

c) The following algorithm should be used to estimate adverse event start dates and stop dates for which only partial information is known:

- When the year is present and the month and day are missing:
  - If the year is same as the year of first day on IV, then the day and month of the start date of IV will be assigned to the missing fields.
  - If the year is prior to the year of first day on IV, then December 31 will be assigned to the missing fields.
  - If the year is after the year of first day on drug, then January 1 will be assigned to the missing fields.
- When year and day are present and the month is missing:
  - If the year of AE start is same as the year of start of IV, then month will be set to the month of start of IV.
  - If the year is prior to the year of first day on IV, then month will be set to December.
  - If the year is after the year of first day on IV, then month will be set to January.
- When year and month are present and day is missing:
  - If the year of AE start is same as year of initiation of IV and:

- The month of AE start is same as month of initiation of IV, then the day will be set to the day of initiation of IV.
- The month of AE start is prior to the month of initiation of IV, then the day will be set to the last day of the month.
- The month of AE start is after the month of initiation of IV, then the day will be set to the 1st day of the month.

- If the year of AE start is earlier than the year of initiation of IV, then the day will be set to the last day of the month.

- If the year of AE start is after the year of initiation of IV, then the day will be set to the 1st day of the month.

- If the AE stop date is complete and the imputed start date as above is after the stop date, the start date will be set to AE stop date.
- Adverse events with partially missing stop dates will be imputed a stop date as follows:

  - *year is missing* - Date left missing.

  - *month is missing* - impute 'December'.

  - *day is missing* - impute 'last date of that month'.

d) Prior and Concomitant Medication Date: If the start date (or end date) of a medication is completely missing or only the day is known, then the start date (or end date) will not be imputed. Unless the end date is before the start date of IV, the medication is considered concomitant.

- For a partial start date of medication,

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

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

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

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

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

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

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

4.5 Subject Disposition

The number of subjects and the reasons for discontinuation (adverse events, protocol deviation, lost to follow-up, death, etc.) of study treatment and discontinuation from study will be listed and summarized by group (by cohort and overall) for the Enrolled Population.

A data listing will be provided to define each cohort and identify subjects by cohort.

Additionally, a listing of screen failures will be provided identifying reasons why they were not enrolled.

4.6 Demographic and Baseline Characteristics

Descriptive summary statistics (n, mean, standard deviation, median, minimum, and maximum) and/or frequency distributions, as appropriate, will be provided by group (y cohort and overall) for the Safety Population. Demographic characteristics summarized will include, age, sex, race, and ethnicity. Baseline information summarized will include Status Epilepticus Severity Score (STESS), epileptic history, and status epilepticus (SE) history. Demographic characteristics and baseline STESS and epileptic history will also be listed.

Other than these characteristics, baseline values for safety and efficacy parameters will be summarized in respective tables.

4.7 Protocol Violations

Protocol violations will be identified prior to database lock to measure adherence to key aspects of the protocol. List of protocol deviations will be prepared before database lock. Specific data fields that will be examined to identify protocol violations include inclusion/exclusion criteria and prohibited prior and concomitant treatments as well as deviations identified by the investigator. All protocol violations will be listed for the Safety Population.

4.8 Efficacy Analyses

All efficacy analyses will be conducted for the Safety Population.

Considering that data from only open-label phase is available for analysis, efficacy assessments are only summarized and listed. There will be no statistical inferential test of any efficacy endpoint.

4.8.1 Status Epilepticus (SE) and Seizure

Status epilepticus and seizure questions will be listed and summarized by group (by cohort and overall) and time point. Additionally, SE cessation time will be listed and summarized (by cohort and overall).

4.8.2 Seizure Burden

Seizure burden will be listed and summarized by group (by cohort and overall) and time point.

4.8.3 Clinical Global Impression of Severity and Improvement (CGI-S and CGI-I)

The CGI-S and CGI-I scores will be listed and summarized by group (by cohort and overall) and time point.

4.8.4 Glasgow Coma Scale (GCS) of Pediatric Glasgow Coma Scale (PGCS)

The GCS or PGCS scores will be listed and summarized by group (by cohort and overall) and time point. Both observed values and change from baseline will be listed and summarized.

4.8.5 Richmond Agitation and Sedation Scale (RASS)

The RASS scores will be listed and summarized by group (by cohort and overall) and time point.

4.8.6 Mini-Mental State Examination (MMSE)

The MMSE total scores will be listed by cohort, subject, and time point.

4.8.7 Detailed Monitoring of EEG Data

Data collected from detailed monitoring of EEG activities will be listed and summarized.

4.9 Safety Analyses

The comprehensive safety analysis is based on all subjects in the Safety Population, unless indicated in the individual safety endpoint analysis. Safety data will be listed and summarized by group (by cohort and overall). The following sections detail the analyses performed on the safety data.

4.9.1 Adverse Events

Adverse events are coded using the MedDRA dictionary, Version 20.1 or higher, and are categorized by system organ class (SOC) and preferred term (PT). Only treatment emergent adverse events are included in the summary tabulations. All adverse events are included in the data listings.

To allow differentiation as to which study period an Adverse Event occurred, two categories are defined based upon onset date. Adverse Events that had onset dates prior to the first dose of study medication are considered "prior". Adverse events with onset dates on or after the first dose of study medication and up to end of follow-up period are considered "on-therapy" or equivalently "treatment emergent". Adverse events with an onset date prior to the first dose of study medication but worsens after treatment starts are considered a treatment emergent AE.

Overall summary of Treatment-emergent adverse events (TEAE) will be provided. The TEAEs will be summarized by MedDRA System Organ Class (SOC) and preferred term (PT), and by group (by cohort and overall). Treatment-emergent adverse events will further be summarized by severity and relationship to treatment medication. Treatment-emergent Serious Adverse Events (SAE) and AEs leading to discontinuation of study drug will also be summarized by SOC, PT, and group (by cohort and overall).

Adverse events and serious adverse events will be listed.

Deaths will be listed and summarized by group (by cohort and overall).

4.9.2 Medical History

Medical history information recorded in eCRF will be listed for the Enrolled Population by cohort and subject.

4.9.3 Prior and Concomitant Treatments and Procedures

Prior treatment includes all non-study treatment received within 30 days prior to the first dose of study medication. Concomitant treatment refers to all treatment taken between the date of the first dose of study medication and the last follow-up visit/contact and are recorded in eCRF pages.

Prior and concomitant medications (Non-AEDs) will be listed and summarized by group (by cohort and overall). Antiepileptic drugs (AEDs) are also collected as part of prior and concomitant treatments. A separate listing and summary table will be presented for AEDs.

Additionally, Prior and concomitant Procedures and Anesthetics will be listed and summarized by group (by cohort and overall).

Medications are coded using the WHO Drug dictionary.

4.9.4 Physical Examination

Physical examination results will be reported for the Safety Population.

Physical examination abnormal findings at baseline will be listed for each subject. Any changes in physical examination findings in subsequent time points from previous time point will also be listed.

4.9.5 Vital Signs

Vital signs are listed and summarized by time point and group (by cohort and overall) for the Safety Population. Systolic blood pressure, diastolic blood pressure, pulse, respiration rate, temperature, oxygen saturation, height, weight, and body mass index (BMI) will be summarized and listed. Both observed values and change from baseline will be summarized.

4.9.6 Laboratory Evaluations

Laboratory findings will be listed and summarized for the Safety Population.

Chemistry, hematology, and urinalysis parameter results will be summarized using descriptive statistics by time point and group (by cohort and overall). Both actual values and change from baseline will be summarized. Similar table will be provided for AED laboratory results.

Summary showing number and percent of subjects with abnormal laboratory test results will be provided by time point and group (by cohort and overall) for hematology, chemistry, and urinalysis parameters.

Lab results, including AEDs, will be listed by cohort, subject, and time point.

4.9.7 Exposure to Investigation Product

Investigational product administration to subjects will be listed and summarized (by cohort and overall) for the Safety Population. Listing should include all doses administered to all subjects.

4.9.8 Electrocardiography

ECG measurements will be listed and summarized by time point and group (by cohort and overall) for the Safety Population. ECG parameters QT, QTcB, QTcF, PR, HR, and QRS will be presented. Summary of interpretation of ECG results will also be listed and summarized.

4.9.9 Acute Physiology and Chronic Health Evaluation (APACHE) Score

For all subjects both APACHE (if blood gas data is available) and APACHE II scores will be listed.

4.10 Pharmacokinetic and Neurosteroid Analyses

Ganaxolone plasma concentration data will be listed and summarized (by cohort and overall) for the Pharmacokinetic Population. Plasma concentration time profile data will also be presented graphically. Individual subject profile of plasma concentration will also be presented graphically.

Additionally, neurosteroid concentration will also be listed.

4.11 Interim Analysis

No formal interim analysis was conducted.

4.12 Data Monitoring Committee (DMC)

A formal DMC to monitor safety data was not established in this study. However, safety data were routinely monitored by investigators, study clinicians, and sponsor.

5 CHANGES TO PLANNED ANALYSES

5.1 Changes from Protocol

The following analyses planned in this SAP deviates from original analyses proposed in protocol:

Protocol Section	Analyses Proposed in the Protocol	Changes from Protocol	Rationale for Change
9.7.1	A statistical comparison of primary efficacy endpoint between treatment groups using a logistic regression model.	Data was only summarized.	Study was closed before entering double-blind phase. This analysis was not relevant.
9.7.2	Detailed statistical analysis of several secondary efficacy endpoints were proposed.	Only a few secondary efficacy endpoints were summarized. Please see Section 4.8 for details.	Study was closed before entering double-blind phase. This analysis was not relevant.
9.7.3	Three specific exploratory endpoints were identified to be evaluated.	Exploratory analyses were not conducted.	Study was closed before entering double-blind phase. This analysis was not relevant.
Section 9.9	Detailed monitoring and analyses of EEG data.	No such analysis was conducted.	Study was closed before entering double-blind phase. This analysis was not relevant.
Section 9.9.1	Besides ganaxolone plasma concentration data analysis, analysis of ganaxolone pharmacokinetic parameters was also proposed.	Only plasma concentration data was analyzed.	Considering lack of sufficient pharmacokinetic data profile, only plasma concentration data was analyzed.

6 STATISTICAL SOFTWARE

All data summaries, statistical analyses, and listings will be performed using SAS® Version 9.2 or later, under Microsoft Windows operating system.

7 REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), September 1998.

2. ASA. (2018) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April, 2018. http://www.amstat.org/ASA/Your-Career/EthicalGuidelines-for-Statistical-Practice.aspx.

3. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), November 1995.

4. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Good Clinical Practice (E6), April 1996.

5. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, General Considerations for Clinical Trials (E8), July 1997.

6. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), September 1998.

APPENDIX 1: STUDY SCHEDULE

STUDY SCHEDULE(S)

Table 1: Schedule of Assessments

Periods	Screening [a]	Treatment				Follow-up [b]		ET
	Prior to dose initiation	Dosing		Taper	Study Drug Discontinuation without Taper	Post–taper (inpatient) Follow-up	Weekly follow-up (Week 2, 3, & 4)	Early Termination
Visit/Time Point or Duration	Day -1 to Day 1 Pre-dose through screening	Day 1 Dose initiation (0 hours) through 24 hours post-dose	Day 2 to 4 Min 48 – Max 96 hours post-dose	Day 3 or 5 18 hours	Collected prior to or as close to study drug stopping as possible	Day 4 or 6 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 stopping as possible
Informed consent/assent	✔							
Inclusion/ exclusion criteria	✔							
Demography and medical/ medication history [c]	✔							
Physical exam [d]	✔			✔	✔	✔		✔
Status Epilepticus Severity Score (STESS)	✔							
Glasgow Coma Scale (GCS)/Pediatric GCS (PGCS) [e]	✔	✔	✔	✔	✔	✔		✔
Mini mental state exam [f]				✔	✔	✔		✔
Vital signs [g]	✔	✔	✔	✔	✔	✔		✔
12-lead ECG [h]	✔	✔	✔	✔	✔	✔		✔

Table 1: Schedule of Assessments

Periods	Screening [a]	Treatment				Follow-up [b]		ET
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Biochemistry, hematology, and antiepileptic drugs [i]	✔	✔	✔	✔	✔	✔	✔	✔
Urinalysis [j]	✔		✔		✔	✔		✔
Urine for drugs of abuse, including alcohol [k]	✔							
Pregnancy test (WCBP only) urine or serum [l]	✔							
EEG [m]	✔	✔	✔	✔	✔	✔		✔
Study Drug infusion [n]		✔	✔	✔				
Pharmacokinetic blood sampling [o]		✔	✔		✔	✔		✔
Neurosteroid levels [p]	✔	✔						
Blood Gas [q]	✔							
Clinical Global Impression of Severity (CGI-S) [r]	✔	✔	✔	✔	✔	✔	✔	✔

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Periods	Screening [a]	Treatment				Follow-up [b]		ET
	Prior to dose initiation	Dosing		Taper	Study Drug Discontinuation without Taper	Post–taper (inpatient) Follow-up	Weekly follow-up (Week 2, 3, & 4)	Early Termination
Visit/Time Point or Duration	Day -1 to Day 1 Pre-dose through screening	Day 1 Dose initiation (0 hours) through 24 hours post-dose	Day 2 to 4 Min 48 – Max 96 hours post-dose	Day 3 or 5 18 hours	Collected prior to or as close to study drug stopping as possible	Day 4 or 6 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 stopping as possible
Clinical Global Impression of Improvement (CGI-I) [s]		✔	✔	✔	✔	✔	✔	✔
Richmond Agitation and Severity Scale (RASS) [t]	✔	✔	✔	✔	✔	✔		✔
SE & Seizure Questions [u]		✔	✔	✔	✔	✔	✔	✔
AEs/SAEs [v]		✔	✔	✔	✔	✔	✔	✔
Concomitant medication [v]	✔	✔	✔	✔	✔	✔	✔	✔

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 dose initiation.

[b] The planned duration of follow-up will be 24 hours after study drug administration is stopped (called the 24-hour post-taper follow-up day) and weekly for an additional 3 weeks. For Weeks 2, 3, and 4 the follow-up can be performed as an inpatient 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 dose 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 at screening or, if not available, collected within 24 hours of dose initiation, prior to initiating the study drug taper, and at the 24-hour post-taper follow-up visit, at the time of study drug termination if there is no study drug taper and something has changed since the last PE was collected, and at the time of early termination, when the decision to stop study drug administration is made and as close as possible to the end of the study drug administration.

[e] GCS/PGCS is collected pre-dose, 60 minutes and 2 hours of dose initiation, once within each 24-hour period through the end of the 24-hour post-taper follow-up day, as well as any time there is a change in subject's state that the investigator thinks is clinically significant. Also collect at the time of study drug termination if there is no taper and something has changed since the last GCS/PGCS was collected, and at the time of early termination, when the decision to stop study drug administration is made and as close as possible to the end of the study drug administration.

[f] Mini Mental State Examination (MMSE) should be performed at the time consent/assent is administered to the subject for continued participation and then on the post–taper follow-up day. Also collect at the time of study drug termination if there is no taper and something has changed since the last MMSE was collected, and at the time of early termination, when the decision to stop study drug administration is made and as close as possible to the end of the study drug administration. If the MMSE is not able to be assessed due to the subject's state this should be recorded.

[g] Vital signs including blood pressure, pulse, respiratory rate, temperature, and oxygen saturation should be assessed at screening, once within the first 2 hours of dosing, 8 and 24 hours after study drug initiation, and then once within each 24-hour period through the 24- hour post-taper follow-up day. Also, at any time there is a change in the subject's state that the investigator thinks is clinically significant. Also collect at the time of study drug termination if there is no study drug taper and at the time of early termination, when the decision to stop study drug administration is made and as close as possible to the end of the study drug administration.
Weight and height should be collected at screening for calculation of BMI inclusion criterion, if feasible. If not collected at screening they need to be collected prior to the end of the 24-hour post-taper follow-up day.

[h] ECG, if possible, should be collected pre-dose, 2-hours post- dose, and then once within each 24-hour period through the 24-hour post-taper follow-up day, plus any time there is a change in the subject's state that the investigator thinks is clinically significant. Also collect at the time of study drug termination if there is no taper and something has changed since the last ECG was collected, and at the time of early termination, when the decision to stop study drug administration is made and as close as possible to the end of the study drug administration.

[i] 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, or lacosamide) should be collected at screening if available, or within 2 hours of dose initiation, once within each 24-hour period through the –24-hour post-taper follow-up day, as well as at any time there is a change in the subject's state that the investigator thinks is clinically significant. Collect at the time of study drug termination if there is no study drug taper and at the time of early termination, when the decision to stop study drug administration is made and as close as possible to the end of the study drug administration. Also collect clinical labs (serum chemistry, AED, and hematology) at one of the weekly follow-up visits for subjects in-house and if possible, for subjects who have been discharged.

[j] Urinalysis samples should be collected at screening if available or within 2 hours of dose initiation, 48 hours after dose initiation, on the 24-hour post-taper follow-up day, and for subjects stopping study drug without a taper or early terminating the study, when the decision to stop study drug administration is made and as close as possible to the end of the study drug administration.

[k] Ideally, collect urine for drugs of abuse, including alcohol testing, prior to dose initiation but if not possible then, collect within the first 24 hours after dose initiation. Enrollment is not contingent upon results.

[l] Urine or serum pregnancy test for women who are of potential childbearing age, should be collected prior to dose initiation. If not possible to collect pre-dose then, collect as soon as possible after dose 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.

[m] EEG recording is required for confirmation of NCSE diagnosis. Continuous EEG recording ideally should start before dose initiation and continue through the 24-hour post-taper 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).

[n] Subjects will receive a 25 mg bolus (over ~3 minutes) with a continuous infusion at a rate of 18-80 mg/hour for approximately 48 to 96 hours followed by an 18-hour taper.

[o] Blood sample collection for pharmacokinetic analysis (venous or arterial) will occur at 60 minutes then at 2, 4, 8, 10, and 24 hours after the start of the infusion, at the time study drug administration is halted, e.g, at the end of the 18-hour study drug taper or, if study drug administration is halted without taper, and/or early termination, when the decision to stop study drug administration is made and as close as possible to the end of the study drug administration. In addition, if the SE relapses after initial SE cessation and the subject does not progress to an IV anesthetic drug (a 3rd line treatment), a pharmacokinetic sample should be collected. If there are multiple SE relapses, additional pharmacokinetic sample collection is not required. The collection windows for pharmacokinetics samples are ± 5 minutes for all collections through 4 hours' post-dose initiation and ± 60 minutes for all other collection points. If an indwelling catheter is used, a 1-mL sample will be drawn and discarded prior to the pharmacokinetic sample collection.

[p] Neurosteroid levels, one blood sample (venous or arterial) will be collected prior to study drug initiation and a second collected anytime within the 24 hours of study drug initiation. If study drug is discontinued during this 24-hour period, the second sample should be collected prior to study drug termination, if possible.

[q] Blood gas including FiO_2, PaO_2, and Arterial pH, should be recorded if collected per the hospital's standard of care. The sample collected closest to the time of SE diagnosis should be recorded. If no sample was collected at diagnosis, then the 1st blood gas sample after SE treatment initiation. Note, this may be prior to the start of study drug. If not collected per the hospital's standard of care, this data will not be recorded.

[r] CGI-S is collected pre-dose, once within each 24-hour period through the 24-hour post-taper follow-up day, and at the Week 4 follow-up visit (via phone if not in person), plus any time there is a change in the subject's state that the investigator thinks is clinically significant. Also collect at the time of study drug termination if there is no taper and something has changed since the last CGI-S was collected, and at the time of early termination, when the decision to stop study drug administration is made and as close as possible to the end of the study drug administration.

[s] CGI-I is collected within 2 hours of dose initiation, once within each 24-hour period through the 24-hour post-taper follow-up day, and at the Week 4 follow-up visit (via phone if not in person), plus any time there is a change in the subject's state that the investigator thinks is clinically significant. Also collect at the time of study drug termination if there is no taper and something has changed since the last CGI-I was collected, and at the time of early termination, when the decision to stop study drug administration is made and as close as possible to the end of the study drug administration.

[t] RASS is collected pre-dose and within 2 hours of dose initiation, once within each 24-hour period through the end of the 24-hour post-taper follow-up day, as well as any time there is a change in subject's state that the investigator thinks is clinically significant. Also collect at the time of study drug termination if there is no taper and something has changed since the last RASS was collected, and at the time of early termination, when the decision to stop study drug administration is made and as close as possible to the end of the study drug administration.

[u] Status Epilepticus and Seizure Questions should be assessed at 60 minutes, 2 hours, 48 hours post-dose, and on the 24-hour post-taper follow-up day. and at weeks 2, 3, and 4. Also collect at the time of study drug termination if there is no taper and something has changed since the last collection timepoint, and at the time of early termination, when the decision to stop study drug administration is made and as close as possible to the end of the study drug administration.

[v] 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 defined here: 1. For subjects who have 2-4 days of treatment with an 18-hour study drug taper, all adverse events and associated concomitant medications will be collected though the 24-hour post-taper follow-up visit. During the weekly follow-up visits only, ongoing AEs and new AEs assessed by the investigator to be related to study will be captured along with their associated concomitant medications. 2. For subjects who stop study drug administration without a taper but continue with the follow-up visits, all adverse events will be collected though the 24-hour post-taper follow-up visit, with their associated concomitant medications. During the weekly follow-up visits only, ongoing AEs and new AEs assessed

by the investigator to be related to study will be captured, with their associated concomitant medications. 3. For subjects who 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 with their associated concomitant medications, especially those that may have led to the early termination. 4. All SAEs regardless of relationship to study drug will be recorded from the time of 1st dose though the last follow-up visit, with their associated concomitant medications.