Statistical Analysis Plan

Protocol No.: 1042-TSC-2001

A Phase 2 Open-label 12-Week Trial of Adjunctive Ganaxolone Treatment (Part A) in Tuberous Sclerosis Complex-related Epilepsy followed by Long-term Treatment (Part B)

Investigational Product:	Ganaxolone
Reference Product：	NA
Indication:	Tuberous Sclerosis Complex-related Epilepsy (TSC)
Phase：	2
Document Type：	Statistical Analysis Plan
Version：	1.0
Date of Issue：	22MAR2021

NCT Number: NCT04285346
This NCT number has been applied to the document for purposes of posting on Clinicaltrials.gov

Statistical Analysis Plan Approval Form

Author:

[redacted], Ph.D.
[redacted] Statistics
CR Medicon Research, Inc.

Date (mm/dd/yyyy)

Review:

[redacted], Ph.D.
[redacted]
CR Medicon Research, Inc.

Date (mm/dd/yyyy)

[redacted], Ph.D.
[redacted] Biostatistics
Marinus Pharmaceuticals, Inc.

Date (mm/dd/yyyy)

[redacted], M.D., Ph.D.
[redacted] Clinical Development
Marinus Pharmaceuticals, Inc.

Date (mm/dd/yyyy)

Approval:

[redacted], PhD
[redacted] Biometrics
Marinus Pharmaceuticals, Inc.

Date (mm/dd/yyyy)

Change Log			
Version No.	**Effective Date**	**Reason for Change/Revision**	**Supersedes**

TABLE OF CONTENTS

ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
AED	Anti-Epileptic Drug
Allo-S	Allopregnanolone Sulfate
ATC	Anatomical Therapeutic Class
BMI	Body Mass Index
bpm	Beats per minute
CGI-C	Caregiver Global Impression of Change
CGI-I	Clinical Global Impression of Improvement
CI	Confidence Interval
cm	centimeters
CRF	Case Report Form
CS	Clinically Significant
ECG	Electrocardiogram
[redacted]	[redacted]
FDA	US Food and Drug Administration
GNX	Ganaxolone
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IP	Investigational Product
IQ	Intelligence Quotient
ITT	Intent-to-Treat
kg	kilograms
LAR	Legally Authorized Representative
LLN	Lower limit of normal
m	meters
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not Clinically Significant
OL	Open label
OLE	Open-label extension
PK	Pharmacokinetic
PP	Per-Protocol
PT	Preferred Term
Q1	1st quartile; 25th percentile
Q3	3rd quartile; 75th percentile
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SI	Systeme International
SIF/DIF	Seizure Identification and Diagnostic Form
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
TSC	Tuberous Sclerosis Complex

ULN	Upper limit of normal
US	United States
WHODDE	World Health Organization Drug Dictionary Enhanced

1 INTRODUCTION

This statistical analysis plan (SAP) provides details and specifications for the statistical analyses of data collected under Marinus Pharmaceuticals, Inc. Protocol 1042-SC-2001, "A Phase 2 Open-label 12-Week Trial of Adjunctive Ganaxolone Treatment (Part A) in Tuberous Sclerosis Complex-related Epilepsy followed by Long-term Treatment (Part B)" (Version 2, Protocol Amendment 1, 12 May 2020).

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

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

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

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

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

The primary objective of this study is to assess preliminary safety and efficacy of Ganaxolone (GNX) adjunctive therapy for the treatment of primary seizure types in patients with genetically- or clinically-confirmed Tuberous Sclerosis Complex (TSC) - related epilepsy through the end of the 12-week treatment period. The primary seizure types (focal motor seizures without impairment of consciousness or awareness, focal seizures with impairment of consciousness or awareness, focal seizures evolving to bilateral, tonic-clonic convulsive seizures, and generalized motor seizures including tonic-clonic, bilateral tonic, bilateral clonic, or atonic/drop seizures) are identified to be the most common, easily identifiable/countable by a parent/caregiver/legally authorized representative (LAR), and are most consequential to the patient's quality of life.

1.1.2 Secondary Objectives

The secondary objectives of this study are the following:

- To assess the long-term efficacy of GNX when administered as adjunctive therapy throughout the open-label extension (OLE) period (Part B).

- To assess the long-term safety and tolerability of GNX when administered as adjunctive therapy throughout the OLE period (Part B).

[redacted]

1.2 STUDY ENDPOINTS

Primary, secondary and exploratory efficacy endpoints described below support the primary study objective of assessing the efficacy of investigational product (IP), GNX, as adjunctive therapy for the treatment of primary seizure types in patients with TSC-related epilepsy through the end of the 12-week treatment period (Part A) and exploratory objectives related to Part A of the study.

Endpoints supporting the secondary study objective of assessing long-term efficacy of GNX with administered as adjunctive therapy throughout the OLE period (Part B) are described in Section 1.2.5 (Open-Label Extension Endpoints).

1.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint (change in seizure frequency) is the percent change in 28-day seizure frequency through the end of the 12-week treatment period (4-week titration and 8-week maintenance) relative to the baseline, based on the primary seizure types. The primary seizure types are defined as the following: focal motor seizures without impairment of consciousness or awareness, focal seizures (motor or non-motor) with impairment of consciousness or awareness, focal seizures evolving to bilateral, tonic-clonic convulsive seizures, and generalized motor seizures including tonic-clonic, bilateral tonic, bilateral clonic, or atonic/drop seizures. Focal aware non-motor and generalized seizures without motor features, infantile or epileptic spasms, and myoclonic seizures do not count as the primary seizure types.

The calculation of post-baseline 28-day seizure frequency and percent change in 28-day seizure frequency are explained in Section 3.1.3.

1.2.2 Secondary Efficacy Endpoints

In addition to evidence about effects of GNX on 28-day seizure frequency, the clinical trial will assess GNX's effects on several secondary endpoints that capture important symptoms and activities of daily living that are meaningfully compromised by TSC.

1.2.2.1 Secondary Efficacy Endpoint – Seizure Control

- Percentage of patients experiencing a ≥ 50% reduction in 28-day primary seizure frequency through the end of the 12-week treatment period compared to the 4-week baseline period.

Derived seizure secondary efficacy endpoints will be based on data through the end of the 12-week treatment period relative to the 4-week baseline period as defined in Section 3.1.3.

1.2.2.2 Secondary Efficacy Endpoint – Other

- CGI-I – parent/caregiver and clinician
- CGI-C - target behavior

These behavioral/neuropsychiatric secondary endpoints will provide information about the overall impact of GNX on the treatment of patients with TSC. The CGI-C and the CGI-I are 7-point scales used to assess change after initiation of GNX. The scores range from 1 = very much improved to 7 = very much worse. Separate CGI-I responses will be collected the patient's parent/caregiver and the clinician at baseline, Week 5 and Week 12 of Part A of the study and at the final visit in Part B, if applicable. The CGI-C will be completed by the patient's parent/caregiver at the same study visits.

[redacted]

[redacted]

1.2.4 Safety Endpoints

Safety and tolerability endpoints for Part A and Part B include:

- Vital signs (height, weight, blood pressure [BP], heart rate [HR], respiratory rate [RR], body temperature)
- Electrocardiograms (ECGs)
- Clinical laboratory tests (hematology, chemistry and urinalysis)
- Physical exam findings
- Neurological exam findings
- Developmental exam findings
- Columbia-Suicide Severity Rating Scale (C-SSRS), if appropriate
- Adverse events (frequency, type and severity)

1.2.5 Open-Label Extension Endpoints

To evaluate the secondary study objectives of assessing the long-term efficacy and safety of GNX, the following endpoints defined above for Part A of the study will be examined in patients participating in Part B of the study:

- Primary seizure frequency during OLE: change in 28-day primary seizure frequency from baseline (Visit 1 to Visit 2) to the OLE period (Visit 5 through Visit 8)
- Percent change in primary seizure frequency during OLE relative to the baseline period.
- Primary seizure frequency across 12-week treatment period and OLE: change in 28-day primary seizure frequency from baseline (Visit 1 to Visit 2) to the cumulative treatment periods A and B (Visit 2 through 8)

- Percent change in primary seizure frequency baseline versus cumulative treatment periods (12-week treatment period + OLE)
- Seizure frequency for all types of seizures in OLE versus baseline and cumulative treatment Parts A and B versus baseline
- Percent change in all-types seizure frequency in OLE versus baseline and cumulative treatment Parts A and B versus baseline
- CGI-C for target behaviour: Week 36 and final visit of the OLE
- CGI-I, parent/caregiver and clinician: Week 36 and final visit of the OLE.
- [redacted] at the final OLE visit.
- Safety endpoints listed in Section 1.2.4.

1.3 STUDY DESIGN

1.3.1 General Study Design and Plan

This is an open-label (OL) proof of concept study of adjunctive GNX treatment in patients with a confirmed clinical diagnosis of TSC and/or a mutation in either the *TSC1* or *TSC2* gene. The trial consists of two parts (Figure 1): Part A consists of a 4-week baseline period followed by a 12-week treatment period (4-week titration and 8-week maintenance). For patients not continuing in the 24-week OLE period (Part B), a 2-week taper period followed by a 2-week safety period would follow. The main difference between Part A and Part B is the length of treatment, less frequent assessments, and the ability to alter drug doses (both GNX and other antiepileptic drug [AED] treatments which includes initiating and stopping other medications) based on investigator evaluation of the patient's clinical course during Part B. Patients with a seizure frequency reduction rate of ≥ 35% during the 12-week treatment period in Part A compared to baseline may continue into Part B ("OLE eligible"). If the investigator believes there is a medical benefit for the patient who does not meet the seizure reduction criterion to enter the OLE, they must discuss the patient with the sponsor medical monitor and receive sponsor approval for that patient to continue into the OLE.

The Schedule of Assessments from the protocol for both Part A and Part B are included in Appendix A and Appendix B, respectively, of this document.

Part A

- 4-week baseline period
- 4-week titration period
- 8-week maintenance period
- 2-week taper period (For patients who do not complete Part A or after completing

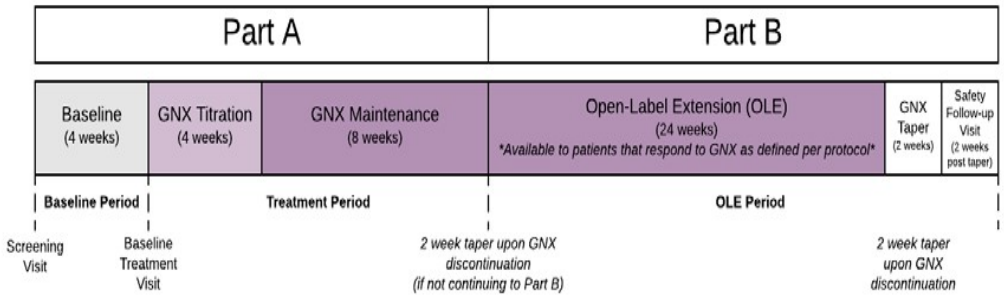
Part A but do not continue into Part B)

- 2-week safety follow-up visit post taper (For patients who taper off GNX)

Part B (Optional for OLE-eligible patients)

- 24-week OLE period
- 2-week taper period (For patients who discontinue GNX due to early termination or completion)
- 2-week safety follow-up visit post-taper (For patients who taper off GNX)

Figure 1: Study Design



1.3.2 Sample Size Estimation

Approximately 36 TSC patients, aged 2 to 65 inclusive, will be screened to achieve 30 TSC patients given IP in Part A. Since this is an OL proof of concept study, sample size was not determined by statistical methods.

1.3.3 Randomization and Blinding

This is an open-label study. Randomization and blinding are not applicable for this study.

2 STATISTICAL CONSIDERATIONS

2.1 GENERAL CONSIDERATIONS

Statistical analyses will be performed using SAS System, Version 9.4 or higher (SAS Institute, Inc., Cary, NC).

No formal hypothesis testing will be performed for this study. Data will be summarized descriptively. Separate summaries will be presented for data collected in Part A and data collected in Part B of the study. Unless otherwise specified, descriptive statistics for continuous variables will include number of non-missing observations (n), arithmetic mean, standard deviation (SD), 25th and 75th percentiles, minimum, median and maximum. For categorical variables, descriptive statistics including counts and percentages will be used. Only observed data will be summarized. Missing data will not

be imputed. Scheduled assessments will be included in summaries with the exception of reports of abnormal laboratory, vital sign, or ECG values.

Study data from all assessments (scheduled and unscheduled) will be displayed in individual data listings by study part (Part A or Part B), patient and visit, if applicable.

2.2 ANALYSIS SETS

Analysis sets for this study are defined as:

- Screened population: all patients who have signed informed consent for the study.
- Safety population: all patients who have received at least one dose of GNX
- Intent-to-treat (ITT) population: all patients who receive at least one dose of GNX and have at least one post-baseline efficacy assessment.
- Per-protocol (PP) population: includes all ITT patients without major protocol violations, as will be defined prior to database lock. Patients that fall below 80% compliance at two consecutive visits during the maintenance period (i.e. Visits 4 and 5, Weeks 5 and 12) will not be included in the PP population.
- Open-label extension (OLE) population: includes all ITT patients who participate in the OLE (Part B) of the study and receive at least one dose of GNX in the Part B.
- Pharmacokinetic (PK) population: all ITT patients who have had at least one PK sample collected and a valid bioanalytical result obtained. Pharmacokinetic data collected from this population may be reported separately.

2.3 POOLING OF CENTERS

This multicenter study is to be conducted at approximately 6 sites in the United States. No significant differences between centers are anticipated. Data from all centers will be pooled for analysis.

2.4 MULTIPLE COMPARISONS/MULTIPLICITY

All analyses of study data will be descriptive. No adjustments for multiple comparisons will be made.

2.5 EXAMINATION OF SUBGROUPS

No subgroup analyses are planned for this study.

3 DATA HANDLING CONVENTIONS

3.1 DERIVED AND TRANSFORMED DATA

3.1.1 Baseline Definition

The Baseline Visit is defined as Visit 2 (Week/Day 0). Baseline values for non-seizure efficacy and safety assessments will be the last values collected prior to the first administration of IP (i.e., GNX), unless otherwise specified.

Baseline seizure frequency data is collected during the four weeks between the Screening Visit (Visit 1, Week -4) and the Baseline Visit (Visit 2, Day 0). This interval may range from no less than 28 days to no more than 32 days.

3.1.2 Study Day

For reporting purposes, Study Day will be calculated from the date of the Baseline Treatment Visit (Visit 2, Week/Day 0). Similarly, Study Week will be calculated from the date of the Baseline Treatment Visit.

For all assessments performed on or after the first day of treatment, i.e. reference date ≥ date of first dose of IP, Study Day is calculated as:

- Study Day = (date of assessments/events - first day of treatment) + 1

For assessments performed prior to the first day of treatment, i.e. reference date < date of first dose of IP, Study Day is calculated as:

- Study Day = date of assessment/event – first day of treatment.

3.1.3 Derivations

3.1.3.1 Baseline seizure frequency

Baseline 28-day seizure frequency will be calculated as the total number of primary seizures in the baseline period, i.e. between screening (Visit 1, Week -4) and baseline treatment (Visit 2, Week/Day 0), divided by the number of days with non-missing seizure data in the baseline period, multiplied by 28.

$$Baseline\ seizure\ frequency\ = \frac{\#\ seizures, baseline\ period}{\#\ baseline\ period\ days\ with\ seizure\ data}\ x\ 28$$

3.1.3.2 Post-baseline seizure frequency – Maintenance Period, Part A, Part B and Overall

Post-baseline 28-day seizure frequency will be calculated as the total number of seizures in the specified post-baseline period divided by the number of days with non-missing seizure data in the same post-baseline period, multiplied by 28. Within Part A of the study, post-baseline seizure activity will be determined based on the days following the first day after the date of the first dose of IP. The first day of treatment is included in neither the baseline nor the post-baseline period since seizures reported on that date could have occurred either before or after the initiation of treatment. Within Part B (OLE

period), post-baseline seizure activity will be determined by the first day of OLE treatment.

Separate frequencies will be calculated for the 8-week maintenance period of Part A (Maintenance), Parts A (12-week treatment period consisting of a 4-week titration period and an 8-week maintenance period) and B of the study (OLE period of up to 24 weeks) and across both study parts.

$$Post\text{-}baseline\ specified\ study\ period\ 28\text{-}day\ seizure\ frequency\ =$$

$$\frac{\#\ seizures, specified\ study\ period}{\#\ specified\ study\ period\ days\ with\ seizure\ data\ reported}\ x\ 28$$

3.1.3.3 Percent change in 28-day seizure frequency – Maintenance Period, Part A, Part B and Overall

$$\%\ change\ from\ baseline\ =$$

$$\frac{[(post\text{-}baseline\ 28\text{-}day\ seizure\ frequency) - (baseline\ 28\text{-}day\ seizure\ frequency)]}{(baseline\ 28\text{-}day\ seizure\ frequency)}\ x\ 100$$

3.1.3.4 Frequency of seizure-free days per 28 days – Baseline

The frequency of seizure-free days per 28 days total for all seizure types during the baseline period will be calculated as the total number of days reported as seizure-free, i.e., with seizure diary response to "Did you have seizures on this date?" equal to "no" or with no approved seizures for a date, multiplied by 28, and divided by the number of days with non-missing seizure data in the baseline period.

$$Baseline\ seizure\text{-}free\ days\ per\ 28\text{-}day\ period$$

$$= \frac{\#\ seizure\text{-}free\ days, baseline\ period\ x\ 28}{\#\ baseline\ period\ days\ with\ seizure\ data}$$

The frequency of seizure-free days per 28 days total for the primary seizure types only will be calculated in the same manner except defining seizure-free as days with seizure diary response to "Did you have seizures on this date?" equal to "no" or with a response to this question equal to "yes" but no primary seizure types reported and approved for that day.

3.1.3.5 Frequency of seizure-free days per 28 days – Part A, Part B and Overall

The percentage of post-baseline seizure-free days per 28 days total within a specified post-baseline study period will be calculated as the

$$Post\text{-}baseline\ specified\ study\ period\ seizure\text{-}free\ days\ per\ 28\text{-}day\ period$$

$$= \frac{\#\ seizure\text{-}free\ days, specified\ study\ period\ x\ 28}{\#\ specified\ study\ period\ days\ with\ seizure\ data}$$

3.1.3.6 Percent change from baseline in seizure-free days per 28 days

The percent change from baseline in seizure-free days will be

$$\%\ change\ from\ baseline\ in\ seizure\text{-}free\ days\ per\ 28\ days =$$

$$\frac{[(post\text{-}baseline\ seizure\text{-}free\ days/28\ days) - (baseline\ seizure\text{-}free\ days/28\ days)]}{(baseline\ seizure\text{-}free\ days\ per\ 28\ days)}\ x100$$

3.1.3.7 Percent compliance with IP

The percent compliance with study drug will be estimated using dosing information reported in the eDiary as follows:

$$\frac{[number\ of\ days\ with\ study\ medication\ taken = Yes]}{(number\ of\ days\ with\ study\ medication\ taken\ reported)}\ x100$$

3.2 ANALYSIS VISIT WINDOWS

Efficacy Analyses

Efficacy analyses will use data only from scheduled visits. Data will be reported by designated visit.

Data collected at unscheduled visits will be provided in listings.

For analysis of data collected across specific study periods, the following definitions will be applied:

- Baseline period: Visit 1 to Visit 2; Study Week -4 (Day -32 ± 4) through Study Day 0 (date of first dose of IP)
- Titration period: Visit 2 + 1 day to Visit 4; Study Day 1 through Study Week 4 (Day 28 ± 3 days; date of Visit 4)
- Maintenance period: Visits 4 + 1 day and 5; Study Week 5 (± 3 days) through Study Week 12 (± 3 days)
- 12-week treatment period: titration period + maintenance period (including taper and safety visits if not continuing in OLE)
- OLE period if continuing in OLE: Visit 5 + 1 day through final visit

Safety Analyses

Safety data will be summarized by actual visit. No visit windowing will be applied.

3.3 PREMATURE WITHDRAWAL AND MISSING DATA

Available data from patients who withdraw from the study prematurely will be included in analyses, unless otherwise indicated. Only observed data will be summarized. No data

will be imputed or carried forward for missing values or for patients who discontinue early.

All missing data and missing or partial dates for AEs and medications will be queried for a value. In the unlikely event that no value can be obtained, substitutions will be made as described below.

3.3.1 **Missing and Partial Start/Stop Dates - AEs and Concomitant Medications**

The handling of partial start and stop dates for AEs are described in Table 3 below. Similar algorithms for handling missing and partial dates of concomitant medication usage are described in Table 4. In both cases, if a stop date is complete and an imputed start date is after the stop date, the start date will be set to the stop date.

Table 3: Adverse Event Start/Stop Date Imputation

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

D=day, M=month, Y=year

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

Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.

.

Table 4: Imputation for Prior/Concomitant Medication Missing and Partial Dates

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

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

3.3.2 Missing Seizure/Medication Diary Entries

The calculation of seizure frequency endpoints will include only days for which diary entries are available. Missing seizure data will not be imputed.

4 STATISTICAL ANALYSES

4.1 SUBJECT INFORMATION

4.1.1 Disposition of Subjects

The number of patients screened for this study, the number of screen failures and the number of patients who received at least one dose of IP in each part of the study (Part A and Part B) will be summarized. Reasons for screen failure will be provided in the data listing.

The final disposition of all patients who receive IP will be summarized by study part (Part A and Part B). Reasons for discontinuation of study treatment and for discontinuation of study participation will be summarized. The total number and percentage of patients who complete Part A of the study will be summarized as will the number and percentage of these patients who continue participation in Part B of the study. In addition, the number and percentage of patients who complete Part B of the study will be summarized

separately.

A listing of patient disposition will be provided.

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

4.1.2 **Protocol Violations**

Protocol violations will be identified prior to database lock. Protocol violations will be listed for patients in the Safety Population.

4.1.3 **Demographics and Baseline Characteristics**

Demographics and baseline characteristics will be summarized and listed for all patients in the Safety Population participating in Part A of the study and OLE patients participating in Part B of the study. Demographic characteristics, including age, height, weight and BMI, will be summarized with descriptive statistics (n, mean, median, SD, minimum and maximum). Categorical characteristics such as age group (≤ 17 years, > 17 years), weight group (≤ 28 kg, > 28 kg), sex, race and ethnicity, will be summarized as counts and percentages.

Additionally, baseline clinical characteristics including results of genetic testing for pathogenic or likely pathogenic TSC1 or TSC2 variant, Tanner Staging, number of AEDs taken and stopped prior to screening, neurological exam results, developmental examination results (pediatric patients aged 2 to 17, inclusive), and Seizure Identification and Diagnostic Review Form (SIF/DRF) responses including baseline seizure types reported as primary and non-primary, IQ, intellectual disabilities, and [redacted].

Baseline values of efficacy and safety parameters will be summarized in the respective analysis tables.

4.1.4 **Medical History**

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA), version 22.0. The number and percent of subjects with clinically significant medical history at screening will be summarized by system organ class (SOC) and preferred term (PT) in the Safety population. Medical history will also be listed.

4.1.5 **Prior and Concomitant Medications**

All investigator terms for medications recorded on the CRF will be coded using the World Health Organization Drug Dictionary Enhanced (WHODDE) Anatomical Therapeutic Chemical (ATC) drug dictionary (Version WHODDE, September 2019). The number (percentage) of subjects who took prior and concomitant medications will be summarized in the Safety population by Anatomic Therapeutic Chemical (ATC) classification level 2 and Preferred Term (PT). September 2019.

Prior medications are defined as medications that started 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. Medications started before the first dose of study drug and continuing at the time of the first dose of study drug are considered both prior medication and concomitant medication. The summary of concomitant medications for Part A of the study will not include concomitant medications that start after Part A; i.e., they will not include any concomitant medications starting on or after the first dosing day of the OLE phase.

The number and percentage of patients in the Safety population reporting use of prior and concomitant treatments will be summarized and listed separately. In addition, antiepileptic prior and concomitant drugs (AEDs) and rescue medications will be presented separately. Prior medications will be summarized for Part A only. All other summaries and listings will be presented separately for Parts A and B of the study.

4.1.6 **Treatment Compliance**

Compliance with GNX treatment will be assessed by inspecting the seizure and medication diary entries and returned drug supply with queries as necessary. Treatment compliance will be calculated as explained in Section 3.1.3.7. Percent compliance for Parts A and B of the study will be summarized for the Safety Population and OLE Population, respectively. Reported dosing by visit and calculated compliance values will be listed.

4.2 EFFICACY ANALYSES

4.2.1 **Primary Efficacy Analysis**

4.2.1.1 Primary Analysis

The primary efficacy endpoints, the percent change in 28-day primary seizure type frequency through the end of the 12-week treatment period (Part A; 4-week titration and 8-week maintenance) relative to the baseline, is defined in Section 1.2.1. The calculation of the primary endpoint is described in Section 3.1.3.

Descriptive summaries including the number of patients with non-missing primary seizure data, mean arithmetic change and percent change in 28-day primary seizure type frequency from baseline and associated 95% confidence intervals, SD, minimum, median and maximum values will be presented for the baseline period, 4-week titration period, 8-week maintenance period and 12-week treatment period. All patients in the ITT population and all available seizure data within Part A of the study will be included in these analyses regardless of whether the patient stopped taking IP or took rescue medication.

Additionally, a by-patient listing of seizure data collected during Part A will be provided.

4.2.1.2 Sensitivity Analysis

The primary analysis will be repeated in the PP population.

4.2.2 **Secondary Efficacy Analysis**

Secondary efficacy endpoints are defined in Section 1.2.2. Analyses of secondary

efficacy endpoints will be based on the ITT population.

4.2.2.1 Seizure Control

To assess seizure control during the 12-week treatment period, the subset of ITT patients who achieve ≥ 50% reduction in 28-day primary type seizure frequency during the 12-week treatment period compared to baseline will be summarized as was described for the primary efficacy analysis. The calculation of percent reduction from baseline in seizure frequency is described in Section 3.1.3.6.

Percent change values meeting criteria of interest, i.e. ≥ 25% reduction, ≥ 50% reduction and ≥ 75% reduction from baseline will be flagged in the by-patient listing of seizure data.

4.2.2.2 CGI-I and CGI-C

The CGI-C in target behavior includes two 7-point Likert items which the parent or caregiver uses to rate the severity of the target behavior at baseline and to assess change in the target behavior after initiation of IP relative to baseline. The severity scale ranges from 1 = normal to 7 = very severe problem, and the change scale ranges from 1 = very much improved to 7 = very much worse.

The target behavior chosen and the baseline severity of this behavior will be summarized. For post-baseline visits, change in this severity since the start of the study will be summarized. The number and percentage of ITT patients receiving each CGI-C change rating will be summarized by visit.

The CGI-I contains two 7-point Likert scales for baseline overall severity of the patient's presentation (ranging from 1 = normal to 7 = very severe problem) and overall global impression of change relative to baseline (ranging from 1 = very much improved to 7 = very much worse). The number and percentage of patients receiving each CGI-C rating will be summarized. The CGI-I responses from the clinician and from the parent/caregiver will be presented separately by visit.

A listing of CGI-C and CGI-I data collected by visit for each patient will be provided.

4.3 SAFETY ANALYSIS

Safety analyses will be based on all patients in the Safety population, unless otherwise indicated. Data will be summarized for Part A, Part B and across the entire study for those patients participating in both parts.

4.3.1 **Extent of Exposure**

Exposure to study medication (GNX) will be summarized as the number of days on treatment, percentage of days dosed, maximum daily dose received, and total dosage received. The denominator for the percentage of days of study drug is the number of days the patient is on treatment in the respective part of the study. If the patient stops taking IP during the study, the last day that drug was taken will be used as the last day of treatment. For patients who are ongoing at the end of a specific part of the study, the last known

treatment date will be used for the last day on treatment. Exposure data will be summarized for Parts A and B of the study separately as well as overall exposure for all patients.

A listing of exposure data for each patient including total daily dose, start and end dates, and reason for any dose change will also be provided.

4.3.2 **Adverse Events**

Adverse events (AEs) are collected from the time of informed consent/assent through the defined follow-up period. AEs are coded using MedDRA dictionary, version 22.0 and are categorized by system organ class (SOC) and preferred term (PT). A treatment-emergent AE (TEAE) is defined as an AE that starts or worsens on or after the first day of dosing with IP. Analyses of TEAEs for Part A of the study will include AEs that start or worsen during Part A and will not include any AE that starts or worsens during Part B. For Part B of the study, TEAEs will be include events that start or worsen after the first day of Part B relative to the first day of Part B. TEAEs over the entire study will be summarized for patients who participate in both Parts A and B of the study.

Tabulations of AEs will be by patient such that an individual is only counted once per summary category. Detailed by-patient listings of all AEs reported during the study will be provided and will include verbatim and coded terms for each AE.

4.3.2.1 Overview of Adverse Events

A summary of AEs reported during the study will be presented. The number and percentage of patients in the Safety Population who reported at least one occurrence of an event in one of the following categories will be summarized:

- Any TEAE
- TEAE with causality related to study drug
- Any SAE
- TEAE leading to discontinuation of study drug
- TEAEs by worst severity
- TEAEs with an outcome of death

4.3.2.2 Incidence of TEAEs

The number and percentage of patients reporting at least one TEAE during Part A, Part B and overall will be summarized by MedDRA System Organ Class (SOC) and preferred term (PT). The summary will be sorted by descending frequency within SOC and PT within SOC.

A detailed listing of AEs for each patient will be provided. The listing will include the

verbatim term reported by the Investigator, MedDRA SOC and PT, onset date/time, end date/time, severity, seriousness (yes/no), seriousness reason, relationship to study drug, action taken, withdrawal from study, treatment required, and outcome.

4.3.2.3 Incidence of TEAEs by Severity

The number and percentage of patients reporting a TEAE will be tabulated by investigator-specified severity, i.e. intensity of mild, moderate or severe. A patient experiencing AEs of the same SOC and PT multiple times during the study will be counted once for the PT based on the worst severity reported. Similarly, if a patient experiences multiple AEs within the same SOC, the patient will be counted once for that SOC at the worst severity reported.

Missing severity for an event will be assigned to severe.

4.3.2.4 Incidence of TEAEs by Relationship to Study Drug

The number and percentage of patients reporting a TEAE will be summarized by SOC, PT, and relationship to study drug (related or not related). A patient experiencing AEs of the same SOC and PT multiple times during the study will be counted once for the PT based on the highest level of relatedness reported (related > not related). Similarly, if a patient experiences multiple AEs within the same SOC, the patient will be counted once for that SOC at the highest level of relatedness reported.

Events missing relationship will be summarized as related to study drug if the AE occurs on or after the administration of study drug.

4.3.2.5 Serious Adverse Events (SAEs)

The number and percentage of patients reporting at least one AE that meets with criteria for an SAE will be summarized by MedDRA SOC and PT. A similar summary of SAEs reported as related to study drug will be presented. The seriousness reason will be provided in the by-patient SAE listing.

4.3.2.6 AEs Leading to Study Discontinuation

A listing of any AEs reported as leading to study discontinuation will be presented as described in Section 4.3.2.2 above.

4.3.2.7 AEs Leading to Death

All deaths occurring during the study, including AEs leading to death and deaths during the post-treatment follow-up period, will be listed.

4.3.3 **Clinical Laboratory Tests**

Laboratory data collected in this study include serum chemistry and hematology values, urinalysis results and [redacted] levels. The baseline laboratory value is defined as the last value observed prior to the first administration of study drug. Any values collected after the administration of study drug are regarded as post-baseline. Change from baseline will be calculated as the post-baseline value minus the baseline value. Only the

numeric part in laboratory values that contain non-numeric qualifiers, such as less than (<) a certain value or greater than (>) a certain value, will be used in the summary statistics.

Laboratory values and change from baseline in these values will be listed and summarized for patients in the Safety Population by group (chemistry, hematology or urinalysis) and by visit. [redacted] will be presented separately by visit. Listings of patients with positive drug screen or pregnancy results will be provided.

Descriptive summaries of continuous laboratory values and change from baseline in these values will include the number of observations, mean, SD, median, minimum and maximum values at each time point. Data will be summarized in SI units. Shift tables comparing baseline classification based on reference range (i.e., normal, low, or high) to the worst classification recorded post-baseline will be presented. In the case that a patient has both "low" and "high" post-baseline results for the same laboratory parameter, the patient will be counted under both "low" and "high". A patient will be counted under the "normal" category post-baseline only if all post-baseline results are categorized as "normal".

For non-numeric urinalysis data, a shift table comparing baseline results (negative, trace or positive) to the maximum post-baseline result will be presented.

Listings of laboratory results for each patient will be presented. Values outside of the laboratory's reference range will be flagged in the listing. A by-patient listing of laboratory values outside the normal reference range for the parameter will be produced.

4.3.4 Vital Signs and Physical, Neurological and Developmental Examination Findings

4.3.4.1 Vital Signs

Vital signs measured in this study include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature. Baseline for vital signs will be the values obtained at the last assessment prior to the first dose of IP, typically Visit 2, Day 0. Change from baseline is calculated as the post-baseline value minus the baseline value. Missing values will not be imputed.

Absolute values and changes from baseline in vital signs at each visit will be summarized for Parts A and B and overall in the Safety Population using descriptive statistics (n, mean, SD, median, minimum, and maximum). A by-patient, by-visit listing of vital signs collected and height and weight recorded will be provided.

All vital signs included the parameter values and overall interpretations will be listed. Changes from baseline physical examination findings will also be listed individually by patient.

4.3.4.2 Physical Examination Findings

Physical examinations will be conducted at all clinic visits and findings will be recorded as normal, abnormal but not clinically significant, and abnormal and clinically significant. Abnormal changes in baseline physical examinations findings will be summarized using counts and percentages of patients in the Safety Population. Abnormal findings noted at baseline will be listed for each patient. Any changes in physical examination findings at post-baseline visits relative to the previous visit will be listed.

4.3.4.3 Neurological Examination Findings

Neurological examinations will be conducted at all clinic visits and will include evaluation of cranial nerves, motor function, sensory function, reflexes and coordination/cerebellar function. Findings will be recorded as normal, abnormal but not clinically significant, and abnormal and clinically significant. The number and percentage of patients with abnormal neurological findings will be summarized by parameter. Abnormal neurological findings at baseline will be listed for each patient. Any changes in neurological findings at post-baseline visits relative to the previous visit will be listed.

4.3.4.4 Developmental Examination Findings

Developmental examinations will be conducted on pediatric patients 2 to 17 years of age, inclusive. Developmental parameters assessed include speech and language skills, motor skills and social skills with findings recorded as normal, abnormal but not clinically significant, and abnormal and clinically significant. The number and percentage of pediatric patients with abnormal developmental findings will be summarized by parameter. Abnormal developmental findings at baseline and any changes in neurological findings at post-baseline visits relative to the previous visit will be listed for each patient.

4.3.5 **Electrocardiogram (ECG)**

Safety ECG measurements will be collected throughout the study. Baseline ECG values are those collected at Visit 2 (Day 0) prior to the first dose of IP.

ECG parameters include heart rate, PR interval, RR interval, QRS interval, QT (uncorrected) interval, QTcF interval, and QTcB interval. In addition, the overall interpretation of the investigator will be documented as normal, abnormal but not clinically significant (NCS), or abnormal and clinically significant (CS). All clinically significant abnormal findings will be reported as AEs also. Absolute values and change from baseline in post-baseline values will be summarized by study part (Part A and Part B). By-patient listings of ECG data and overall interpretations collected during Part A and Part B will be provided.

4.3.6 **Other Safety Analysis**

4.3.6.1 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS suicidal behavior and suicidal ideation scores recorded at baseline and any changes in post-baseline scores from the previous visit will be summarized descriptively by visit, including the number and percentage of subjects reporting any suicidal behavior and any suicidal ideation as defined in Table 5. Adult and pediatric C-SSRS data will be

summarized separately.

C-SSRS data collected, including scores for suicidal ideation, intensity of ideation and actual suicide attempts, will be listed by patient and visit.

Table 5: C-SSRS Categories for Analysis

Category	C-SSRS Item response is "YES"
Suicidal behavior	Preparatory acts or behavior Aborted attempt Interrupted attempt Actual attempt Complete suicide
Suicidal ideation	Wish to be dead Non-specific active suicidal thoughts Active suicidal ideation with any methods (not plan) without intent to act Active suicidal ideation with some intent to act, without specific plan Active suicidal ideation with specific plan and intent
Non-suicidal self-injurious behavior	Non-suicidal self-injurious behavior

4.3.6.2 Tanner Scale

The Tanner scale is a scale of physical development in children, adolescent and adults. Patients will be rated as Tanner I, Tanner II, Tanner III, Tanner IV or Tanner V at baseline and end of Parts A and B of the study. The number and percentage of patients in each category will be summarized and listed by visit.

[redacted]

[redacted]

4.5 PHARMACOKINETIC (PK) ANALYSES

A listing of pharmacokinetic collection times will be provided.

Pharmacokinetic analyses will be conducted using data from patients in the PK Population. Analyses will be limited to listings of concentrations because sufficient concentration-time data will not be available for noncompartmental analyses.

Pharmacokinetic data from this study may be used for Population PK analyses to be conducted and reported separately from this study.

5 PLANNED ANALYSES

5.1 INTERIM ANALYSIS

No formal interim analysis is planned.

5.2 FINAL ANALYSIS

Data collected during this study will be summarized descriptively.

6 SUMMARY OF MAJOR CHANGES IN THE PLANNED ANALYSES

No changes to planned analyses are anticipated. Any further analysis changes made after this SAP is finalized will be documented with an SAP amendment or described in the clinical study report (CSR).

7 PROGRAMMING SPECIFICATIONS

Detailed programming specifications will be provided in a separate document.

8 TABLES/LISTINGS/FIGURES TEMPLATES

Templates for planned tables, listings and figures will be provided in a separate document.

9 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.

10 APPENDICES

10.1 APPENDIX A: SCHEDULE OF ASSESSMENTS PART A

Table 1: Schedule of Assessments - Part A

			Part A								
	Screen/Baseline					Titration and Maintenance					
WEEK	-4 (Screening Visit – Start of Baseline)	0 (Baseline Treatment Visit)	Day 1	Day 2	Day 3	1	2, 3, 4	5	9	12	16 Taper/Safety Visits[p]
Visit Windows		+ 4 days			± 1 day	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days
VISIT	Visit 1[a]	Visit 2[o]	Phone Follow-up	Phone Follow-up	Phone Follow-up	Visit 3	Phone Follow-up	Visit 4	Phone Follow-up	Visit 5	Visit 5a
Informed Consent[b]	X										
Demographics & Medical History	X	X[s]									
Inclusion/Exclusion Criteria	X	X									
Genetic testing	X[c]	X[r]									
Seizure Identification and Diagnostic Review Form (Epilepsy Study Consortium)	X	X									
Vital Signs (BP, HR, RR, and body temperature)	X	X				X		X		X	X
Height / weight	X[d]	X[e]				X[e]		X[e]		X[e]	
Physical/Neurological/ Developmental Exam[t]	X	X				X		X		X	
ECG		X				X		X		X	
Clinical Laboratory Tests[f]	X	X				X		X		X	
Urinalysis	X[g]	X[g]				X		X		X	
Drug Screen[h]	X	X								X	
Pregnancy Test (WCBP)[i]	X	X						X		X	

Table 1: Schedule of Assessments - Part A

	Part A										
	Screen/Baseline					Titration and Maintenance					
WEEK	-4 (Screening Visit – Start of Baseline)	0 (Baseline Treatment Visit)	Day 1	Day 2	Day 3	1	2, 3, 4	5	9	12	16 Taper/Safety Visits[p]
Visit Windows		+ 4 days			± 1 day	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days
VISIT	Visit 1[a]	Visit 2[o]	Phone Follow-up	Phone Follow-up	Phone Follow-up	Visit 3	Phone Follow-up	Visit 4	Phone Follow-up	Visit 5	Visit 5a
Tanner Staging	X										X
IP PK								X[j]		X[j]	
Concomitant AED Review and Levels if Per Standard of Care[k]	X	X				X		X		X	
[redacted]											
Adverse Event	X	X	X	X	X	X	X	X	X	X	X
Seizure and Medication Diary Review[l]	X[l]	X	X	X	X	X	X	X	X	X	X
[redacted]											
CGI-C - Target Behavior		X[m]						X		X	
CGI-I (caregiver)		X						X		X	
CGI-I (clinician)		X						X		X	
C-SSRS (baseline form)[q]		X									
C-SSRS (since previous visit)[q]								X		X	X
Dispense GNX[n]		X						X		X	

AED = antiepileptic drug, BP = blood pressure, CBD = cannabidiol, CGI-C = Caregiver Global Impression of Change, CGI-I = Clinical Global Impression – Improvement, C-SSRS = Columbia-Suicide Severity Rating Scale, D/C = discontinuation, ECG = electrocardiogram, EEG = electroencephalogram, GNX = ganaxolone, HR = heart rate, IP = investigational product, LAR = legally authorized representative, PK = pharmacokinetic, RR = respiratory rate, THC = tetrahydrocannabinol, WCBP = women of childbearing potential.

Table 1: Schedule of Assessments - Part A

			Part A								
	Screen/Baseline					Titration and Maintenance					
WEEK	-4 (Screening Visit – Start of Baseline)	0 (Baseline Treatment Visit)	Day 1	Day 2	Day 3	1	2, 3, 4	5	9	12	16 Taper/Safety Visits[p]
Visit Windows		+ 4 days			± 1 day	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days
VISIT	Visit 1[a]	Visit 2[o]	Phone Follow-up	Phone Follow-up	Phone Follow-up	Visit 3	Phone Follow-up	Visit 4	Phone Follow-up	Visit 5	Visit 5a

a. Patient rescreening is allowed as agreed by the sponsor and the investigator unless there is a general concern for patient safety or an inability for the patient to become eligible (e.g., GNX allergy, sensitivity or exposure, non-TSC and/or other ineligible epilepsy, chronic prohibited medical condition or treatment). Subsequent screening should take place at least 30 days from the patient's last visit.
b. Written informed consent/assent must be obtained from patient, parent or LAR before any study assessments are performed. Pediatric assent should be obtained, if appropriate.
c. Previous genetic testing results will be accepted and reviewed to assess if a pathogenic *TSC1* or *TSC2* variant is present. If genetic testing has not previously been performed, then a biological sample will be obtained to complete genetic testing at the sponsor's designated lab. Note: TSC diagnosis does not require pathogenic *TSC1* or *TSC2* mutations if the clinical criteria are met.
d. Height and weight will be measured. Length will be measured if height cannot be obtained.
e. Only weight will be measured. At each visit, dosing will be reviewed and adjusted as needed based on a patient's current weight.
f. Chemistry and Hematology.
g. 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 if possible.
h. A drug screen (plasma) will be performed to test for THC and CBD at screening. If the screening drug test is positive, the patient can be retested, via plasma, after two weeks. A positive drug test during the treatment period will result in early termination.
i. Serum pregnancy test is required for all girls/women of childbearing potential.
j. Population PK will be conducted at these visits (Visit 4: between 1-5 hours since last IP dosing, Visit 5: between 4-8 hours since the last IP dosing).
k. Concomitant AEDs or their dose must be stable for 1 month prior to screening and cannot be changed at any time prior to Visit 4, but may be adjusted during Part B.
l. Caregiver given seizure and medication diary and instructions for use.
m. During the baseline visit, the investigator and parent/caregiver/LAR will decide on a domain and identify the specific behavior that the patient exhibits that denotes the domain. This behavior will be used at subsequent visits to assess change after the initiation of IP.
n. Patients who discontinue IP early will be encouraged to continue with all procedures and scheduled visits.
o. The 4 weeks between Screening Visit and Baseline Treatment Visit can be no less than 28 days and no more than 32 days.
p. Only for patients who do not continue into Part B. This will occur after 2 weeks of taper and 2 weeks after completion of treatment.
q. Only for patients ≥ 7 years old if appropriate. Otherwise clinical judgment will be used.
r. Only for patients that were Screened without previous genetic testing results and had a genetic test performed at the sponsor's designated lab.

s. Review of medical history only.
t. Developmental examination is limited to pediatric patients 2 to 17 years of age, inclusive.

10.2 APPENDIX B: SCHEDULE OF ASSESSMENTS PART B

Table 2: Schedule of Assessments - Part B

Part B								
	Final Part A Visit/ First Part B Visit	Open-Label Extension (Visits will be every 8 weeks with a telephone follow-up in-between)					Final OLE Visit or Taper Visit	Safety Follow-up Post-taper
WEEK	12	16	20	24	28	32	36 or early D/C	2 weeks post last dose
Visit Windows		± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 3 days
VISIT	Visit 5	Phone follow-up	Visit 6	Phone follow-up	Visit 7	Phone follow-up	Visit 8 (Week 36) or Visit X (early D/C)	Visit X
Confirm patient is "OLE eligible" (≥ 35% reduction in seizure frequency)	X							
Vital signs (BP, HR, RR, and body temperature)	X		X		X		X	X
Weight[a]	X		X		X		X	
Physical/Neurological/ Developmental Exam	X		X		X		X	X
ECG	X				X		X[d]	
Clinical Laboratory Tests[b]	X		X		X		X	X
Urinalysis	X				X		X	X
Drug Screen	X				X			
Pregnancy Test (WCBP)[c]	X		X		X		X	X
Tanner Staging							X[d]	
IP PK[e]	X		X		X		X	X
Concomitant AED Review and levels if per standard of care	X		X		X		X	X

Table 2: Schedule of Assessments - Part B

Part B								
	Final Part A Visit/ First Part B Visit	Open-Label Extension (Visits will be every 8 weeks with a telephone follow-up in-between)					Final OLE Visit or Taper Visit	Safety Follow-up Post-taper
WEEK	12	16	20	24	28	32	36 or early D/C	2 weeks post last dose
Visit Windows		± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 3 days
VISIT	Visit 5	Phone follow-up	Visit 6	Phone follow-up	Visit 7	Phone follow-up	Visit 8 (Week 36) or Visit X (early D/C)	Visit X
[redacted]								
Adverse Event	X	X	X	X	X	X	X	X
Seizure and Medication Diary Review	X	X	X	X	X	X	X	X
[redacted]								
CGI-C - Target Behavior	X						X	
CGI-I (caregiver)	X						X	
CGI-I (clinician)	X						X	
C-SSRS (since last visit form)[f]	X		X		X		X	
Dispense GNX	X		X		X		X	

AED = antiepileptic drug, BP = blood pressure, CGI-C = Caregiver Global Impression of Change, CGI-I = Clinical Global Impression – Improvement, C-SSRS = Columbia-Suicide Severity Rating Scale, D/C = discontinuation, ECG = electrocardiogram, EEG = electroencephalogram, GNX = ganaxolone, HR = heart rate, IP = investigational product, OLE = open-label extension, PK = pharmacokinetic, RR = respiratory rate, WCBP = women of childbearing potential.

a. Weight will be measured at every visit, except the safety follow-up visit.
b. Chemistry and Hematology.
c. Serum pregnancy test is required for all girls/women of childbearing potential.
d. Conduct at Week 36/Visit 8 or the last open-label extension visit if prior to Week 36/Visit 8.
e. PK samples can be drawn when convenient during the study visits.
f. Only for patients ≥ 7 years old if appropriate. Otherwise clinical judgment will be used.