Statistical Analysis Plan

Protocol No.: 1042-0900

A Multicenter, 26 week Open-Label Proof-of-Concept Trial of Ganaxolone in Children with PCDH19 Female Pediatric Epilepsy and Other Rare Genetic Epilepsies Followed by 52 Week Open-Label Treatment

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ABBREVIATIONS

Abbreviation	Term
AEs	adverse events
AEDs	anti-epilepsy drugs
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BID	two times daily
BMI	body mass index
BUN	blood urea nitrogen
CDKL5	Cyclin-Dependent Kinase Like 5
CGII-C	Clinical Global Impression of Improvement -Clinician
CGII-P	Clinical Global Impression of Improvement – Patient/Caregiver
cm	centimeter
CNS	central nervous system
CO2	carbon dioxide
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	clinical study report
CSWS	Continuous Spike Wavei Sleep
EC	ethics committee
ECG	electrocardiogram
EEG	electroencephalogram
eCRF	electronic case report form
°F	degrees fahrenheit
FDA	Food and Drug Administration
GNX	ganaxolone
ITT	intent-to-treat
kg	kilogram
kg/m2	kilogram per square Meter
lb	pound
LGS	Lennox-Gastaut Syndrome
m	meter
mg	milligram
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximally tolerated dose
OLE	Open-label extension
PCDH19	Protocadherin 19

Abbreviation	Term
PP	per protocol
SAEs	serious adverse events
SAP	statistical analysis plan
SD	standard deviation
SI	Système International
SOC	system organ class
IRB	Institutional Review Board
TEAE	treatment-emergent adverse event
TID	three times daily
USA	United States of America
VAS	Visual Analogue Scale
WHO	World Health Organization

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for Protocol 1042-0900 (Amendment 8.1, August 28, 2017).

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

To evaluate the efficacy of open-label GNX as adjunctive therapy for uncontrolled seizures in children with Protocadherin 19 (PCDH19) Female Pediatric Epilepsy, Cyclin-Dependent Kinase Like 5 (CDKL5) Disorder, Dravet Syndrome, and other epileptic syndromes such as Lennox-Gastaut Syndrome (LGS) and Continuous Spike Wave in Sleep (CSWS) in an open-label proof-of-concept study.

1.1.2 Secondary Objectives

To evaluate the safety and tolerability of open-label GNX as adjunctive therapy for uncontrolled seizures in children with PCDH19 Female Pediatric Epilepsy, CDKL5 Disorder, Dravet Syndrome, and other epileptic syndromes such as LGS and CSWS in an open-label proof-of-concept study.

1.2 STUDY ENDPOINTS

1.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the percent change in total seizure frequency (sum of individual seizures and clusters) per 28 days relative to baseline (clusters counted once regardless of the number of seizures within them).

1.2.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

1. Percent change in individual seizure frequency per 28-day period from baseline
2. Percent change in cluster frequency per 28-day period from baseline
3. Percent change in the average number of seizures per cluster from baseline
4. Percent change in total seizure frequency (individual seizures and clusters) per 28-day period from baseline per seizure subtype
5. Change in the percentage of individual seizure and cluster free days from baseline
6. Change in the percentage of individual seizure free days from baseline
7. Change in the percentage of cluster free days from baseline
8. Change in the longest period of time individual seizure and cluster free (% relative to number of days with seizure data) from baseline
9. Proportion of subjects with >= 25%, 50%, or 75% reduction in 28-day total seizure frequency (sum of individual seizures and clusters) compared with baseline

10. The Clinical Global Impression of Improvement: Clinician (CGII-C)
11. Clinical Global Impression of Improvement: Patient/Caregiver (CGII-P)

1.2.3 Safety Endpoints

Safety endpoints include:

- Adverse events (AEs)
- Clinical laboratory tests
- Vital signs including temperature, blood pressure, pulse rate, and weight
- Neurological and physical examinations
- 12-lead Electrocardiogram (ECG)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Electroencephalogram (EEG)

1.2.4 Other Endpoints

Other endpoints include: Visual Analog Scale of Targeted Behaviors, Serum levels of GNX, concomitant antiepileptic drug (AED) medications, allopregnanolone, and related endogenous central nervous system (CNS) active steroids (analysis methods for the serum levels are not included in this SAP). The serum level analyses will not be in the CSR, but in a separate report.

1.3 Summary of the Study Design

1.3.1 General Study Design and Plan

The purpose of this proof-of-concept study is to evaluate GNX as adjunctive therapy for uncontrolled seizures in female children with PCDH19 mutations, CDKL5 mutation and SCN1A mutation (Dravet syndrome), and other epileptic syndromes such as LGS and CSWS in an open-label proof-of-concept study. After establishing baseline seizure frequency, qualifying subjects entered the main portion of the study and were treated with open-label GNX oral suspension or GNX capsules at doses up to a maximum of 1800 mg/day (63 mg/kg/day for those dosed on a mg/kg basis) for up to 6 months. Maximum study participation will be 94 weeks: a screening period to establish baseline seizure frequency, up to 26 weeks treatment, and a 52-week open-label extension (OLE) for patients who benefit from GNX treatment and up to 4 weeks down-titration. Patients who continue to benefit from GNX treatment during the 52-week OLE will be permitted to continue to receive GNX.

Approximately 10 subjects with PCDH19, 10 subjects with CDKL5 Disorder, 10 subjects with Dravet Syndrome, and up to 10 subjects with LGS, and up to 10 subjects with CSWS, were originally planned to participate. But, no subjects with Dravet Syndrome were recruited for enrollment and only 2 subjects with CSWS actually participated.

After signing the informed consent form, subjects or their legally authorized representatives were asked to chart seizures in a subject seizure calendar in order to establish baseline frequency for up to 12 weeks. After establishing baseline seizure frequency, eligible subjects entered the study and were treated with open-label GNX oral suspension or GNX capsules.

The Schedule of Events for 26-week treatment period is presented in Table 1. The Schedule of

Events for 52-week OLE is presented in

Table 2.

Table 1: Schedule of Events – 26 Week Treatment Period

Week		0	2	4	8	17	26	
Visit	**V1 Screening**	**V2 Baseline**	**V3 ± 3 days**	**V4 ± 3 days**	**V5 ± 3 days**	**V6 ± 7 days**	**V7 Final Visit[4] ± 7 days**	**Unscheduled Visit or Dose Escalation Visit[6]**
Screening & Diagnosis								
Informed consent	X							
Demographics	X							
Medical History	X	X						
Retrospective Seizure Diary Collection and Review	X							
Inclusion/Exclusion criteria	X	X						
Background AEDs Review	X	X	X	X	X	X	X	X
Concomitant Med Review	X	X	X	X	X	X	X	X
Safety Assessments								
ECG	X			X				
Vital Signs[5]	X	X	X	X	X	X	X	X
Physical Examination[1]	X	X	X	X	X	X	X	X
Neurological Examination[1]	X	X	X	X	X	X	X	X
Safety Labs (Blood[7] and Urine[2])		X			X		X	X
Urine Pregnancy Test (WCBP)		X		X	X	X	X	
Administer C-SSRS		X	X	X	X	X	X	X
EEG		X[9]		X[9]	X	X	X[9]	
Review safety and record AEs			X	X	X	X	X	X
Efficacy Assessments								
Instruct/ Provide Seizure Calendar	X	X	X	X	X	X	X	X
Subject Calendar Review	X	X	X	X	X	X	X	X
Complete CGII-C				X	X	X	X	
Instruct and Collect CGII-P				X	X	X	X	
Other Assessments								

Week		0	2	4	8	17	26	
Visit	**V1 Screening**	**V2 Baseline**	**V3 ± 3 days**	**V4 ± 3 days**	**V5 ± 3 days**	**V6 ± 7 days**	**V7 Final Visit[4] ± 7 days**	**Unscheduled Visit or Dose Escalation Visit[6]**
VAS		X			X		X	
PK/PD Assessments								
Concomitant AED medications		X			X		X	
Study Drug Blood Samples					X		X	
Neurosteroid levels		X			X		X	
Study Medication								
Dispense Medication		X	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
Collect bottles from prior visit study medication			X	X	X	X	X	X
Instruct on Down-titration							X[8]	

AEs = adverse events; AED = antiepileptic drug; CGII-C = Clinical Global Impression of Improvement-Clinician; CGII-P = Clinical Global Impression of Improvement-Parent/Guardian; C-SSR = Columbia Suicide Severity Rating; ECG = electrocardiogram; EEG = Electroencephalography; VAS = Visual Analogue Scale; WBCP=women of childbearing potential

1 Physical and neurological exam records performed at the same center within 60 days of screening visit may be used in place of screening exam. Visits 3, 4, 5 and 6 may be follow-up exams. Tanner Scores will be collected.

2 Obtain urine sample for those who are toilet trained.

3 Adjust dose if necessary.

4 This visit could also be an Early Termination visit. The subject should be instructed on down-titration and should be scheduled for the Follow-up Visit (V11) when down-titration has been completed. At this visit, investigator confirms if the subject qualifies for the 52-week extension, subjects must have completed all scheduled clinical study visits and have shown a minimum 35% improvement in mean seizure frequency per 28 days vs. baseline.

5 Vital signs including temperature, blood pressure, pulse, and weight. Height will be measured at Visit 1 (Screening) only.

6 A dose escalation visit is required 4 to 6 days after escalation to any dose level above 54 mg/kg/day or above 1500 mg/day. A regularly scheduled visit may serve as a dose escalation visit. An unscheduled visit can occur at any time during the 26 week open-label treatment period or the 52-week extension. Samples for concomitant AEDs and study drug levels may also be drawn if warranted in the opinion of the investigator.

7 Safety labs can be collected at any visit if warranted in the opinion of the investigator.

8 If this is the last study visit, the subject should be instructed on down-titration and scheduled for Visit 11 which is the follow-up visit.

9 CSWS subjects: a 24-hour ambulatory or continuous EEG recorded at an epilepsy monitoring unit will be collected at Visits 1, 4 and 7. Routine/standard EEG collected at remaining visits.

Table 2: Schedule of Events – 52 Week Open-Label Extension

Week	44	62	78	
Visit	V8 ± 14 days	V9 ± 14 days	V10[6] ± 14 days	V11[7] Follow-up ± 7 days
AEDs Review	X	X	X	X
Concomitant Med Review	X	X	X	X
Safety Assessments				
Vital Signs[1]	X	X	X	X
Physical Examination[2]	X	X	X	
Neurological Examination	X	X	X	
Safety Labs (Blood[3]and Urine[4])	X	X	X	
Urine Pregnancy Test (WCBP)	X	X	X	
Administer C-SSRS	X	X	X	X
EEG	X	X	X	
Review safety and record AEs	X	X	X	X
Efficacy Assessments				
Instruct/ Provide Seizure Calendar	X	X	X	
Subject Calendar Review	X	X	X	X
Complete CGI-I-C	X	X	X	
Instruct and Collect CGI-I-P	X	X	X	
Other Assessments				
VAS		X	X	
PK/PD Assessments				
Concomitant AED medications	X	X	X	
Study Drug Blood Samples	X	X	X	
Neurosteroid levels	X	X	X	
Study Medication				
Dispense Medication	X[5]	X[5]	X[5]	
Collect bottles from prior visit study medication	X	X	X	X
Instruct on Down-titration			X[6]	

Week	44	62	78	
Visit	V8 ± 14 days	V9 ± 14 days	V10[6] ± 14 days	V11[7] Follow-up ± 7 days

AEs = adverse events; AED = antiepileptic drug; CGI-I-C = Clinical Global Impression of Improvement-Clinician; CGI-I-P = Clinical Global Impression of Improvement-Parent/Guardian; C-SSR = Columbia Suicide Severity Rating; EEG = Electroencephalography; VAS = Visual Analogue Scale; WCBP=women of childbearing potential

1 Vital signs including temperature, blood pressure, pulse, and weight.

2 Visits 8 and 9 may be follow up exams. Tanner Scores will be collected.

3 Safety labs can be collected at any visit if warranted in the opinion of the investigator.

4 Obtain urine sample for those who are toilet trained.

5 Adjust dose if necessary.

6 If this is the last study visit, the subject should be instructed on down-titration and schedule for the Follow-up Visit (V11) when down titration has been completed.

7 Not applicable for subjects who continue GNX dosing after completing the 52 week OLE.

1.3.2 Randomization and Blinding

This is an open-label, uncontrolled, proof of concept study. No randomization was planned.

1.3.3 Sample Size and Statistical Power Considerations

Up to 10 subjects were planned for enrollment in this open-label, uncontrolled, proof of concept study for each patient cohort.

2. STATISTICAL METHODS

2.1 General Considerations

The initial clinical study report will analyze only the main portion of the study, the 26-week open-label period. The 52-week OLE portion will be analyzed and reported separately, as will the extension to the OLE portion. Separate tables and data listings will be prepared for each portion of the study. Except where noted, the tables and listings will include only events occurring within the respective periods; however demographic, background and baseline events will be included for all the periods.

In general, continuous variables will be summarized by number of subjects, mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables will be summarized by counts and percentage of subjects in each category.

Summary tables will present data within cohort, alphabetically, and overall if appropriate. Source data for the summary tables and statistical analyses will be presented as subject data listings, which include data collected on the electronic case report forms (eCRFs) as well as any derived efficacy variables for all enrolled subjects.

After the informed consent is signed, baseline seizure activity will be determined by the recordings in the subject's daily seizure calendars for a period up to 12 weeks prior to the first day of treatment. Post-baseline seizure activity will be determined by the days following the first day after the first treatment. (Since times of seizures were not recorded, determinations of whether seizures on the first day of treatment preceded or followed the treatment cannot be made.)

Baselines for the VAS and safety assessments are defined as the last non-missing value of the assessment before the first dose of treatment.

The study day for all assessments that are performed on or after the first day of treatment will be calculated as:

Study Day = date of the assessment – date of first treatment + 1.

For assessments performed before the first day of treatment, the study day calculation is:

Study day = date of the assessment – date of first treatment.

2.1.1 Reporting Precision

Summary statistics will be presented to the following degree of precision, unless otherwise specified:

Statistics	Degree of Precision
Mean, Geometric mean, Median, Quartiles, Confidence limit boundaries	One decimal place more than the raw data.
Standard deviation, Standard error	Two decimal places more than the raw data.
Minimum, Maximum	The same as the raw data.
p-value	Rounded to 4 decimal places and therefore presented as 0.xxxx; p-values smaller than 0.0001 as '<0.0001'; p-values greater than 0.9999 as '>0.9999'.
Percentage	One decimal place. A percentage of 100% will be reported as 100%. Percentages of zero will be reported as 0.

For weight and height, one decimal place will be used for summary statistics. Fractional numeric values will be presented with a zero to the left of the decimal point (for example, 0.12 – 0.30).

2.2 Definitions of Analysis Populations (Analysis Sets)

2.2.1 Safety Population

The safety population includes all subjects who entered into the study and received at least 1 dose of study drug.

2.2.2 Modified Intention-To-Treat Population (MITT)

The MITT population includes all subjects who entered into the study and received at least 1 dose of study drug and provided at least 1 day of post-baseline seizure calendar data. This is the primary population for the efficacy analyses.

2.2.3 Per-Protocol Population (PP)

The PP population includes all subjects who received study drug for at least 6 weeks without major protocol violations. The PP population includes all subjects in the MITT population and without major protocol violations.

2.3 Time Windows for Analysis

For by visit safety or efficacy summaries, only scheduled visits will be analyzed.

2.4 Pooling of Centers

Data of all sites will be pooled together for analysis.

2.5 HANDLING OF MISSING DATA

Unless otherwise specified, missing data will not be imputed. All analyses will be based on available data.

2.6 ANALYSIS SOFTWARE

All summaries and statistical analyses will be generated using SAS® version 9.2 or later.

3. STUDY SUBJECTS

3.1 DISPOSITION OF SUBJECTS

Disposition will be summarized by cohort and overall in all enrolled subjects.

The disposition will include the following:

- Subjects enrolled
- Subjects in the Safety Population
- Subjects in the MITT Population
- Subjects in the PP Population
- Subjects who completed the period
- Subjects who discontinued study drug before the end of the period
- Reasons for study drug discontinuation

For the 26-week open-label treatment period, completing subjects are those completing the 26-week open-label treatment period, regardless of whether they entered the 52-week OLE. Likewise, for the 52-week OLE period, completing subjects are those completing the 52 week OLE period, regardless of whether they continued beyond the extension period. A listing of dispositions will be provided for all subjects.

3.2 PROTOCOL DEVIATIONS

The clinical team will identify deviations and the deviations will be recorded into the database. A subject data listing will be provided.

4. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

4.1 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic data (age, gender, race, and ethnicity) and baseline characteristics (including height and weight) collected at study screening and derived BMI will be summarized using descriptive statistics by cohort and overall in the safety population, MITT population and PP population if they differ.

Height (in cm) = Height (in inches) * 2.54

Weight (in kg) = Weight (in lbs) * 0.4536

BMI (kg/m^2) = Weight (kg)/[Height$(m)^2$]

A subject data listing of demographics and baseline characteristics will be provided.

4.2 MEDICAL HISTORY

Medical history will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) Terminology version 16.0. The number and percent of subjects with clinically significant medical history at screening will be summarized by system organ class (SOC) and Preferred Term by cohort and overall in safety population.

5. PRIOR AND CONCOMITANT MEDICATIONS

Prior medications are defined as medications that started and stopped prior to the first dose of study drug. Concomitant medications are defined as medications (other than the study drug) taken on or after the first dose of the study drug during the study, regardless of when they were first taken. The summary of concomitant medications for the main 26-week open-label treatment period of the study will not include concomitant medications that start after the main 26-week open-label treatment period of the study; i.e. they will not include any concomitant medications starting on or after the first dosing day of the OLE period.

All investigator terms for medications recorded on the CRF will be coded using the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) drug dictionary (Version WHO Drug Dictionary, March 2014). The number (percentage) of subjects who took prior and concomitant medications will be summarized by cohort and overall in the safety population, by ATC Classification and WHO Drug Preferred Term. Prior and concomitant Non AEDs and AEDs will be summarized separately.

A subject data listing of prior and concomitant medications will be provided, separately for non-AED and AEDs.

To define prior or concomitant medication, the following table describes how missing date information will be handled:

Partial Missing Start or Stop Date	Imputed Start Date	Imputed Stop Date
Missing year, month, and day	First dose date	
Missing month and day, and the year is present	First dose date if the year is the same as the year of first dose date, else first dose date of the OLE if the year is the same as the year of the first OLE dose date, else January 1 of the medication start year.	December 31 of that year
Missing day, but year and month are present	First dose date if the year and month are the same as the year and month of first dose date, else first dose date of the OLE if the year and month are the same as the year and month of the first OLE dose date, else the 1st of the medication start month.	Last day of that month
Missing month, but year and day are present	Assume day is also missing and impute as above	Missing month imputed as December

If an imputed start date is later than the stop date, then the stop date (after any needed imputations) will be used instead for the imputed start date.

6. EFFICACY ANALYSES

All efficacy analyses will be summarized by cohort in the MITT population. These summaries will include only the CDKL5, LGS, and PCDH19 cohorts since only 2 patients were enrolled in the CWS cohort. However, the CWS cohort will be included in the subject data listings. For the analyses of seizures and clusters, the baseline period consists of up to 12 weeks before the first day of treatment, and the 26-week open-label treatment period starts with the day following the first day of treatment until the final visit for subjects who do not enter the OLE and up to the day before the first dose of OLE treatment for those who do. The first day of treatment is not in either period since the times of seizures were not collected.

Seizure diary compliance will be summarized by cohort. The calculated compliance is:
100 x (Number of Days with Available Seizure or Cluster Diary) / (Last Available Seizure or Cluster Diary Date – First Available Seizure or Cluster Diary Date + 1).

6.1 PRIMARY EFFICACY ANALYSIS

The primary efficacy endpoint is the percent change in 28-day total seizure frequency in the 26-week open-label treatment period relative to the baseline in the MITT population. Frequency of total seizures includes all seizure subtypes presented as individual seizures or clusters. Post-baseline 28-day total seizure frequency will be calculated as the total number of individual seizures and clusters in the 26-week open-label treatment period divided by the number of days with available seizure/cluster data in the period, multiplied by 28. Baseline 28-day total seizure

frequency will be calculated as the total number of individual seizures and clusters in the baseline period divided by the number of days with available seizure/cluster count data in the period, multiplied by 28. The calculation for percent change from baseline in 28-day total seizure frequency will be done as follows for each subject:

$$\left(\frac{[(\text{Post-baseline 28-day seizure frequency}) - (\text{Baseline 28-day seizure frequency})]}{(\text{Baseline 28-day seizure frequency})}\right)\times 100\%$$

The baseline and post-baseline values and the arithmetic and percent changes from baseline in 28-day total seizure frequency will be summarized by cohort separately using descriptive statistics in the MITT population and PP population if they differ. A subject data listing will be provided.

6.2 Secondary Efficacy Analysis

6.2.1 Percent Change in Individual Seizure Frequency per 28-day Period from Baseline

Baseline and post-baseline values and arithmetic and percent changes in 28-day individual seizure frequency will be calculated in the same way as the primary efficacy endpoint but only individual seizures (not clusters) will be considered. Summary statistics will be presented by cohort separately using descriptive statistics. A subject data listing will be provided.

6.2.2 Percent Change in Cluster Frequency per 28-day Period from Baseline

Post-baseline 28-day cluster frequency will be calculated as the total number of clusters in the 26-week open-label treatment period divided by the number of days with available cluster count data in the period, multiplied by 28. Baseline 28-day cluster frequency will be calculated as the total number of clusters in the baseline period divided by the number of days with available cluster count data in the period, multiplied by 28. The percent change from baseline in 28-day cluster frequency will be calculated as (post-baseline 28-day cluster frequency minus baseline 28-day seizure frequency) divided by baseline 28-day cluster frequency, multiplied by 100%. (If on a given day seizure data are available then if no cluster data are available the cluster count for that day will be considered as zero. This is done since parents/caregivers often did not record the cluster information if there were no seizures.)

Summary statistics for the baseline and post-baseline values and the arithmetic and percent changes will be presented by cohort separately using descriptive statistics. A subject data listing will be provided.

6.2.3 Percent Change in the Average Number of Seizures per Cluster from Baseline

Post-baseline number of seizures per cluster will be calculated as total number of cluster seizures divided by total number of clusters during the 26-week open-label treatment period. Baseline number of seizures per cluster will be calculated as total number of cluster seizures divided by total number of clusters during the baseline period. The percent change in the number of seizures per cluster from baseline will be calculated as follow for each subject:

$$\left(\frac{(\text{Postbaseline number of seizures per cluster} - \text{Baseline number of seizures per cluster}}{\text{Baseline number of seizures per cluster}}\right)\times 100\%$$

Summary statistics for baseline and post-baseline values and the arithmetic and percent changes will be presented by cohort separately using descriptive statistics. A subject data listing will be provided.

6.2.4 Percent Change in Total Seizure Frequency (Individual Seizures and Clusters) per 28-day Period from Baseline per Seizure Subtype

This endpoint is the same as the primary efficacy endpoint, except that the frequencies are calculated for each seizure subtype separately.

Summary statistics for baseline and post-baseline values and the arithmetic and percent changes will be presented by cohort separately using descriptive statistics for each seizure subtype that has more than 5 subjects with positive baseline seizure count. A subject data listing will be provided.

6.2.5 Change in the Percentage of Individual Seizure and Cluster Free Days from Baseline

Post-baseline percentage of individual seizure and cluster free days will be calculated as the number of days in the 26-week open-label treatment period free of both individual seizures and clusters divided by the number of days with available individual seizure or cluster occurrence data in the period and multiplied by 100. Baseline percentage of individual seizure and cluster free days will be calculated as the number of days in the baseline period free of both individual seizures and clusters divided by the number of days with available individual seizure or cluster data in the baseline period, multiplied by 100.

Baseline and post-baseline values and arithmetic changes from baseline in seizure and cluster free days will be summarized by cohort separately using descriptive statistics. A subject data listing will be provided.

6.2.6 Change in the Percentage of Individual Seizure Free Days from Baseline

Post-baseline percentage of individual seizure free days will be calculated as the number of individual seizure free days in the 26-week open-label treatment period divided by the number of days with available individual seizure occurrence data in the period and multiplied by 100. Baseline percentage of individual seizure free days will be calculated as the number of individual seizure free days in the baseline period divided by the number of days with available individual seizure or cluster data in the baseline period, multiplied by 100.

Baseline and post-baseline values and arithmetic changes from baseline in seizure free days will be summarized by cohort separately using descriptive statistics. A subject data listing will be provided.

6.2.7 Change in the Percentage of Cluster Free Days from Baseline

Post-baseline percentage of cluster free days will be calculated as the number of cluster free days in the 26-week open-label treatment period divided by the number of days with available cluster occurrence data in the period and multiplied by 100. Baseline percentage of cluster free days will

be calculated as the number of cluster free days in the baseline period divided by the number of days with available individual seizure or cluster data in the baseline period, multiplied by 100.

On days where sites recorded individual seizure data, some recorded cluster data only when there were clusters; hence days for which individual seizure data are available and no cluster data are available will be considered as cluster free days.

Baseline and post-baseline values and arithmetic changes from baseline in cluster free days will be summarized using descriptive statistics by cohort. A subject data listing will be provided.

6.2.8 Change in the Longest Period of Time Individual Seizure and Cluster Free (%) from Baseline

The post-baseline longest period of time seizure/cluster-free is defined as the longest individual seizure and cluster free period (days) in the 26-week open-label treatment period divided by the number of days with available individual seizure or cluster occurrence data during the 26-week open-label treatment period, and then multiplied by 100%. The baseline longest period of time seizure/cluster-free is defined as the longest individual seizure and cluster free period (days) in the baseline period divided by the number of days with available individual seizure or cluster data during the baseline period, and then multiplied by 100%. For both periods, the longest period is based on the number of days without an interruption of a day with an individual seizure or cluster. If there is an interruption of a day without seizure of cluster data, then that day will not count. For example, if there are seizures on January 1st, no seizures or clusters on January 2nd thru 4th, no seizure or cluster data on January 5th, no seizures or clusters on January 6th, and there are seizures on January 7th, then the longest period of time seizure/cluster free in this interval would be 4 days (January 2nd thru 4th and January 6th).

Baseline and post-baseline values and arithmetic changes from baseline in the longest period of time seizure or cluster free will be summarized by cohort separately using descriptive statistics. A subject data listing will be provided.

6.2.9 Proportion of Subjects with >= 25%, 50%, or 75% Reduction in 28-day Total Seizure Frequency (Sum of Individual Seizures and Clusters) Compared with Baseline

An R% responder is an individual whose reduction of percent change from baseline to the end of the 26-week open-label treatment period in 28-day total seizure frequency is greater than or equal to R%. R% will be 25%, 50%, and 75%. Frequency of seizures is based on the sum of the individual seizures and the clusters.

The number and percentage of responders will be summarized by cohort. In addition, for the main 26-week open-label treatment period of the study, a cumulative responder curve figure will be provided, in which the X-axis represents amount of improvement in increments of 5%, and the Y-axis represents the percentage of subjects improving by at least the amount on the X-axis. The cohorts will be presented separately within the figure. A subject data listing will be provided.

6.2.10 CGII-C and CGII-P

Clinical Global Impression of Improvement –Clinician (CGII-C), or Clinical Global Impression of Improvement –Patient/Caregiver (CGII-P): A 7-point Likert scale completed by the Clinician

or Patient/Caregiver representing the degree to which the subject's epilepsy symptoms have changed relative to baseline. On the CGII-C, 1=very much improved and 7=very much worse.

Frequency and percentage of the responses will be summarized by visit for CGII-C and CGII-P separately. The analysis will be conducted by cohort separately. A subject data listing will be provided.

6.3 Analysis of Months 1 – 3

In order to explore early signals of efficacy, the seizure and cluster analyses described above will be repeated using just the first 3 months of the post-baseline period, defined as the first 90 days following the first day of treatment (Study Days 2 to 91).

7. SAFETY ANALYSIS

All safety analyses will be performed by cohort and overall in the Safety Population. The highest percentage of the maximum allowable daily dose that subjects received will be summarized with descriptive statistics. The cumulative dosage that subjects received will be summarized with descriptive statistics, separately for subjects receiving their dosage on a mg/kg basis and those receiving it on a mg basis. For subjects who received dosing on a mg/kg basis at the start of the study and then switched to a mg basis, the doses with a mg basis will be converted to a mg/kg basis by dividing the mg by the subjects' most recent weight prior to the mg basis. A subject data listing will be provided with full details of the study drug dispensation.

Safety assessments include:

- AEs
- Clinical laboratory tests
- Vital signs including temperature, blood pressure, pulse rate, and weight
- Neurological and physical examinations
- 12-lead ECG
- EEG
- C-SSRS

Baseline is defined as the last non-missing value obtained before the first treatment. Assessments performed at multiple post-baseline time points will be summarized at each time point for which they are scheduled. The listings will include any assessments performed at unscheduled time points.

7.1 Adverse Events

Adverse events will be coded by SOC and Preferred Term using MedDRA®, version 16.0. The verbatim term will be included in the AE listings.

A treatment-emergent adverse event (TEAE) is defined as an AE that starts or worsens on or after the first dosing day of study drug. The AE analyses for the main 26-week open-label treatment period of the study will include AEs that start during that period and will not include AEs that start during the OLE period of the study; i.e. they will not include any AEs starting on or after the first dosing day of the OLE period. Pre-treatment emergent AEs will be summarized

by SOC and Preferred Term. Only TEAEs will be included in the other summary tables. Pre-treatment AEs and TEAEs will be presented in subject data listings.

The TEAEs will be summarized as the number of events and the number (percentage) of subjects with TEAEs. Subjects who report the same Preferred Term on multiple occasions will be counted once for the Preferred Term: under the highest severity (severe > moderate > mild) when summarized by severity and under the closest relationship (related > probably related > possible related > unlikely related > not related) to study drug when summarized by relationship. Treatment related AEs are defined as those events recorded in the CRF as 'Related', 'Probably Related' or 'Possibly Related'; AEs recorded in the CRF as 'Unlikely Related' or 'Not Related' will be considered as not related to treatment. TEAEs with missing relationships will be considered as related.

If a subject reports multiple Preferred Terms for an SOC, the subject will be counted only once for that SOC. For the counting of events, all the Preferred Terms will be included in the counts, even when subjects have multiple Preferred Terms.

TEAEs will be summarized as below.

- An overview table, including number of events and subjects with
    - TEAEs
    - serious AEs (SAEs)
    - Treatment related TEAEs
    - TEAEs by severity
    - TEAEs leading to study discontinuation
    - TEAEs leading to death
- TEAEs by SOC and Preferred Term
- TEAEs by SOC, Preferred Term, and Severity
- Study drug related TEAEs by SOC, Preferred Term
- SAEs by SOC and Preferred Term
- TEAEs leading to study drug discontinuation by SOC and Preferred Term
- TEAEs by Preferred Term

All AE tables will be sorted by SOC and Preferred Term in decreasing frequency of the number of subjects in the combined cohorts. In cases of ties the sorting will be alphabetical.

For purposes of determining treatment emergent events, missing start dates will be imputed as shown in the following table; however, the actual dates, not the imputed ones, will display in the data listing.

Partial Missing Start or Stop Date	Imputed Start Date	Imputed Stop Date
Missing year, month, and day	First dose date	
Missing month and day, and the year is present	First dose date if the year is the same as the year of first dose date, else first dose date of the OLE if the year is the same as the year of the first OLE dose date, else January 1 of the AE start year.	December 31 of that year
Missing day, but year and month are present	First dose date if the year and month are the same as the year and month of first dose date, else first dose date of the OLE if the year and month are the same as the year and month of the first OLE dose date, else the 1st of the AE start month.	Last day of that month
Missing month, but year and day are present	Assume day is also missing and impute as above	Missing month imputed as December

If an imputed start date is later than the stop date, then the stop date (after any needed imputations) will be used instead for the imputed start date.

7.1.1 Deaths, Serious and Other Significant Adverse Events

The listings of deaths, SAEs, and AEs leading to study drug discontinuation will be provided.

7.2 Clinical Laboratory Parameters

Laboratory assessments include hematology, clinical chemistry, and urinalysis:

- Clinical Chemistry: Total Bilirubin, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Blood Urea Nitrogen (BUN), Glucose, Potassium, Sodium, Calcium, Alkaline Phosphatase, Chloride, Creatinine, Carbon Dioxide (CO2).
- Hematology: Hemoglobin, Hematocrit, Erythrocytes, Leukocytes + differential, Thrombocytes (platelet count).
- Urinalysis: pH, Color, Transparency, Specific Gravity, Urobilinogen, Ketones, Protein, Glucose

All laboratory parameters will be presented in SI units. 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 group above. Laboratory test results were evaluated as normal, abnormal (not clinically significant) or abnormal (clinically significant). The number and percentage of subjects of each category will be summarized by baseline and post-baseline time point for each parameter.

All laboratory data will be included in the listings. A pregnancy listing will be provided separately.

7.3 VITAL SIGNS, NEUROLOGICAL AND PHYSICAL EXAMINATIONS FINDINGS, ECG, EEG, AND CSSRS

7.3.1 Vital Signs

Vital signs include weight, height, temperature, blood pressure (BP), and pulse rate.

All vital signs will be presented in SI units. Quantitative results (including actual value and change from baseline to each post-baseline visit) will be summarized using descriptive statistics by baseline and post-baseline time point for each parameter.

Vital sign test results will be assigned an LNH classification according to whether the value was below (L), within (N), or above (H) the normal reference range. The number and percentage of subjects in each category will be summarized by baseline and post-baseline time point for each parameter. The normal reference ranges are: Systolic Blood Pressure: 110-130 (mmHg); Diastolic Blood Pressure: 70-90 (mmHg); Temperature: 97.0–101.5(F) or 36.1 – 38.61(C); Pulse Rate: 60-100 beats/min. For weight, the number (%) of subjects with >= 7% change from baseline will be summarized by post-baseline time point.

A listing of vital signs, including abnormal flags, will be provided.

7.3.2 Physical and Neurological Examinations

Physical and Neurological examination data will be summarized separately using descriptive statistics by baseline and post-baseline visit, for each component. Listings for both physical and neurological examinations will be provided.

7.3.3 ECG

The 12-lead ECG parameters including value and changes from baseline will be summarized using descriptive statistics. ECG results were interpreted as normal, abnormal (not clinically significant) or abnormal (clinically significant). The number and percentage of subjects of each category will be summarized by baseline and post-baseline visit.

Subject listing will be provided. SI units will be used for both summarization and data listings. The critically significant abnormalities will also be flagged in data listings.

7.3.4 EEG

The EEG results will be listed.

7.3.5 C-SSRS

The C-SSRS data will be summarized and listed for each question by visit.

8. OTHER ASSESSMENTS

Visual Analog Scale of Targeted Behaviors will be summarized descriptively for each visit and for change from baseline by cohort.

Blood samples were drawn at baseline, and at Visits 5 and 7 for measurements of concomitant AED and neurosteroid levels, and at Visits 5 and 7 for measurement of study drug serum levels. A listing will be provided to present the serum sample collection status.

9. ANALYSIS OF OPEN-LABEL EXTENSION PERIOD

Baseline for the OLE period is the same as for the main period. The key background and efficacy tables to be provided for the main 26-week open-label treatment period of the study will also be provided for the 52-week OLE. These include:

- Subject disposition
- Demographics and baseline characteristics
- Concomitant non-AED medications and AED medications
- 28-day total seizure frequency for the sum of individual seizures and clusters
- Percentage of both individual seizure free and cluster free days

All of the safety tables provided for the main 26-week open-label period will also be provided for the 52-week OLE.

The concomitant medications summary will include only those medications taken during the OLE period; i.e., those taken on or after the first dosing day of the OLE period and, for those subjects who enter the extension of the OLE, before the first dosing day of that extension.

The seizure endpoints will be based on both 6 and 12 months of OLE experience. The 6-month endpoints will be derived based on the first dosing day of OLE treatment through the last day of OLE treatment or 6 months of OLE treatment, whichever is earlier. The 12-month endpoints will be derived based on the first dosing day of OLE treatment through the end of the study, or if the subject enters the extension of the OLE, through the last day of OLE treatment.

Only the MITT population will be used for the efficacy analyses.

The adverse events will be summarized over just the OLE period as well as over the entire study (26-week main study and OLE periods). The summarizations over just the OLE period will include only those AEs that start or worsen on or after the first dosing day of GNX in the OLE period and, for subjects who enter the extension of the OLE period of the study, before the first

dosing day of that extension. The summarizations over the entire study will include AEs that start or worsen on or after the first dosing day of GNX and, for subjects who enter the extension of the OLE period of the study, before the first dosing day of that extension. Just the TEAEs will be summarized; there will be no table of pre-treatment emergent AEs.

10. INTERIM ANALYSES AND DATA AND SAFETY MONITORING BOARD (DSMB)

10.1 INTERIM ANALYSES

No interim analyses are planned.

10.2 DATA AND SAFETY MONITORING BOARD (DSMB)

A DSMB was not utilized in this study.

11. SUMMARY OF MAJOR CHANGES IN THE PLANNED ANALYSES

From prior version of SAP:

Study population: added definition of safety population. All safety analyses will be based on safety population.

Additional details were provided for the analysis of the OLE period of the study.

Each cohort was to be analyzed separately upon completion. Upon completion of the 26-week open-label period, an analysis of the PCDH19 cohort was analyzed but the other cohorts were not analyzed until the main 26-week open-label and OLE periods of the study completed.

From protocol:

The analysis of the seizures and clusters during the first 3 months of the 26-week open-label period, described in Section 6.3 of this SAP, was not in the protocol.

Section 9.5.2 of the protocol implied that the analyses combining individual seizures and clusters would be based on the number of individual seizures and seizures within clusters; however, they will be based on the number of individual seizures and clusters (ignoring the number of seizures within the clusters). The section indicated that the proportion of subjects with at least 30%, 50%, and 80% reduction in individual seizures and clusters might be analyzed, but the percentage thresholds will be 25%, 50%, and 75%. The section also indicated that weekly seizure frequency and proportion of subjects with at least 30%, 50% or 80% reduction in cluster frequency might be analyzed but they will not. Finally, the section stated that data will be analyzed for the modified intent-to-treat (MITT) and per protocol (PP) populations, if they differ, but only the primary efficacy endpoint will be analyzed using the PP population if it differs from the MITT population.

12. PROGRAMMING SPECIFICATIONS

12.1 FORMAT OF APPENDIX TABLES/ LISTINGS

1. Unless otherwise specified, all computer-generated tables and listings (TL) will be produced (via SAS® ODS) into RTF output, which can be imported in table format via Microsoft® Word. The TLs should be in landscape mode with required margins: at least 1.5 inches on top (the binding margin or left for portrait output) and 1 inch on left, right, and bottom. All output should have the following headers on each page:

   - Two-line header at the upper left margin:

     ```
     Marinus, Inc.
     Study No 1042-0900
     ```

   - Header with page number at the upper right margin:

     ```
     PAGE: X of N
     ```

     TLs should be internally paginated in relation to total length (i.e., page number should appear sequentially as page X of N, where N is the total number of pages within a table or listing).

   - Footer with the date the output was generated:

     ```
     ddMMMyyyy: hh:mm
     ```

2. Each TL should be identified by in a sequential numeric order, and the TL number should be centered above the title. The title is centered in initial capital characters and should include the population type analyzed (*e.g.* Safety Population). The title and designation are single-spaced but are separated from the TL by at least a double space.

   ```
   Table xx.x.x.x

   First Line of Title
   Second Line of Title (if needed)
   Population Type Analyzed
   ```

3. Column headings for tables and listings should be in initial upper-case characters.

4. Footnotes should be single spaced but separated by at least a double space from the bottom line of the TL. The notes are left justified, with each note starting on a new line. Following the last footnote insert a single space. Tables and listings should then display the source listing number and all outputs should display the source SAS program name. For example, the set of footnotes for a table:

   ```
   Note: [1] Footnote 1
   [2]Footnote 2

   Source Data: Listing X
   Program: Program name.sas
   ```

5. All data listings should be sorted alphabetically by cohort with a page break between them, subject number, parameter (where appropriate), and study visit date/time where appropriate. If data for a subject and/or parameter is displayed on multiple lines, then display the subject number and/or parameter on only the first line. However, if the data for a subject or parameter is split between pages, then the subject number and parameter should be displayed on the page following the split.

6. For tables that summarize categorical (discrete) data, all categories between the maximum and minimum category should be presented in the table, even if there is a zero count for a particular category. A Missing category should be added to any variables to indicate missing information, if appropriate, but the percentages should be based on the number of subjects with non-missing categories.

7. If the categories are not ordered (*e.g.*, Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 patient represented in 1 or more groups should be included.

8. All fractional numeric values should be printed with a zero to the left of the decimal point (*e.g.*, 0.12, 0.3).

9. Missing descriptive statistics or p-values due to non-estimability in tables, as well as missing data in patient listings should be represented as either a hyphen ("-") with a corresponding footnote (" - = unknown or not evaluated"), or as "N/A" with the footnote "N/A = not applicable" whichever is appropriate.

10. Date values in the listings should be in the format ddMMMyyyy. If part of the date is unknown then leave it out; e.g., APR2019. (In the unlikely event that the date and year are available, but the month is not, insert a hyphen between the date and year.)

11. Any data listing for which there were no events should be produced, stating, "There were no events"

In addition, Section 2.1.1 contains information on reporting precision.