Statistical Analysis Plan

Protocol No.: 1042-PCDH19-3002

A double-blind, randomized, placebo-controlled trial of adjunctive ganaxolone treatment in female children with protocadherin 19 (PCDH19)-related epilepsy followed by long-term open-label treatment

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Reference Product:	Placebo
Indication:	PCDH19 (Protocadherin 19-related epilepsy)
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ABBREVIATIONS

Abbreviation	Term
ABC-C	Aberrant Behavior Checklist – Community
AE	adverse event
AED	anti-epilepsy drug
Allo-S	Allopregnanolone Sulfate
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
bpm	beats per minute
BMI	body mass index
BRIEF	Behavior Rating Inventory of Executive Function
BUN	blood urea nitrogen
CGI-C	Clinical Global Impression of Change
CGI-I	Clinical Global Impression of Improvement
cm	centimeter
CO2	carbon dioxide
CRF	case report form
CSHQ	Children's Sleep Habit Questionnaire
D/C	discontinuation
DB	double-blind
DMC	Data Monitoring Committee
ECG	electrocardiogram
EEG	electroencephalogram
eCRF	electronic case report form
°C	degrees Celsius
FDA	Food and Drug Administration
GNX	ganaxolone
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IP	investigational product
ITT	intent-to-treat
IWRS	Interactive Web Response System
kg	kilogram
kg/m2	kilogram per square meter
LAR	legally authorized representative

Abbreviation	Term
lb	pound
LLN	lower limit of normal
m	meter
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mmHg	millimeters mercury
OL	open-label
OLE	open-label extension
PBO	placebo
PCDH19	protocadherin 19
PedsQL-FIM	Pediatric Quality of Life Inventory – Family Impact Module
PK	pharmacokinetics
PP	per protocol
PT	preferred perm
QI	Quality of Life Inventory
SAEs	serious adverse events
SAP	statistical analysis plan
SD	standard deviation
SI	Système International
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
WHO	World Health Organization
wks	weeks

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-PCDH19-3002 (Version 6.0, Protocol Amendment 5, 20 January 2021). This statistical plan does not include the analyses of the pharmacokinetic and pharmacodynamic (exposure response analysis) data.

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 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 Association[2] 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.

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

- To assess the efficacy of ganaxolone (GNX) compared with placebo (PBO) as adjunctive therapy for the treatment of primary seizures in children with genetically confirmed PCDH19-related epilepsy during the 17-week double-blind (DB) phase.

1.1.2 Secondary Objectives

- To assess the effect of GNX on primary seizure rate in biomarker-positive subjects.
- To assess behavioral/neuropsychiatric changes in subjects receiving GNX compared with subjects receiving PBO as adjunctive during the 17-week double-blind (DB) phase.
- To assess the safety and tolerability of GNX compared with PBO as adjunctive therapy during the 17-week DB phase.
- To assess pharmacokinetic (PK) parameters in subjects receiving GNX doses up

to 63 mg/kg/day (1800 mg/day maximum) throughout the study.

- To assess the long-term efficacy of GNX when administered as adjunctive therapy throughout the open-label (OL) phase.
- To assess the long-term safety and tolerability of GNX when administered as adjunctive therapy throughout the OL phase.

1.1.3 Exploratory Objectives

[redacted]

1.2 STUDY ENDPOINTS

1.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the percent change in 28-day primary seizure frequency during the 17-week DB phase relative to the baseline in all subjects. The primary seizure types are defined as countable focal seizures that include progressive hypotonia and impaired awareness, or any countable focal or generalized seizure with a clear motor component. Focal and generalized nonmotor seizures and myoclonic seizures do not count as the primary seizure types.

1.2.2 Secondary Efficacy Endpoints

1.2.2.1 Seizure Control Endpoints:

- The percent change in 28-day primary seizure frequency during the 17-week DB phase relative to baseline in biomarker positive subjects.
- Percentage of subjects experiencing a ≥ 50% reduction in 28-day primary seizure frequency compared to baseline.

1.2.2.2 Behavioral/Neuropsychiatric Endpoints

- Behavior Rating Inventory of Executive Function (BRIEF, preschool version BRIEF-P)
- Aberrant Behavior Checklist – Community (ABC-C)

- Children's Sleep Habit Questionnaire (CSHQ)

1.2.3 Exploratory Efficacy Endpoints

[redacted]

1.2.4 Pharmacokinetic Assessments

- Pharmacokinetic concentrations

The samples will be drawn between 1 and 5 hours or between 4 and 8 hours after the last dose during the double-blind and open-label periods.

1.2.5 Safety and Tolerability Endpoints

- Vital signs: blood pressure [BP], heart rate [HR], respiratory rate [RR], body temperature, weight, and height.
- Electrocardiograms (ECGs).
- Clinical laboratory tests - hematology, chemistry, and urinalysis.
- Physical, neurological, and developmental examinations.
- Concomitant Anti-Epilepsy Drug (AED) levels.
- Concomitant medications and therapies.
- Frequency, type and severity of adverse events (AEs)

1.2.6 Open-Label Extension Phase Endpoints

Except for the changes in seizure frequency during the titration portion and during the maintenance portion, the same efficacy, exploratory, quality of life, and safety endpoints for the DB phase will also be used for the OL phase. Analyses of OL phase data will be summarized separately.

1.3 STUDY DESIGN

1.3.1 General Study Design and Plan

This is a global, biomarker-stratified, DB, randomized, PBO-controlled trial of adjunctive GNX treatment of primary seizures in female children with a confirmed pathogenic or likely pathogenic PCDH19 mutation. The trial consists of a prospective baseline period of 8 to 12 weeks in duration to collect seizure data, followed by a 17-week DB treatment phase, which is then followed by a long-term OL phase (Figure 1). An interactive web response system (IWRS) will be used to randomize subjects, dispense drug, track treatment, and maintain the blind throughout the duration of the study.

During the screening visit, each subject's allopregnanolone sulfate (Allo-S) biomarker level will be assessed via a blood draw and subsequent analytical quantification. Each subject will then be assigned to 1 of 2 groups: biomarker-positive or biomarker-negative. A subject will be considered biomarker-positive if the baseline Allo-S level is less than or equal to 2500 pg/mL (Pinna Lab method or similar). A subject with a baseline Allo-S level greater than 2500 pg/mL will be classified as biomarker-negative. The biomarker group assignment will remain blinded until database unblinding. Based on the 11-subject

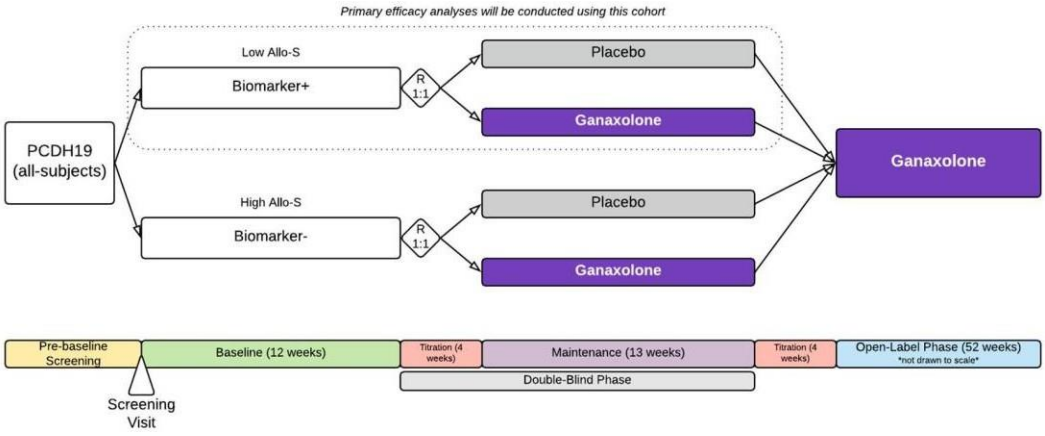
OL study, it is estimated that approximately 65% of subjects will be biomarker-positive.

The DB phase includes 4 weeks of investigational product (IP) titration followed by 13 weeks of dose maintenance. After meeting the eligibility criteria, approximately 25 children aged 1 to 17 years (inclusive) with PCDH19-related epilepsy will be randomly assigned to receive GNX or PBO (1:1 ratio within each biomarker stratum) for 17 weeks in addition to their standard anti-seizure treatment. Subjects will be titrated to 63 mg/kg/day (max 1800 mg/day) over 4 weeks and then maintained at that dose for another 13 weeks. Subjects who are not able to tolerate 63 mg/kg/day (or 1800 mg/day maximum) may be maintained on a lower dose. A minimum dose of 33 mg/kg/day or900 mg/day is generally required following the DB escalation period, unless a lower dose is agreed to with the sponsor due to the tolerability such as somnolence. At each visit, dosing will be reviewed and adjusted as needed based on subject's current weight.

Subjects who discontinue IP treatment before the completion of the DB phase will continue to be followed per protocol and, at a minimum, subjects will be encouraged to maintain daily seizure eDiary entries until the DB phase is completed. These subjects will also return to the site 2 to 4 weeks after the taper for safety follow-up post-taper assessments.

After completing the initial 17-week, DB, PBO-controlled phase, all subjects will be treated with GNX in the OL phase of the study. Ganaxolone subjects will continue GNX treatment and PBO subjects will titrate onto GNX. To maintain the blind, subjects initially randomized to GNX will undergo a blinded titration (increasing PBO doses) for 4 weeks, whereas PBO subjects will titrate up to 63 mg/kg/day GNX (1800 mg/day maximum) during the same time period. Any subject who completes the study or discontinues IP treatment at any time during the study should undergo a 2-week drug de-escalation (taper) period and return to the site 2 weeks later for safety follow-up post-taper assessments. Taper is not required if the subject is receiving the dose of 18 mg/kg/day or 450 mg/day (or lower).

Figure 1. Study Design



Subjects will be required to complete an eDiary to determine the effect of GNX on drug-resistant seizures. An electronic eDiary is the standard. In rare cases when an eDiary completion is not feasible, a paper diary will be used. These cases will need approval by the sponsor. A variety of clinician- and caregiver- administered instruments will be used to assess the efficacy of adjunctive GNX in PCDH19, and will include the following:

- Behavior Rating Inventory of Executive Function (BRIEF)
- Aberrant Behavior Checklist – Community (ABC-C)
- Children's Sleep Habit Questionnaire (CSHQ)
- Pediatric Quality of Life Inventory – Family Impact Module (PedsQL-FIM)
- Quality of Life Inventory – Disability (QI-Disability)
- Caregiver Global Impression of Change (CGI-C) – Target Behavior, Clinical Global Impression – Improvement [caregiver], and Clinical Global Impression – Improvement [clinician].

Safety and tolerability will be assessed by monitoring vital signs (blood pressure [BP], heart rate [HR], respiratory rate [RR], body temperature, weight, and height); 12-lead ECGs, clinical laboratory tests (hematology, chemistry, and urinalysis); physical, neurological, and developmental examinations; and frequency, type, and severity of AEs during the 17-week, DB phase and the OL phase.

The Schedule of Assessments for the 17-week pre-randomization and DB phase and for the OL is presented in the Appendix 14.1.

1.3.2 Sample Size and Power Considerations

A total of 50 subjects (25 in each treatment group) was planned to be enrolled in the

study.

As indicated in Protocol Amendment 4, Version 5 (dated 30 June 2020), enrollment in the study was discontinued early due to administrative reasons. As a result, the final sample size is not based on statistical considerations. Formal hypothesis testing will be performed based on all available sample size at the time of the study discontinuation.

2 STATISTICAL METHODS

2.1 GENERAL CONSIDERATIONS

In general, non-categorical variables will be summarized by number of subjects, mean, standard deviation (SD), median, 25th and 75th percentiles, minimum, and maximum values. Categorical variables will be summarized by counts and percentage of subjects in each category.

Except where noted, separate tables and data listings will be prepared for the DB and OL phases of the study. Only events occurring before entry into the OL phase will be included in the DB phase outputs, and except where indicated, only baseline events and events occurring after entry into the OL phase will be included in the OL phase outputs.

Tables will be provided using the intent-to-treat (ITT) subject population as well as within each of the biomarker positive and biomarker negative strata. The within-stratum placebo group will consist of only the subjects within the corresponding stratum. The tables for the DB phase will show the results for each DB treatment group, and, where noted, combined over the groups as well. The tables for the OL phase, during which all subjects will be receiving GNX, will show the results by assigned DB treatment group and for all OL subjects combined. For the efficacy endpoints, the results will be derived according to the randomized treatment group; for the other endpoints, data will be analyzed according to the treatment actually received. As such, any subject randomized to receive PBO but taking at least one dose of GNX will be reported in GNX group.

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 randomized subjects.

Baseline seizure activity will be determined by the subject's daily seizure eDiary entries for the 8 or 12 week period immediately prior to Visit 2 (Day 0), depending on eligibility criteria in the applicable protocol version. For primary seizures only, if a subject's baseline seizure count from this prospective baseline period is less than 4, the primary seizure count from the Historical Seizure Calendar Review CRF will be used to calculate a baseline 28-day seizure count. Within the DB phase of the study, determination of post-baseline seizure activity will begin on the day following the first day of DB treatment. The first day of DB treatment (Day 0) is included in neither the baseline nor DB phase since seizures could occur both before and after the initiation of treatment. Determination of post-baseline seizure activity assigned to the OL phase will begin on the day following the first OL treatment.

Baseline values for non-seizure efficacy and safety assessments are defined as the last non-missing value of the assessment before the first dose of treatment.

The OL phase will use the same baseline as the DB phase.

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 degree of precision specified in Table 1, unless otherwise specified:

Table 1: Reporting Precision

Statistics	Degree of Precision
Mean, Median, Quartiles, Confidence limit boundaries	One decimal place more than the raw data.
Standard deviation	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 Randomized Population

The randomized population comprises all subjects who are randomized to one of GNX or PBO treatment group.

2.2.2 Intention-to-Treat Population (ITT)

The ITT population comprises all randomized subjects who received at least one dose of study drug and have at least one post-baseline efficacy assessment.

2.2.3 Safety Population

The Safety population comprises all randomized subjects who received at least one dose of study drug.

2.2.4 Per-Protocol Population (PP)

The PP population includes all ITT subjects without major protocol violations (defined prior to database lock). There will be no PP population for the OL phase of the study.

2.3 TIME WINDOWS FOR ANALYSIS

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

In the analysis of seizure diary data, entries after the date of the first dose of study drug in the DB phase of the study but prior to the date of the first dose of study drug in the OL phase will be considered DB data. For subjects participating in the OL phase, entries dated after the date of first dose of study drug in the OL phase, including during the OL titration period, will be considered OL data.

2.4 POOLING OF CENTERS

Data from all sites will be pooled for analysis.

2.5 HANDLING OF MISSING DATA

Missing data will not be replaced except as noted. Missing efficacy data will be imputed in a sensitivity analysis as described in Section 7.1.6.

2.6 ANALYSIS SOFTWARE

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

3 STUDY SUBJECTS

3.1 DISPOSITION OF SUBJECTS

A data listing of Screening failures for the DB phase of the study will be provided.

Disposition will be summarized within the DB treatment groups and overall among all subjects within both the DB and OL phases of the study.

The summary of disposition will include the following:

- Subjects screened (DB phase only)
- Screen failures (DB phase only)
- Subjects in the Safety Population

- Subjects in the ITT Population
- Subjects in the PP Population
- Subjects who entered OL phase
- Subjects who completed the DB phase
- Subjects who discontinued from the study before the end of the DB phase
- Reasons for study discontinuation before the end of the DB phase
- Subjects who discontinued study drug before the end of the DB phase
- Reasons for study drug discontinuation before the end of the DB phase

Subjects completing the DB phase of the study are those who completed the 17-week DB treatment phase, regardless of whether they entered the OL. A listing of dispositions will be provided for all randomized subjects.

3.2 ELIGIBILITY CRITERIA AND PROTOCOL DEVIATIONS

The clinical team will identify protocol deviations before database lock.

A data listing of subjects who violate any of the inclusion/exclusion characteristics will be provided as well as a data listing of subjects with other protocol violations.

4 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic data (age, sex race, height, weight and body mass index (BMI), and ethnicity) and baseline characteristics (Tanner staging and number of AED medications taken and stopped) collected prior to the first dose of IP will be summarized using descriptive statistics in the ITT population, the Safety population and the PP population. The statistics will be shown by DB treatment group and for all subjects combined. Tables will be provided for the ITT population overall and by biomarker stratum. Subject data listings will also be provided.

Where units differ across data points, the following conversions will be applied:

- Height (cm) = Height (inches) * 2.54
- Weight (kg) = Weight (lbs) * 0.4536
- BMI (kg/m^2) = Weight (kg)/[Height$(m)^2$]

5 MEDICAL HISTORY AND GENETIC TESTING

Medical history will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) Terminology version 22.0 or higher. The number and percent of subjects reporting each diagnosis will be summarized by system organ class (SOC) and preferred

term (PT) by treatment and overall in the Safety population.

The results of the genetic testing and historical seizure information will be summarized and listed as available.

6 PRIOR AND CONCOMITANT MEDICATIONS AND THERAPIES

Prior medications/therapies are defined as medications/therapies that started and stopped prior to the first dose of DB study drug. Concomitant medications/therapies are defined as medications/therapies (other than the study drug) administered on or after the first dose of the DB study drug, regardless of when the medications/therapies started. The summary of concomitant medications/therapies for the main 17-week DB treatment phase of the study will not include concomitant medications/therapies that start after that phase; i.e., they will not include any starting on or after the first dosing day of the OL phase.

The summary of concomitant medications/therapies for the OL phase will include all medications/therapies, other than study drug, administered on or after the first dosing day of the OL phase. There will be no summary of prior medications/therapies for the OL phase.

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 or later). The number and percentage of subjects who took prior and concomitant medications will be summarized by treatment and overall in the Safety population and, if it differs substantially from the Safety population, the PP population as well, by ATC Classification and WHO Drug PT. Prior and Concomitant AEDs will be summarized and listed separately.

Rescue medications and associated prescribed doses reported as concomitant medications will be summarized and listed as described above. In addition, rescue medication usage data, including date and time of dosing and administered dose, which are obtained from eDiary entries, will be analyzed as exploratory endpoints as described in Section 7.1.4.6. Dose levels reported in these two sources of rescue medication data may differ.

The number (percentage) of subjects who received prior and concomitant therapies will be summarized by treatment and overall in the Safety population and, if it differs substantially from the Safety population, the PP population as well. The therapies will also be presented in a subject data listing.

To define prior or concomitant medications/therapies, Table 2 describes how missing date information will be handled; however, the actual dates, not the imputed ones, will be displayed in the listing.

Table 2: Handling of Partial or Missing Medication Dates

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 OL if the year is the same as the year of the first OL dose date, else January 1 of the 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 OL if the year and month are the same as the year and month of the first OL dose date, else the 1st of the 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 EFFICACY ANALYSES

In addition to the descriptive statistics mentioned in Section 2.1, the baseline, post-baseline, and relevant changes from baseline for the seizure endpoints will also be summarized. Wilcoxon rank-sum tests will be used to compare differences in percent change from baseline between the two treatment groups.

Fisher's exact test will be used to compare the percentage of subjects achieving notable reductions, e.g. ≥ 25% reduction, ≥ 50% reduction, etc., in seizure rates between the two treatment groups.

The baseline, post-baseline, and changes from baseline for the other non-categorical endpoints will be summarized descriptively with 95% confidence intervals for the means and differences in means between the treatment groups.

7.1 DOUBLE-BLIND PHASE

All efficacy analyses will be conducted in the ITT population as well as by biomarker stratum. A supportive analysis of the primary efficacy endpoint also will be conducted in

the PP population.

All analyses in the ITT population will include all available data, even if they were collected after the subject stopped taking study medication, regardless of whether the subject took rescue medication. Section 7.1.1 details the handling of missing data.

For the analyses of seizures, the baseline phase consists of the 8- to 12-week period before the first day of treatment, and the DB phase starts the day following the first day of DB treatment until the final visit for subjects who do not enter the OL and up to the day before the first dose of OL treatment for those who do. Also, if a subject's baseline primary seizure count based on the prospective baseline period is less than 4, the primary seizure count from the Historical Seizure Calendar Review CRF will be used to calculate a baseline 28-day seizure count.

Tests of significance between the two treatment groups will be performed for the primary endpoint with a 2-sided significance level of 0.05.

Seizure diary compliance for the baseline and post-baseline DB phase intervals will be calculated as:
100 x (Number of Days with Available Seizure Diary) / (Last Available Seizure Diary Date – First Available Seizure Diary Date + 1).

Seizure diary compliance between visits will be calculated as:
100 x (Number of days with available seizure data between visits) / Number of days between visits), with the days between visits defined as the day of the prior visit up to the day before the current visit.

Diary compliance values will be summarized with descriptive statistics and the percentage of subjects at least 80% compliant.

7.1.1 Handling of Missing Data

The primary analysis will use all available data. Careful educating and monitoring of the study sites will attempt to limit the amount of missing data. Sensitivity analyses, with replacement of missing data, will be performed for the primary efficacy endpoint; see Section 7.1.6.

For non-seizure variables, data for subjects prematurely discontinuing from the study will be assigned to the first visit subsequent to the discontinuation at which the assessment was scheduled, as long as the discontinuation visit is within 32 days of the next scheduled performance of that assessment.

7.1.2 Primary Efficacy Endpoint

The primary efficacy endpoint is the percent change in 28-day primary seizure frequency during the 17-week DB phase relative to the baseline. The primary seizure types are defined as countable focal seizures that include progressive hypotonia and impaired awareness, or any countable focal or generalized seizure with a clear motor component. Focal and generalized nonmotor seizures and myoclonic seizures do not count as the

primary seizure types.

The analyses of the primary endpoint will be performed on the sum of the individual countable seizures and each series of continuous uncountable seizures (each contributes 1 to the sum).

Post-baseline 28-day seizure frequency will be calculated as the total number of seizures in the 17-week DB treatment phase divided by the number of days with seizure data in the phase, multiplied by 28. Baseline 28-day seizure frequency will be calculated as the total number of seizures in the baseline phase divided by the number of days with seizure data in the phase, multiplied by 28. For primary seizures only, if a subject's baseline seizure count from this prospective baseline period is less than 4, the primary seizure count from the Historical Seizure Calendar Review CRF will be used to calculate a baseline 28-day seizure count.

The calculation for percent change from baseline in 28-day 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, post-baseline, and arithmetic and percent changes from baseline in 28-day seizure frequency will be summarized using descriptive statistics. A subject data listing will be provided.

The difference between the GNX and placebo groups in the percent changes will be tested using the Wilcoxon Rank-Sum statistic. Testing will be conducted in the following order:

- The primary analysis will be conducted in the ITT population.
- If nominal statistical significance is achieved in the ITT population, the primary analysis will be similarly conducted in the biomarker-positive stratum of the ITT population as a secondary endpoint (Section 7.1.3).
- In addition, as an exploratory analysis, efficacy will be assessed in the biomarker-negative stratum. (Section 7.1.4.1) and compared with the biomarker positive result.

The analysis of the primary efficacy endpoint will be conducted in the ITT population and within the biomarker strata of the ITT population; a supportive analysis in the PP population will also be done.

7.1.3 Secondary Efficacy Endpoints

All secondary efficacy endpoints will compare GNX and PBO during the 17-week DB treatment phase relative to the prospective baseline phase, unless specifically indicated otherwise.

All secondary analyses will be done in the ITT population for all subjects and by biomarker stratum, and if the ITT and PP analyses notably differ for the primary endpoint, they will also be done in the PP population. All seizure control endpoints will be included in data listings.

7.1.3.1 Percent Change in Primary Seizure Frequency in Biomarker Positive Stratum

If the results of the primary endpoint analysis in the full ITT population indicate efficacy in the GNX treatment arm, the primary efficacy analysis described in Section 7.1.2 will be repeated for subjects in the biomarker-positive stratum.

7.1.3.2 Percentage of Subjects Experiencing Primary Seizure Reduction

Percentages of subjects experiencing a ≥ 50% reduction in 28-day primary seizure frequency relative to baseline will be compared between GNX and PBO for both biomarker-positive and negative strata, separately, and for the combined strata. A Fisher's Exact test will be used to compare rates between treatment groups.

7.1.3.3 Behavior Rating Inventory of Executive Function (BRIEF, preschool version BRIEF-P)

The BRIEF is an 86-item questionnaire designed to assess executive function behaviors in the school and home environments in individuals 5-18 years of age. The preschool version (BRIEF-P) is a 63-item modified form and will be administered to individuals 2-5 years of age. The BRIEF version to be administered will be based on the subject's age at Screening. The same version of the BRIEF will be administered during the entire study regardless of the subject's age at the time of post-screening assessment. The questionnaire is completed by the parents/caregiver/ legally authorized representative (LAR).

The BRIEF items are partitioned to create 8 component scores:

- Inhibit
- Shift
- Emotional Control
- Initiate
- Working Memory
- Plan/Organize
- Organization of Materials
- Monitor

The first three components are summed to create a Behavioral Regulation Index (BRI), and the remaining five components are summed to create a Metacognition Index (MI). The BRI and MI are then summed to create a Global Executive Composite (GEC).

The BRIEF-P items are partitioned to create 5 component scores:

- Inhibit
- Shift
- Emotional Control
- Working Memory
- Plan/Organize Scales

The Inhibit and Emotional Control components are summed to create an Inhibitory Self-Control Index (ISCI), the Shift and Emotional Control components are summed to create a Flexibility Index (FI), the Working Memory and Plan/Organize components are summed to create an Emergent Metacognition Index (EMI), and all five components are summed to create a Global Executive Composite (GEC).

All component scores, index scores, and composite scores will be descriptively summarized. Both baseline, post-baseline, and change from baseline will be summarized. These scores will also be listed. Statistical comparison between treatment groups will not be performed.

7.1.3.4 Aberrant Behavior Checklist – Community (ABC-C)

The ABC-C is a 58-item questionnaire designed to assess problematic behavior at home, in educational and work setting, and in residential and community-based facilities. The item scores range from 0=”not at all a problem” to 3=”the problem is severe in degree”. The items are partitioned into 5 domains:

1. Irritability (items 2, 4, 8, 10, 14, 19, 25, 29, 34, 36, 41, 47, 50, 52, 57)
2. Social withdrawal (items 3, 5, 12, 16, 20, 23, 26, 30, 32, 37, 40, 42, 43, 53, 55, 58)
3. Stereotypy behavior (items 6, 11, 17, 27, 35, 45, 49)
4. Hyperactivity (items 1, 7, 13, 15, 18, 21, 24, 28, 31, 38, 39, 44, 48, 51, 54, 56)
5. Inappropriate speech (items 9, 22, 33, 46)

The domain subtotals and the total of all the items will be summarized with descriptive statistics of the baseline and post-baseline values and the arithmetic changes from baseline. Difference in mean scores between two treatment groups will be provided along with 95% confidence intervals.

7.1.3.5 Children’s Sleep Habit Questionnaire (CSHQ)

The CSHQ is a psychological questionnaire designed to measure sleep behaviors in children and adolescents and is filled out by the parent/caregiver/LAR. An abbreviated version contains 33 items.

The first 31 items are scored as 1 = Rarely (0-1 times per week), 2 = Sometimes (2-4 times per week), or 3 = Usually (5 - 7 times per week). Item 32 (Watching TV) and 33 (Riding in car) ask how sleepy the child has appeared during those activities (1 = Not sleepy, 2 = Very sleepy, or 3 = Falls asleep). The questionnaire includes 2 other quantitative questions:

- Child's usual amount of sleep each day
- Number of minutes a night waking usually lasts

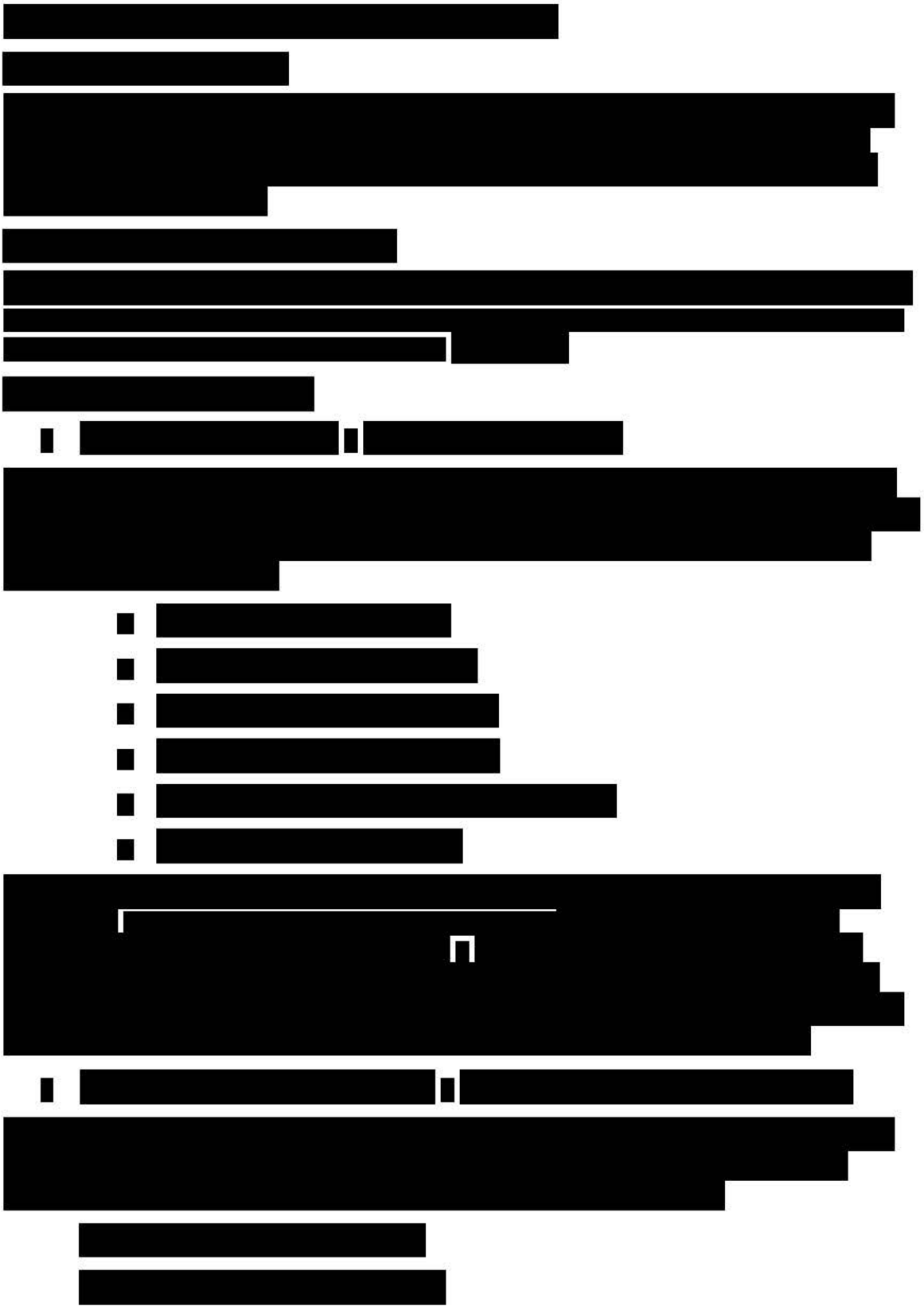
The 33 items are partitioned into 8 domains:

1. Bedtime resistance (items 1, 3, 4, 5, 6, 8)
2. Sleep onset delay (item 2)
3. Sleep duration (items 9, 10, 11)
4. Sleep anxiety (items 5, 7, 8, 21)
5. Night wakings (items 16, 24, 25)
6. Parasomnias (items 12-15, 17, 22, 23)
7. Sleep disordered breathing (items 18, 19, 20)
8. Daytime sleepiness (items 26-33)

For scoring, first, items 1, 2, 3, 10, 11, and 26 are reversed (4-score). The item scores are then summed within each domain. The domain subtotals, the total of the 33 items, and the 2 other quantitative questions will be summarized with descriptive statistics of the baseline and post-baseline values and the arithmetic changes from baseline. Differences in mean scores between two treatment groups will be provided along with 95% confidence intervals.

The usual amount of sleep each day will be summarized in hours.

7.1.4 Exploratory Endpoints



[redacted]

7.1.5 Subgroup Analyses

Other than the within-stratum analyses, no subgroup analyses are planned at this time.

7.1.6 Sensitivity Analyses

Two sensitivity analyses of the primary efficacy endpoint of change in 28-day frequency of the primary (i.e., all countable motor) seizure types will be performed:

Intermittent (random/sporadic) missing data during the 17-week DB phase and any missing data during the baseline phase will be assumed missing completely at random and the collected data will be used to calculate the 28-day seizure frequencies. For early drug termination prior to the end of the 17-week DB phase, caregivers will be instructed to continue to provide daily seizure records until the end of the 17-week DB phase (hence further preventing missingness).

In the first sensitivity analysis, the following imputation approach will be used for the primary outcome measure when a subject stops recording measurements permanently (anticipated to be zero or minimal in occurrence) prior to the end of the 17-week DB phase. For days with missing seizure count data, the corresponding median PBO data will be imputed (irrespective of treatment arm), within each stratum, as follows:

- Compute the median 28-day seizure frequency in the PBO arm based on all available PBO measurements during the 17-week DB treatment phase. Label that

'X' and define 'A' to be 'X'/28, (i.e., the daily average on placebo during the 17-week during the DB phase).

- For any days (whether they be in the PBO or GNX arm) that occur AFTER a subject has become lost to follow up, impute 'A' on that day.

The second sensitivity analysis will explore the possibility that subjects who stop recording their seizure counts tend to have higher seizure counts than the other subjects. The imputation method described above will be modified to use the median of the 5 highest counts, rather than the median count, among the PBO subjects with data.

7.1.7 Protections for Multiplicity

As explained in Section 7.1.2, analyses of the 28-day seizure frequency will be conducted in the following sequence:

- The primary analysis will be conducted using all subjects in the ITT population.
- If nominal statistical significance is achieved in the ITT population, the primary analysis will be similarly conducted in the biomarker-positive stratum of the ITT population as a secondary endpoint (Section 7.1.3).
- In addition, as an exploratory analysis, efficacy will be assessed in the biomarker-negative stratum. (Section 7.1.4.1)

7.2 OPEN LABEL EXTENSION

All of the analyses for the DB phase will be repeated for the OL phase, with the following differences:

- All results will only be summarized descriptively.
- The results will be presented overall and classified according to the DB treatment received by the subjects
- The post-baseline seizure endpoints will be derived based on the first full day of OL treatment (one day after OL start).
- No sensitivity analyses will be performed.
- Analyses of seizure frequencies during titration and maintenance phases are only applicable to the DB phase and will not be included in the OL phase analyses.
- The time points for the efficacy, exploratory, and quality of life endpoints will be after 19 weeks, 51 weeks, and every 16 weeks thereafter of open-label treatment relative to the prospective baseline phase.
- The differences between the DB treatment groups in the percent changes from baseline of the 28-day seizure frequencies will not be tested for statistical significance.

- No PP analyses will be performed.

8 PHARMACOKINETICS

A listing of the pharmacokinetic collection times will be provided, but the analyses will be described in a separate report.

9 SAFETY ANALYSIS

All safety analyses will be performed in the Safety Population. The results in the DB and OL phases will be summarized separately. In both phases, the results will be summarized by the DB treatment actually received and, for the OL phase of the study, combined over the treatment groups. Baseline for safety endpoints is defined as the last non-missing value obtained before the first day of DB treatment. Assessments performed at multiple post-baseline time points will be summarized at each time point for which they are scheduled, but the listings will also include any assessments performed at unscheduled time points.

The number and percentage of days that subjects received investigational product, the highest percentage of the maximum allowable daily dose (1800 mg or 63 mg/kg) that subjects received, and the total amount of investigational product received will be summarized. For the OL phase, they will be summarized over just the OL phase as well as over the entire study (combined DB and OL phases) but the classification by the DB treatment applies only for the OL phase summary. The summarization over the entire study will include only subjects who were in the GNX group during the DB phase, regardless of whether they entered the OL, and all the subjects from the OL phase. 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 BP, HR, RR, body temperature, weight, and height
- 12-lead Electrocardiogram (ECG)
- Physical, neurological and developmental examinations
- Neurosteroid levels
- Tanner staging (OL phase only)

9.1 ADVERSE EVENTS

AEs will be coded by System Organ Class (SOC) and Preferred Term (PT) using MedDRA®, version 22.0 or higher. The verbatim term will be included in the AE listings. Except where indicated, the summary tables will include only treatment-emergent adverse events (TEAEs). All AEs, treatment-emergent or otherwise, will be

presented in subject data listings.

A 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 DB treatment phase of the study will include AEs that start or worsen during that phase and will not include AEs that start or worsen during the OL phase; i.e., they will not include any AEs starting or worsening on or after the first dosing day of the OL phase.

For the OL phase of the study, the adverse event results will be summarized over just the OL phase as well as over the entire study (DB and OL phases) but the classification by the DB treatment applies only for the OL phase summary. The summarization over the entire study will include only subjects who were in the GNX group during the DB phase, regardless of whether they entered the OL, and all the subjects from the OL phase; i.e., it will include only the TEAEs following GNX exposure. The summarizations over just the OL phase will include TEAEs that occur or worsen on or after the first day of the OL phase; the summarizations over the entire study will include TEAEs that start or worsen on or after the first dosing day of GNX.

The TEAEs will be summarized as the number of events and the number and percentage of subjects with TEAEs. Subjects who report the same PT on multiple occasions will be counted once for the PT: under the highest severity (severe > moderate > mild) when summarized by severity and under the closest relationship (related > not related) to study drug when summarized by relationship.

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

Non-treatment emergent AEs will only be listed.

TEAEs will be summarized as follows:

- An overview table of TEAEs, including number of events and number (%) of subjects with:
    - TEAEs
    - Serious AEs (SAEs)
    - Study drug related TEAEs
    - TEAEs by severity
    - TEAEs leading to study discontinuation
    - TEAEs leading to death
    - Adverse events of special interest (AESI)
- TEAEs by SOC and PT

- TEAE by SOC, PT, and Severity
- Study drug related TEAEs by SOC, PT
- SAEs by SOC and PT
- TEAEs leading to study drug discontinuation by SOC and PT
- TEAEs leading to dose reduction by SOC and PT
- Adverse events of special interest (AESI)

All AE tables will be sorted by SOC and PT in decreasing frequency of the number of subjects in the GNX group, in the DB summaries and the combined groups in the OL summaries; in case of tied frequencies, the sorting will be alphabetical.

Adverse event listing will identify serious AEs, AE leading to study drug discontinuation, AEs leading to dose reduction, AEs of special interest, and subjects who died during the study.

For purposes of determining treatment emergence, missing start dates will be imputed as shown in Table 3; however, the actual dates, not the imputed ones, will be displayed in the data listing.

Table 3: Handling of Partial or Missing Adverse Event Dates

Partial Missing Start or Stop Date	Imputed Start Date	Imputed Stop Date
Missing month, day, and year	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 OL if the year is the same as the year of the first OL 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 OL if the year and month are the same as the year and month of the first OL 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

9.2 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 Système International (SI) units. Quantitative results (including actual values 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 will be assigned an LH classification according to whether the value was below (L) or above (H) the normal reference range (some urinalysis labs are assigned only normal and abnormal classifications) (See also Appendix 14.2). Values outside the normal range will also be classified as to whether

they were potentially clinically significant (Appendix 14.3). Shift tables cross-tabulating the baseline and post-baseline classifications (below (L), Normal (N), or above (H) the reference range), by visit, will be provided.

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

9.3 OTHER SAFETY ENDPOINTS

9.3.1 Vital Signs

Vital signs include weight (kg), height (cm), temperature (°C), systolic and diastolic blood pressure (mmHg), respiration rate (breaths per minute), and pulse rate (bpm).

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 visit for each parameter.

Listings of vital signs will be provided.

9.3.2 Electrocardiogram (ECG)

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

A subject listing will be provided.

9.3.3 Physical, Neurological, and Developmental Examinations

Physical examination results were interpreted as normal, abnormal (not clinically significant) or abnormal (clinically significant). Neurological examination results were interpreted as normal or abnormal. Physical, neurological, and developmental examination findings will be summarized and listed.

9.3.4 Neurosteroid Levels

The baseline and post-baseline values and the arithmetic changes from baseline of the neurosteroid levels will be summarized using descriptive statistics and listed.

To examine response by neurosteroid levels, change from baseline in 28-day seizure frequency will be summarized in the subsets of the ITT subject population with low allopregnanolone-sulfate (Allo-S) levels, defined as baseline Allo-S ≤ 2,500 pg/mL, mid Allo-S levels, defined as baseline Allo-S > 2,500 pg/mL and <6,000 pg/mL, and high All-S levels, defined as Allo-S ≥ 6,000 pg/mL.

9.3.5 Tanner Staging

The Tanner scale (also known as the Tanner stages) is a scale of physical development in children, adolescents, and adults. The scale defines physical measurements of

development based on external primary and secondary sex characteristics. Subjects will be evaluated and rated as Tanner I, Tanner II, Tanner III, Tanner IV and Tanner V. Tanner staging will occur at Screening (Visit 1), Visit 8 (Week 52) and will continue to be assessed annually for the duration of the subject's participation in the open-label phase and at the final OL visit.

The number and percentage of subjects of each category will be summarized by Screening and OL visit, and a listing will be provided.

10 INTERIM ANALYSES AND DATA MONITORING COMMITTEE (DMC)

No formal interim analysis is planned for this study. After all active subjects complete the 17-week DB phase, the DB data in the database will be locked and used to perform endpoint analysis. Data collected during the open label phase will be analyzed separately.

The emerging study data will be reviewed on a regular basis by an independent DMC. The mission of the DMC will be to safeguard the interests of study participants and to enhance the integrity and credibility of the trial. To enable the DMC to achieve their mission, the DMC will have ongoing access to efficacy and safety data and data regarding quality of trial conduct and will ensure the confidentiality of these data will be preserved. A DMC Charter will provide the principles and guidelines for the DMC process. Specific details of the monitoring guidelines are provided in the DMC Charter.

11 SUMMARY OF MAJOR CHANGES IN THE PLANNED ANALYSES

There are no major changes in the planned analyses. The contents of this SAP are consistent with the most current version of the protocol.

Any future changes to these analyses will be documented in an SAP amendment or described in the clinical study report (CSR).

12 PROGRAMMING SPECIFICATIONS

12.1 FORMAT OF APPENDIX TABLES/FIGURES/LISTINGS

1. Unless otherwise specified, all computer-generated tables, figures and listings (TFL) will be produced (via SAS® ODS) into RTF output, which can be imported in table format via Microsoft® Word. The TFLs 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 Pharmaceuticals, Inc.
     Protocol 1042-PCDH19-3002
     ```

   - Header with page number and date/time at the upper right margin:

     ```
     Page X of N
     ddMMMyyyy: hh:mm
     ```

TFLs 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).

2. Each TFL should be identified by in a sequential numeric order, and the TFL 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 TFL 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 TFL. 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

Data Sets: xxxx, xxxx                          Program Name: xxxx.sas
```

5. All data listings should be sorted by, treatment group and biomarker stratum 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.

12.2 SAS PROCEDURES FOR SEIZURE ANALYSES

The following code will provide the Wilcoxon rank-sum test:

```
proc npar1way data=dataset (where=(specify analysis
 population, endpoint, study phase, and time point)
 wilcoxon
 HL(refclass='formatted value of Placebo group');
  by stratum; *stratum is the name of the stratum variable
  class trtp; *trtp is the name of the randomized
    treatment variable;
  var pchg; *pchg is the name of the percent change
variable;
run;
```

13 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.

14 APPENDICES

14.1 SCHEDULE OF ASSESSMENTS

14.1.1 Schedule of Assessments for the 17-Week, Double-Blind Phase of the Study:

	Pre-screen/Screen/Baseline			DB Titration + Maintenance					Final DB Visit
WEEK	**- (Pre-baseline Screening Visit)**	**-12 (Screening Visit – Start of Baseline)**	**0 (Baseline Visit – Randomization)**	**3 days**	**1, 2, 3, 4**	**5**	**9**	**11, 13**	**17**
Visit Windows	**N/A**	**N/A**	**+ 6 days**	**± 1 day**	**± 3 days**	**± 3 days**	**± 3 day**	**± 3 days**	**± 3 days**
VISIT	**Visit 0**	**Visit 1[a]**	**Visit 2[r]**	**Phone Follow-up**	**Phone Follow-up**	**Visit 3**	**Visit 4**	**Phone Follow-up**	**Visit 5**
Screening and Diagnosis									
Informed Consent[b]	X[c]	X							
Demographics & Medical History		X	X[d]						
Historical Seizure Calendar Review[c]	X	X							
Inclusion/Exclusion Criteria	X	X	X						
Genetic testing[e]	X	X							
Seizure Identification and Diagnostic Review Form (Epilepsy Study Consortium)		X	X						
Safety Assessments									
Vital signs (BP, HR, RR, and body temperature)		X[f]	X[g]			X[g]	X[g]		X[g]
Physical/Neurological/ Developmental Exam		X	X			X	X		X

	Pre-screen/Screen/Baseline			DB Titration + Maintenance					Final DB Visit
WEEK	**- (Pre-baseline Screening Visit)**	**-12 (Screening Visit – Start of Baseline)**	**0 (Baseline Visit – Randomization)**	**3 days**	**1, 2, 3, 4**	**5**	**9**	**11, 13**	**17**
Visit Windows	**N/A**	**N/A**	**+ 6 days**	**± 1 day**	**± 3 days**	**± 3 days**	**± 3 day**	**± 3 days**	**± 3 days**
VISIT	**Visit 0**	**Visit 1[a]**	**Visit 2[r]**	**Phone Follow-up**	**Phone Follow-up**	**Visit 3**	**Visit 4**	**Phone Follow-up**	**Visit 5**
ECG			X			X			X
Clinical Laboratory Tests[h]		X	X			X	X		X
Urinalysis		X[i]	X[i]			X			X
Drug screen[j]		X	X						X
Pregnancy Test (WCBP)[k]		X	X			X	X		X
Tanner Staging		X							
Investigational Product PK						X[l]	X[l]		X
Concomitant AED Review and levels if per standard of care[m]		X	X			X	X		X
Neurosteroid levels		X							X
Adverse Event		X	X	X	X	X	X	X	X
Efficacy Assessments									
Seizure and Medication eDiary review[n]		X[o]	X	X	X	X	X	X	X
Children's Sleep Habit Questionnaire (CSHQ)			X						X
Behavior Rating Inventory of			X						X

	Pre-screen/Screen/Baseline			DB Titration + Maintenance					Final DB Visit
WEEK	**- (Pre-baseline Screening Visit)**	**-12 (Screening Visit – Start of Baseline)**	**0 (Baseline Visit – Randomization)**	**3 days**	**1, 2, 3, 4**	**5**	**9**	**11, 13**	**17**
Visit Windows	**N/A**	**N/A**	**+ 6 days**	**± 1 day**	**± 3 days**	**± 3 days**	**± 3 day**	**± 3 days**	**± 3 days**
VISIT	**Visit 0**	**Visit 1[a]**	**Visit 2[r]**	**Phone Follow-up**	**Phone Follow-up**	**Visit 3**	**Visit 4**	**Phone Follow-up**	**Visit 5**
Executive Function (BRIEF)									
Aberrant Behavior Checklist – Community (ABC-C)			X						X
Exploratory Assessments									
[redacted]			[redacted]						[redacted]
[redacted]			[redacted]						[redacted]
[redacted]			[redacted]						[redacted]
[redacted]			[redacted]			[redacted]	[redacted]		[redacted]
[redacted]			[redacted]			[redacted]	[redacted]		[redacted]
[redacted]			[redacted]			[redacted]	[redacted]		[redacted]

	Pre-screen/Screen/Baseline			DB Titration + Maintenance					Final DB Visit
WEEK	**- (Pre-baseline Screening Visit)**	**-12 (Screening Visit – Start of Baseline)**	**0 (Baseline Visit – Randomization)**	**3 days**	**1, 2, 3, 4**	**5**	**9**	**11, 13**	**17**
Visit Windows	**N/A**	**N/A**	**+ 6 days**	**± 1 day**	**± 3 days**	**± 3 days**	**± 3 day**	**± 3 days**	**± 3 days**
VISIT	**Visit 0**	**Visit 1[a]**	**Visit 2[r]**	**Phone Follow-up**	**Phone Follow-up**	**Visit 3**	**Visit 4**	**Phone Follow-up**	**Visit 5**
Dispense Investigational Product[q]			X			X	X		X

AED = antiepileptic drug, BP = blood pressure, CBD = cannabidiol, D/C = discontinuation, DB = double-blind, ECG = electrocardiogram, EEG = electroencephalogram, HR = heart rate, LAR = legally authorized representative, PK = pharmacokinetic, RR = respiratory rate, THC = tetrahydrocannabinol, WCBP = women of childbearing potential.

a. Subject rescreening is allowed as agreed by Sponsor and Investigator unless there is a general concern for subject safety or an inability for the subject to become eligible (eg, GNX allergy, sensitivity or exposure, non-PCDH19 and/or other ineligible epilepsy, chronic prohibited medical condition or treatment). Subsequent screening should take place at least 30 days from the subject's last visit.
b. Written informed consent/assent must be obtained from subject, parent or LAR before any study assessments are performed.
c. In the event that the parent/caregiver/LAR does not routinely maintain a daily seizure calendar per standard of care, written informed consent will be obtained from the parent/LAR and subject assent, and the subject will be asked to return to the clinic for the screening visit after she has maintained a 12-week daily historical seizure calendar.
d. Review of medical history only.
e. Genetic testing to be performed to confirm pathogenic or likely pathogenic *PCDH19* variant. If genetic testing is not performed as Standard of Care, a pre-baseline screening visit will be scheduled to obtain informed consent/assent and complete the genetic testing. If genetic testing results are available per SOC, the genetic testing will be done at screening to confirm the results by the Sponsors designated lab.
f. In addition, height and weight will be measured.
g. In addition, weight will be measured. At each visit, dosing will be reviewed and adjusted as needed based on a subject's current weight.
h. Chemistry & Hematology.
i. An attempt should be made to collect a urine sample for a urinalysis at screening; otherwise, the urine sample can be collected at baseline for the urinalysis.
j. A drug screen (plasma) will be performed to test for THC and CBD at screening. If the screening drug test is positive, the subject can be retested, via plasma, after two weeks. A drug screen may be performed at any time at Investigator's discretion. A positive drug test during the DB phase will result in early termination.
k. Serum pregnancy test is required for all girls/women of childbearing potential.
l. Population PK will be conducted at these visits (Visit 3: between 1-5 hours since last IP dosing, Visit 4: between 4-8 hours since the last investigational product dosing).
m. Concomitant AEDs must be stable for 1 month prior to screening and cannot be changed at any time prior to Visit 5, but may be adjusted during the open-label phase of the study.

n. For recording of seizures in the eDiary, seizure events will be recorded either as a countable seizure or a series of continuous uncountable seizures. Both of these events will be counted as 1 seizure (equally weighted) in the efficacy analysis. A seizure cluster will be defined as 3 or more seizure events (either a countable or a series of continuous uncountable seizures), occurring within a period of time, followed by a period of at least 24 hours of seizure-freedom.
   Examples: (Protocol Figure 2):
   - If a child experiences 3 seizure events at 5:00, 5:30, and 6:00 PM on Monday, and the next seizure event occurs before 6:00 PM on Tuesday, the Monday and Tuesday seizure events are considered part of the same seizure cluster (Protocol **Error! Reference source not found.**, Scenario 1).
   - If a child experiences 3 seizure events at 5:00, 5:30, and 6:00 PM on Monday, and the next seizure event occurs at 6:00 PM or later on Tuesday, the Tuesday seizure event is not considered part of the same cluster (Protocol **Error! Reference source not found.**, Scenario 2).

o. Caregiver given eDiary and instructions for use.

p. During the screening visit, the principal investigator and parent/caregiver/LAR will decide on a domain and identify the specific behavior that the subject exhibits that denotes the domain. This behavior will be used at subsequent visits to assess change after the initiation of investigational product.

q. Subjects who discontinue investigational product early will be encouraged to continue with all procedures and scheduled visits.

r. The 12 weeks between Screening and Randomization can be no less than 84 days and no more than 90 days.

14.1.2 Schedule of Assessments for Open-Label Phase

	Final DB Visit/ First OL Visit	Titration (4 weeks blinded)			Open-Label Maintenance (Visits will be every 16 weeks with a telephone follow up in-between, this schedule continues after 68 weeks)						Final OL Visit or Taper Visit[J]	Safety Follow-up post taper[J]
WEEK	**17**	**Week 17 +3 Days**	**18, 19, 20**	**21**	**28**	**36**	**44**	**52**	**60**	**68[a] and X visit**	**X/ or early D/C[J]**	**2 weeks post last dose**
Visit Windows		**± 1 day(s)**	**± 3 days**	**± 3 days**	**± 14 days**	**± 14 days**	**± 14 days**	**± 14 days**	**± 14 days**	**± 14 days**	**± 14 days**	**± 3 days**
VISIT	**Visit 5**	**Phone Follow-up**	**Phone Follow-up**	**Visit 6**	**Phone follow-up**	**Visit 7**	**Phone follow-up**	**Visit 8**	**Phone follow-up**	**Visit 9 and Visit X**	**Visit X**	**Visit X**
Safety Assessments												
Vital signs (BP, HR, RR, and body temperature)[b]	X[b]			X[b]		X[b,c]		X[b,c]		X[b, c]	X[b,c]	X
Physical/Neurological/ Developmental Exam	X			X		X		X		X	X	X
ECG	X			X				X[d]			X	
Clinical Laboratory Tests[e]	X			X		X		X		X	X	X
Urinalysis	X					X		X		X[g]	X	X
Drug Screen	X											
Pregnancy Test (WCBP)[f]	X			X		X		X		X	X	X
Tanner Staging								X		X[g]	X	
Investigational Product PK	X			X[i]		X		X[i]		X	X	X

	Final DB Visit/ First OL Visit	Titration (4 weeks blinded)			Open-Label Maintenance (Visits will be every 16 weeks with a telephone follow up in-between, this schedule continues after 68 weeks)						Final OL Visit or Taper Visit[J]	Safety Follow-up post taper[J]
WEEK	**17**	**Week 17 +3 Days**	**18, 19, 20**	**21**	**28**	**36**	**44**	**52**	**60**	**68[a] and X visit**	**X/ or early D/C[J]**	**2 weeks post last dose**
Visit Windows		**± 1 day(s)**	**± 3 days**	**± 3 days**	**± 14 days**	**± 14 days**	**± 14 days**	**± 14 days**	**± 14 days**	**± 14 days**	**± 14 days**	**± 3 days**
VISIT	**Visit 5**	**Phone Follow-up**	**Phone Follow-up**	**Visit 6**	**Phone follow-up**	**Visit 7**	**Phone follow-up**	**Visit 8**	**Phone follow-up**	**Visit 9 and Visit X**	**Visit X**	**Visit X**
Concomitant AED Review and levels if per standard of care	X			X		X		X		X	X	X
Neurosteroid Levels	X							X		X[g]	X	
Adverse Event	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Assessments												
Seizure eDiary review[h]	X	X	X	X	X	X	X	X	X	X	X	X
Children's Sleep Habit Questionnaire (CSHQ)	X					X				X	X	
Behavior Rating Inventory of Executive Function (BRIEF)	X					X				X	X	
Aberrant Behavior Checklist – Community (ABC-C)	X					X				X	X	

	Final DB Visit/ First OL Visit	Titration (4 weeks blinded)			Open-Label Maintenance (Visits will be every 16 weeks with a telephone follow up in-between, this schedule continues after 68 weeks)						Final OL Visit or Taper Visit[J]	Safety Follow-up post taper[J]
WEEK	17	Week 17 +3 Days	18, 19, 20	21	28	36	44	52	60	68[a] and X visit	X/ or early D/C[J]	2 weeks post last dose
Visit Windows		± 1 day(s)	± 3 days	± 3 days	± 14 days	± 14 days	± 14 days	± 14 days	± 14 days	± 14 days	± 14 days	± 3 days
VISIT	Visit 5	Phone Follow-up	Phone Follow-up	Visit 6	Phone follow-up	Visit 7	Phone follow-up	Visit 8	Phone follow-up	Visit 9 and Visit X	Visit X	Visit X
Exploratory Assessments												
[redacted]	■										■	
[redacted]	■					■				■	■	
[redacted]	■					■				■	■	
[redacted]	■					■				■	■	
[redacted]	■					■				■	■	

	Final DB Visit/ First OL Visit	Titration (4 weeks blinded)			Open-Label Maintenance (Visits will be every 16 weeks with a telephone follow up in-between, this schedule continues after 68 weeks)						Final OL Visit or Taper Visit[J]	Safety Follow-up post taper[J]
WEEK	17	Week 17 +3 Days	18, 19, 20	21	28	36	44	52	60	68[a] and X visit	X/ or early D/C[J]	2 weeks post last dose
Visit Windows		± 1 day(s)	± 3 days	± 3 days	± 14 days	± 14 days	± 14 days	± 14 days	± 14 days	± 14 days	± 14 days	± 3 days
VISIT	Visit 5	Phone Follow-up	Phone Follow-up	Visit 6	Phone follow-up	Visit 7	Phone follow-up	Visit 8	Phone follow-up	Visit 9 and Visit X	Visit X	Visit X
[redacted]	[redacted]					[redacted]				[redacted]	[redacted]	
Dispense Investigational Product	X			X		X		X		X	X	

AED = antiepileptic drug, BP = blood pressure, DB = double-blind, D/C = discontinuation, ECG = electrocardiogram, EEG = electroencephalogram, HR = heart rate, PK = pharmacokinetic, OL = open-label, RR = respiratory rate, WCBP = women of childbearing potential.

Note: The timing of the final OL visit is not defined at this time, as the study is anticipated to continue until either the investigational product is approved and marketed, or the Sponsor discontinues development of investigational product in PCDH19 (approximately an additional 3 years).

a. If the subject continues in the OL phase beyond Week 68, a telephone follow-up visit will occur in between clinic visits (8 weeks ± 14 days after each clinic visit) to assess the following adverse events and seizure and medication diary review.
b. In addition, weight will be measured at every visit, except the safety follow-up visit.
c. In addition, height will be measured annually after Visit 8 (Week 52), except the safety follow-up visit.
d. After Visit 8 (Week 52), ECGs to be performed annually (and at last OL visit).
e. Chemistry & Hematology.
f. Serum pregnancy test is required for all girls/women of childbearing potential.
g. Conduct annually and at the final OL visit.

h. For recording of seizures in the eDiary, seizure events will be recorded either as a countable seizure or a series of continuous uncountable seizures. Both of these events will be counted as 1 seizure (equally weighted) in the efficacy analysis. For recording of seizures in the eDiary, seizure events will be recorded either as a countable seizure or a series of continuous uncountable seizures. Both of these events will be counted as 1 seizure (equally weighted) in the efficacy analysis. A seizure cluster will be defined as 3 or more seizure events (either a countable or a series of continuous uncountable seizures), occurring within a period of time, followed by a period of at least 24 hours of seizure-freedom.

   Examples: (Protocol **Error! Reference source not found.**):

   - If a child experiences 3 seizure events at 5:00, 5:30, and 6:00 PM on Monday, and the next seizure event occurs before 6:00 PM on Tuesday, the Monday and Tuesday seizure events are considered part of the same seizure cluster (Protocol **Error! Reference source not found.**, Scenario 1).
   - If a child experiences 3 seizure events at 5:00, 5:30, and 6:00 PM on Monday, and the next seizure event occurs at 6:00 PM or later on Tuesday, the Tuesday seizure event is not considered part of the same cluster (Protocol **Error! Reference source not found.**, Scenario 2).

i. Population PK will be conducted at these visits (Visit 6: between 1-5 hours since the last IP dosing and Visit 8: between 1-5 hours since last IP dosing)

j. Subjects who discontinue IP treatment before the completion of the DB phase will continue to be followed per protocol and, at a minimum, subjects will be encouraged to maintain daily seizure eDiary entries until the DB phase is completed. These subjects will also return to the site 2 to 4 weeks after the taper for safety follow-up post-taper assessments.

14.2 CLINICAL LABORATORY TESTS AND NORMAL RANGES

14.2.1 Clinical Laboratory Tests

Clinical Chemistry	Hematology	Urinalysis	Other
Total Bilirubin[a]	Hemoglobin	pH	Drug Screen[d]
AST (SGOT)[b]	Hematocrit	Color	
ALT (SGPT)[b]	Erythrocytes	Clarity	
BUN	Leukocytes + differential	Specific Gravity	
Glucose	Thrombocytes (platelet count)	Urobilinogen	
Potassium		Ketones	
Sodium		Protein	
Calcium		Glucose	
Alkaline Phosphatase		Bilirubin	
Chloride		Blood	
Creatinine		Leukocyte esterase	
CO_2		Nitrite	
eGFR[c]			
Quantitative serum β-human chorionic growth hormone (β-HCG) serum pregnancy			

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, eGFR = estimated glomerular filtration rate.

[a] If total bilirubin increases to 1.5 x ULN or more during study, the subject will be discontinued.

[b] If AST or ALT increases > 3 × ULN during the study, subject should be followed with weekly laboratory repeat testing and continue in study if levels trending down. Subject will be discontinued if levels do not decline to under 3 x ULN.

[c] Subjects with significant renal insufficiency, eGFR < 30 mL/min (calculated using the Cockcroft-Gault formula), will be discontinued if the criterion is met post baseline.

[d] Plasma drug screen for tetrahydrocannabinol (THC) and unapproved cannabidiol (CBD).

14.2.2 Normal Ranges

Age-adjusted normal ranges for laboratory tests assessed by the central lab are defined in the laboratory manual for the study and are imported with laboratory data. Normal ranges for local laboratories are captured directly in the clinical database with results.

14.3 CRITERIA FOR POTENTIALLY CLINICALLY SIGNIFICANT ABNORMAL VALUES

14.3.1 Potentially Clinically Significant Abnormal Laboratory Values

Clinical Chemistry	Hematology	Urinalysis
Total Bilirubin ≥ 1.5x ULN	Hemoglobin < 0.85x LLN or >1.25x ULN	pH ≤ 4 or >9
AST (SGOT) ≥ 3x ULN	Hematocrit < 0.85x LLN or >1.25x ULN	Color N/A
ALT (SGPT) ≥ 3x ULN	Erythrocytes < 0.85x LLN or >1.25x ULN	Clarity N/A
BUN ≥ 1.5x ULN	Leukocytes + differential (total) < 0.50x LLN or >1.50x ULN	Specific Gravity < 1.001 or > 1.035
Glucose < 0.8x LLN or >1.5x ULN	Thrombocytes (platelet count) < 0.50x LLN or >1.50x ULN	Urobilinogen > 4.0 mg/dL
Potassium < 0.9x LLN or >1.1x ULN		Ketones positive value if negative pre-Rx or ≥2 unit increase from pre-Rx
Sodium < 0.95x LLN or >1.05x ULN		Protein positive value if negative pre-Rx or ≥2 unit increase from pre-Rx
Calcium < 0.9x LLN or >1.1x ULN		Glucose positive value if negative pre-Rx or ≥2 unit increase from pre-Rx
Alkaline Phosphatase ≥ 1.5x ULN		Bilirubin positive value if negative pre-Rx or ≥2 unit increase from pre-Rx
Chloride < 0.9x LLN or >1.1x ULN		Blood positive value if negative pre-Rx or ≥2 unit increase from pre-Rx
Creatinine ≥ 1.5x ULN		Leukocyte esterase positive value if negative pre-Rx or ≥2 unit increase from pre-Rx
CO2 < 0.8x LLN or >1.2x ULN		Nitrite positive value if negative pre-Rx or ≥2 unit increase from pre-Rx

eGFRc < 0.8 x LLN (LLN=90, regardless of calculation method)		

14.3.2 Potentially Clinically Significant ECG Criteria

HR:

See criteria in Vital Signs

PR interval:

< 0.9 x LLN or >1.1 x ULN

QRS:

>1.1 x ULN

QTc B/FN interval:

≥ 470 msec (females)

or increase ≥ 60 msec from baseline (note. QTc is not changing with age)

QT Prolongation analysis uses the reported, corrected QT interval from the study data, and it also computes corrected QTc intervals using the following three industry-standard formulas, which are the same except for the correction factor applied to the RR interval:

- QTcB is the length of the QT interval corrected for the RR interval by Bazett's formula: $QTcB = QTmsec / (RR\ sec)^{0.5}$
- QTcN is the length of the QT interval corrected for the RR interval by FDA Neuropharmacological Division's formula: $QTcN = QTmsec / (RR\ sec)^{0.37}$
- QTcF is the length of the QT interval corrected for the RR interval by Fridericia's formula: $QTcF = QTmsec / (RR\ sec)^{0.33}$

PR, QRS Normal Ranges:

Age	PR Interval (sec)*	QRS Duration (sec)†
1–3 yr	0.10–0.14	<= 0.07
4–5 yr	0.11–0.15	<= 0.08
6–8 yr	0.12–0.16	<= 0.08
9–11 yr	0.12–0.17	<= 0.09
12–16 yr	0.12–0.17	<= 0.10
>16 yr	0.12–0.20	<= 0.10

14.3.3 Potentially Clinically Significant Vital Signs Values

HR:

High: 1.20 x ULN; or an ≥ 15 bpm increase from baseline if clinically significant at baseline

Low: 0.80 x LLN; or an ≥ 15 bpm decrease from baseline if clinically significant at baseline

Systolic BP:

High: 1.5 x ULN; or an ≥ 20 increase from baseline if clinically significant at baseline

Low: 0.75 x LLN; or an ≥ 20 decrease from baseline if clinically significant at baseline

Diastolic BP:

High: 1.3 x ULN; or an ≥ 15 increase from baseline if clinically significant at baseline

Low: 0.70 x LLN; or an ≥ 15 decrease from baseline if clinically significant at baseline

Respiratory Rate

Low: 0.80 x LLN

High 1.25 x ULN

Vital Signs Normal Ranges by Age

Age	HR (beats/min)	BP (mm Hg)	RR (breaths /min)
1 – 3 yrs	80 - 125	90 – 105 / 55 - 70	20 - 30
3 – 6 yrs	70 - 115	95 – 110 / 60 - 75	20 - 25
6 – 12 yrs	60 – 100	100 – 120 / 60 – 75	14 - 22
>12 yrs	60 – 100	100 – 120 / 70 – 80	12 - 18