Marinus Pharmaceuticals, Inc.

Statistical Analysis Plan Cover Page

Protocol Number: 1042-TSC-3002

Investigational Product: Ganaxolone (GNX)

Indication: Tuberous Sclerosis Complex (TSC)

Protocol Title: A Phase 3, Open-label Study of Adjunctive Ganaxolone (GNX) Treatment in Children and Adults with Tuberous Sclerosis Complex (TSC)-related Epilepsy (TrustTSC OLE)

Protocol Number: 1042-TSC-3002

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Marinus Pharmaceuticals, Inc.

Statistical Analysis Plan

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Investigational Product	Ganaxolone (GNX)
Indication	Tuberous Sclerosis Complex (TSC)
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Date of SAP (Version 1.0)	03 March 2025

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Statistical Analysis Plan Version 1.0

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LIST OF ABBREVIATIONS

AE	Adverse event
ASM	Anti-Seizure Medication
BMI	Body Mass Index
CRF	Case Report Form
CGI-CSID	Caregiver Global Impression of Change in Seizure Intensity/Duration
CGI-I	Clinical Global Impression of Improvement
CS	Clinically Significant
DB	Double-blind
ECG	Electrocardiogram
eDiary	Electronic Diary
GNX	Ganaxolone
IP	Investigational Product
ITT	Intent-to-treat
kg	Kilogram
kg/m^2	Kilogram per Meter Squared
LAR	Legally authorized representative
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
OLE	Open-Label Extension
NCS	Not Clinically Significant
PT	Preferred Term

SAE	Serious adverse event
SAP	Statistical Analysis Plan
SF-36	Short Form 36
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
TLF	Table, Listing and Figure
TSC	Tuberous Sclerosis Complex

1. INTRODUCTION

This is a Phase 3, global, open-label extension (OLE) study and all participants will receive treatment with GNX after completing Study 1042-TSC-3001 (in this study participants previously randomized to placebo will be titrated to GNX under double-blind conditions prior to study completion) or Study 1042 TSC 2001. In both parent studies, GNX is to be titrated to a maximum dose of 1800 mg/day and given as an oral suspension (50 mg/mL) with food. Participants will continue the GNX dose determined in Study 1042-TSC-3001 or Study 1042-TSC-2001 in this OLE unless a dose change is clinically indicated. Participants who discontinue the IP should undergo a 2-week taper period, which may be shortened, if necessary, for patient safety. Participants who discontinue the IP before the scheduled completion of the study will have an Early Termination Visit, as per Visit 5 (Week 52), and also return to the site 2 weeks after the end of the taper period to complete the safety follow-up assessments. It is estimated that the maximum duration of participation in this study will be approximately 3 years. The purpose of this Statistical Analysis Plan (SAP) is to define the methodology for analyzing and summarizing the data collected during the conduct of Study 1042-TSC-3002.

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on 1042-TSC-3002 Protocol Amendment 3 v4.0 dated 19APR2023 and case report forms (CRFs) v6.0 dated 12Sep2024. Unless superseded by an amendment, this SAP will be effective for all subsequent Protocol amendments and CRF versions.

2.2. Study Objectives

2.2.1. Primary Objective

The primary objective of the study is: to assess the long-term safety and tolerability of GNX as adjunctive therapy for seizures associated with TSC in children and adults.

2.2.2. Secondary Objectives

The secondary objectives of the study are:

- For the first year, to determine the percentage of change from baseline in 28-day seizure frequency during open-label treatment.
- For the first year, to assess the change in frequency of countable focal seizures frequency from baseline during open label treatment.
- For the first year, to assess changes in mood, behavior, and quality of life using SF-36.
- To assess overall clinical outcome using CGI-I scores by the clinician and the parent(s)/caregiver(s)/LAR(s).
- To evaluate the changes in seizure intensity and duration using the CGI-CSID.

2.2.3. Exploratory Objectives

- To evaluate the long-term effects of GNX as add-on therapy to antiepileptic medications.

2.3. Study Endpoints

2.3.1. Primary Endpoint

The primary endpoints are the following safety endpoints:

- Incidence and severity of AEs, SAEs and withdrawals and dose-reductions due to AEs

- Vital sign measurements including blood presure, heart rate, respiratory rate, body temperature, height, and body weight
- Physical, neurological, and developmental examination
- 12-lead ECG
- Clinical laboratory tests
- C-SSRS.

2.3.2. Secondary Endpoints

The secondary endpoints are:

- Percentage change from baseline in 28-day seizure frequency during open-label treatment (first year only)
- Number (%) of participants considered treatment responders (first year only)
- CGI-I at the last scheduled study visit
- Change from baseline in the quality-of-life scale SF-36 (first year only)
- Change from baseline in the percentage of seizure-free days during treatment, based on seizure type (first year only)
- Change from baseline of CGI-CSID

Note that original baseline in 28-day seizure frequency in the parent study will be applied. For other assessments, the baseline is considered to be Visit 1, the first visit of the OLE.

3. STUDY DESIGN

3.1. Sample Size Considerations

Approximately 150 participants will be enrolled, which is a combination of participants who completed Study 1042-TSC-3001 or Study 1042-TSC-2001. The total sample size is not powered for the primary and secondary endpoints.

3.2. Multiplicity

All endpoints will be assessed descriptively. No multiplicity control methodology will be used.

3.3. Interim Analysis

No formal interim analysis is planned.

4. STATISTICAL METHODOLOGY

4.1. General Methodology

Unless otherwise stated, SAS®software (Version 9.4 SAS Institute Inc, Cary, NC) will be used for the generation of all tables, graphs, and statistical analyses. Summary statistics including the number of subjects (n), mean, standard deviation, median, minimum and maximum will be presented for continuous variables. Generally, the minimum and maximum values will be presented to the same decimal precision as the raw values, the mean and median values to one more, and the standard deviation, to two more decimal places than the raw values. For categorical variables, per category, the absolute counts (n) and percentages (%) of subjects with data, and if appropriate, the number of subjects with missing data, will be presented. Percentages will be presented to one decimal place.

For AEs, medical history and concomitant medications reported on a per-subject basis, the denominator for the percentage calculation will be the number of subjects in each treatment group. A subject will be considered at risk if the subject is in the analysis set and in the subgroup of interest.

If a p-value is less than 0.0001 it will be displayed as "< 0.0001". All p-values larger than 0.0001 will be rounded to 4 decimal places.

The results of the primary and secondary endpoints will be summarized separately. The results will be summarized by the treatment received by participants in the parent study. Participant demographics, characteristics, and medical history at randomization or the start of the parent study will be summarized using descriptive statistics.

4.2. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

- Intent-to-treat (ITT) Set – Includes all enrolled participants. This set will be used for efficacy analyses.
- Safety Analysis Set – Includes all enrolled participants who receive at least 1 dose of the IP. This set will be used for the safety analyses.

The full analysis analysis set is used to analyze endpoints related to the efficacy objectives and the safety analysis set is used to analyze the endpoints and assessments related to safety.

4.3. Statistical Methods for Primary Safety Analyses

4.3.1. 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 24.0 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. Detailed by-patient listings of all AEs reported during the study will be provided and will include verbatim and coded terms for each AE.

For the safety Analysis Set, the following tabular summaries will be created:

- An overall summary of TEAEs will present the number and percentage of subjects with at least 1 reported TEAE, study drug related TEAE, serious TEAE, TEAE of Grade 3 or higher, study drug infusion interruption, and death
- TEAEs by system organ class and preferred term
- TEAEs by system organ class, preferred term, and maximum severity
- Study drug related TEAEs by system organ class and preferred term
- TEAEs by decreasing frequency of preferred term
- Moderate or severe TEAEs by system organ class and preferred term
- Moderate or severe study drug related TEAEs by system organ class and preferred term
- TEAEs that led to study drug infusion interruption by system organ class and preferred term
- Serious TEAEs by system organ class and preferred term
- Serious study drug related TEAEs by system organ class and preferred term

For incidence reporting, if a subject reported more than 1 AE that was coded to the same preferred term/system organ class, the subject will be counted only once for that specific preferred term/system organ class. For TEAEs presented by severity, the worst severity for each event during the clinical trial will be presented for each subject. If the severity is missing for a TEAE, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, while the actual values will be used in data listings.

For TEAEs presented by relationship to study drug, the closest relationship to study drug for each event during the clinical trial will be presented for each subject. If the relationship to investigational product is missing for a TEAE, a causality of "Related" will be assigned. The imputed values for relationship assessment will be used for incidence summaries, while the actual values will be presented in data listings.

All AEs, SAEs, TEAEs leading to study drug interruption, and SAEs leading to death will be displayed in separate listings.

4.3.2. Clinical Laboratory Evaluations

Laboratory data collected in this study include serum chemistry and hematology values, and urinalysis results. The baseline laboratory value is defined as the last value observed prior to the first administration of study drug, typically Visit 1, the first visit of the OLE. 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 Analysis Set by group (chemistry, hematology or urinalysis) and 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.

4.3.3. Vital Signs, Physical, Neurological and Developmental Examination Findings

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 1, the first visit of the OLE. 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 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.

The observed data at baseline and change from baseline for each measurement day will be summarized for each parameter with descriptive statistics. Plots of mean vital signs values (and standard error bars) over week 4 will be produced.

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.

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.

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.

4.3.4. Electrocardiogram (ECG)

Safety ECG measurements will be collected throughout the study. Baseline ECG values are those collected at Visit 1, the first visit of the OLE 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-patient listings of ECG data and overall interpretations will be provided.

4.3.5. Columbia-Suicide Severity Rating Scale (C-SSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a patient questionnaire that evaluates suicidal ideation and behaviors. The results (yes/no) from the 5 questions under suicidal ideation and the 5 questions under suicidal behavior will be summarized at baseline and post baseline using percentages and counts. The denominator for percentages will be the number of subjects with a C-SSRS assessment at baseline or at any time post baseline. The post-baseline by-question summary will list a subject as "yes" if they selected yes at any time after baseline.

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 1**. 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 1: 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

4.4. Statistical Methods for Secondary Efficacy Analyses

4.4.1. Percentage change from baseline in 28-day seizure frequency during open-label treatment.

Seizure types are defined as the following: focal motor seizures without impairment of consciousness or awareness, focal seizures with impairment of consciousness or awareness with motor features, focal seizures evolving to bilateral, tonic-clonic convulsive seizures, and generalized motor seizures including tonic-clonic, bilateral tonic, bilateral clonic, or atonic/drop seizures. Seizures must have a motor component sufficiently prominent and distinct to clearly establish the observed symptoms as epileptic in origin. Seizures that do not count towards the efficacy endpoints include: focal aware seizures without motor features (eg, absence or focal nonmotor seizures with or without impairment of awareness), infantile or epileptic spasms, and myoclonic seizures.

Baseline for efficacy assessments is defined as based on the participant's prior study as follows:

- Study 1042-TSC-2001 – the original 4-week screening period for participants continuing in Study 1042 TSC-3002
- Study 1042-TSC-3001 – the original 4-week screening period for participants previously randomized to GNX.

Post-baseline 28-day seizure frequency will be calculated as the total number of seizures in the open-label phase divided by the number of days with seizure data in the same period, 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 same period, multiplied by 28. The calculation for percent change from baseline in 28-day seizure frequency will be done as follows for each participant:

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

The baseline, post-baseline, and arithmetic and percent changes from baseline in 28-day seizure frequency will be summarized using descriptive statistics. The following subgroup summarizations will be also applied:

- Gender (Female vs Male).
- Age groups (1 to 6 years; 7 to 12 years; 13 to 17 years; and 18 years and above).

4.4.2. Number (%) of participants considered treatment responders

The number and percentage of subjects experiencing a reduction (improvement) of at least 50% from baseline in the 28-day seizure frequency of the primary seizure types will be summarized. In addition, a cumulative responder curve figure will be provided, in which the X-axis represents amount of improvement in increments of 5%, and the Y-axis represents the percentage of subjects improving by at least the amount on the X-axis. The treatment groups will be presented separately within the figure. Subgroup summaries for gender and age groups listed in section 4.4.1 will be also applied.

4.4.3. CGI-I at the last scheduled study visit

The CGI-I is 7-point scale, and the number and percentage of subjects with each score will be summarized. The scores range from 1=very much improved and 7=very much worse. The CGI-I is completed by both parent/caregiver/LAR and clinician.

4.4.4. Change from baseline in the quality-of-life scale SF-36

The SF-36 is a multi-purpose survey designed to capture participant or parent/caregiver perceptions of own health and well-being. The SF-36 has 36 items grouped in 8 dimensions: physical functioning, physical and emotional limitations, social functioning, bodily pain, general, and mental health.

Scoring the 36-Item Health Survey is a two-step process. First, precoded numeric values are recoded per the scoring key given in

Table 2. Note that all items are scored so that a high score defines a more favorable health state. In addition, each item is scored on a 0 to 100 range so that the lowest and highest possible scores are 0 and 100, respectively. Scores represent the percentage of total possible score achieved. In step 2, items in the same scale are averaged together to create the 8 scale scores.

Table 3 lists the items averaged together to create each scale. Items that are left blank (missing data) are not considered when calculating the scale scores. Hence, scale scores represent the average for all items in the scale that the respondent answered.

Table 2: Recoding Items for SF-36

Item numbers	Change original response category	To recoded value of:
1, 2, 20, 22, 34, 36	1 →	100
	2 →	75
	3 →	50
	4 →	25
	5 →	0
3, 4, 5, 6, 7, 8, 9, 10, 11, 12	1 →	0
	2 →	50
	3 →	100
13, 14, 15, 16, 17, 18, 19	1 →	0
	2 →	100
21, 23, 26, 27, 30	1 →	100
	2 →	80
	3 →	60
	4 →	40
	5 →	20
	6 →	0
24, 25, 28, 29, 31	1 →	0
	2 →	20
	3 →	40
	4 →	60
	5 →	80
	6 →	100
32, 33, 35	1 →	0
	2 →	25
	3 →	50
	4 →	75
	5 →	100

Table 3: Averaging Items to Form Scales for SF-36

Scale	Number of items	After recoding per Table 1, average the following items
Physical functioning	10	3 4 5 6 7 8 9 10 11 12
Role limitations due to physical health	4	13 14 15 16
Role limitations due to emotional problems	3	17 18 19
Energy/fatigue	4	23 27 29 31
Emotional well-being	5	24 25 26 28 30
Social functioning	2	20 32
Pain	2	21 22
General health	5	1 33 34 35 36

4.4.5. Change from baseline in the percentage of seizure-free days during treatment, based on seizure type

The percentages of seizure-free days will be based on the primary seizure types. Post-baseline percentage of seizure-free days will be calculated as the number of days in the open-label treatment phase with zero seizures divided by the number of days with seizure data in the phase, multiplied by 100. The baseline percentage of seizure-free days will be calculated as the number of days in the 4-week baseline phase with zero seizures divided by the number of days with seizure data in the baseline phase, multiplied by 100.

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

4.4.6. Change from baseline of CGI-CSID

The CGI-CSID is from the 7-point Caregiver Global Impression of Change in Seizure Intensity/Duration instrument. The scores range from 1=very much improved and 7=very much worse. The number and percentage of subjects with each score will be

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

4.5. Handling of Missing Data

Available data from patients who withdraw from the study prematurely will be included in analyses, unless otherwise indicated. Summary statistics will be reported based upon observed data. 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.

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

The handling of partial start and stop dates for AEs are described in

Table 4 below. Similar algorithms for handling missing and partial dates of concomitant medication usage are described in **Table 5**. 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.

- **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.

Table 4: 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.

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Table 5: 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.

5. BASELINE, DISPOSITION, AND EXPOSURE

5.1. Study Day and Analysis Window

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.

5.2. 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 for efficacy assessments is defined as based on the participant's prior study as follows:
    - Study 1042-TSC-2001 – the original 4-week screening period for participants continuing in Study 1042 TSC-3002
    - Study 1042-TSC-3001 – the original 4-week screening period for participants previously randomized to GNX.
- 3-year open-label treatment period: Visit 2 to Visit 13. All windows for these visits are ± 14 days.

Safety Analyses

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

5.3. Demographics

Demographics will be summarized and listed for all patients in the Safety Population. 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.

5.4. Subject Disposition

The number of patients screened for this study, the number of rollerover (from TSC-2001 and 3001) and the number of patients who received at least one dose of IP will be summarized. The final disposition of all patients who receive IP will be summarized. Reasons for discontinuation of study participation will be summarized. The total number and percentage of patients who complete the study will be summarized.

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.

5.5. 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. 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).

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 number and percentage of patients in the Safety population reporting use of prior and concomitant treatments will be summarized and listed separately. In addition, anti - seizure medication (ASM) and rescue medications will be presented separately.

5.6. Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA), version 23.0. 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.

5.7. Study Drug 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.

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.

5.8. Study Drug Compliance

Compliance with GNX treatment will be assessed by inspecting the seizure and medication diary entries and returned drug supply with queries as necessary. The percent compliance with study drug will be estimated using dosing information reported in the eDiary as follows:

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

Reported dosing by visit and calculated compliance values will be listed.

6 SUMMARY OF MAJOR CHANGES IN THE PLANNED ANALYSES

No other changes are made to the protocol specified analyses.

Any further analysis changes made after this SAP is finalized, but prior to database lock, will be documented with an SAP amendment. If after database lock, analysis changes or additional analyses required to supplement the planned analyses within this SAP will be described in the clinical study report (CSR).

7 PROGRAMMING SPECIFICATIONS

Programming specifications will be provided in the SAP table, listing, and figures shells document.

8 TABLES, LISTINGS, AND FIGURES SHELLS

The tables, listing, and figures shells will be provided as a separate document.