Statistical Analysis Plan

Protocol No.: 1042-CDD-3001

A double-blind, randomized, placebo-controlled trial of adjunctive ganaxolone treatment in children and young adults with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) followed by long-term open-label treatment

Sponsor:	Marinus Pharmaceuticals, Inc.
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ABBREVIATIONS

Abbreviation	Term
ABC-C	Aberrant Behavior Checklist – Community Edition
AEs	adverse events
AED	anti-epilepsy drugs
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
BUN	blood urea nitrogen
CDD	CDKL5 Deficiency Disorder
CDKL5	Cyclin-Dependent Kinase Like 5
CGICA	Caregiver Global Impression of Change in Attention
CGI-CSID	Caregiver Global Impression Of Change in Seizure Intensity/Duration
CGI-C	Clinical Global Impression Of Change
CGI-I	Clinical Global Impression Of Improvement
cm	centimeter
CNS	central nervous system
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
ITT	intent-to-treat
kg	kilogram
kg/m2	kilogram per square meter
LAR	legally authorized representative
lb	pound
LLN	Lower limit of normal

Abbreviation	Term
m	meter
MedDRA	Medical Dictionary For Regulatory Activities
mg	milligram
mmHg	millimeters mercury
OL	open label
OLE	open-label extension
PBO	placebo
PCS	potentially clinically significant
PK	pharmacokinetics
PP	per protocol
PSI	Parenting Stress Index
PT	Preferred Term
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-CDD-3001 (Protocol Amendment 1.0: 05 May 2019). This statistical plan does not include the analyses of the pharmacokinetic and pharmacodynamic (exposure response analysis) data.

1.1 Study Objectives

1.1.1 Primary Objective

To assess the efficacy of GNX compared with PBO as adjunctive therapy for treatment of primary seizures in children and young adults with genetically confirmed CDD at the end of the 17-week DB phase. The primary seizure types include bilateral tonic (sustained motor activity ≥ 3 seconds), generalized tonic-clonic, atonic/drop, bilateral clonic, and focal to bilateral tonic-clonic.

1.1.2 Secondary Objectives

- To assess behavioral/neuropsychiatric changes correlated with domains of attention, sleep, and a target behavior chosen by the parent/caregiver, using objective tests of CNS function for GNX compared with PBO as adjunctive therapy at the end of the 17-week DB phase.
- To assess the safety and tolerability of GNX compared with PBO as adjunctive therapy at the end of the 17-week DB phase.
- To assess 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 phase.
- To assess the long-term safety and tolerability of GNX when administered as adjunctive therapy throughout the open-label phase.

[redacted]

1.2 Study Endpoints

The primary interest in the study is the effects of GNX treatment following 17 weeks of DB treatment, and so the endpoints will be based upon data through the end of the 17-week DB treatment. But as indicated in Section 7.1.6, they will also be examined from earlier time points.

Three categories of seizures will be assessed in this study; individual seizures, clusters with countable seizures, and clusters with uncountable seizures. The analyses will be performed on the sum of the individual seizures, the seizures within a cluster in which the seizures are countable, and the clusters with uncountable seizures (each cluster with uncountable seizures contributes 1 to the sum).

1.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the percentage change from baseline in 28-day primary seizure frequency during the 17-week DB treatment phase.

Baseline is defined as the 6-week prospective baseline phase.

The primary seizure types include bilateral tonic (sustained motor activity ≥ 3 seconds), generalized tonic-clonic, atonic/drop, bilateral clonic, and focal to bilateral tonic-clonic. The seizure data is taken from the patient diaries.

1.2.2 Secondary Efficacy Endpoints

Derived seizure secondary efficacy endpoints will be based on data through the end of the 17-week DB treatment phase relative to the 6-week prospective baseline phase.

Seizure control:

- Change from baseline in the percentage of seizure-free days during the 17-week DB treatment phase, based on the primary seizure types
- Number (%) of subjects with a ≥50% reduction from baseline in primary seizure frequency
- Caregiver Global Impression of Change in Seizure Intensity/Duration (CGI-CSID).

Behavioural/Neuropsychiatric:

- Caregiver Global Impression of Change in Attention (CGICA) score
- Clinical Global Impression-Change (CGI-C) in parent/caregiver/LAR identified behavioural target - potential domains include sociability, communication, irritability, and hyperactivity
- Clinical Global Impression of Improvement (CGI-I): overall improvement by both parent/caregiver/LAR and clinician.

[redacted]

1.2.4 Safety and Tolerability Endpoints

Safety and tolerability endpoints include:

- Adverse events (AEs)
- Clinical laboratory tests
- Vital signs including temperature, blood pressure, pulse rate, respiration rate, and weight
- Physical, neurological and developmental examinations
- 12-lead Electrocardiogram (ECG)
- Concomitant AED levels

1.2.5 Open-Label Phase Endpoints

Except for the changes in seizure frequency during the titration phase and during the maintenance phase, the same efficacy, exploratory, quality of life, and safety endpoints for the DB phase will also be used for the open-label phase. In addition, the Tanner Staging, which is performed only at Screening in the DB phase of the study unless the subject does not enter the OLE phase, is another safety endpoint. When the DB phase is completed in all the subjects, a cutoff date will be declared for purposes of NDA submission and all open label data collected up to the cutoff will be analyzed. When the full study is completed, the open-label data will be re-analyzed.

The results for the open-label phase should be interpreted cautiously because there is no control group in that phase, and the intent-to-treat principle may be compromised since several subjects may not enter the phase and, among those entering, several may withdraw from the study prior to its completion. In addition, there is no blinding during the open-label phase.

1.3 Summary of the Study Design

1.3.1 General Study Design and Plan

This is a phase 3 global, DB, randomized, PBO-controlled trial of adjunctive GNX treatment in children and young adults with CDD. The trial consists of a 6-week prospective baseline period to collect seizure data, followed by a 17-week DB treatment phase, which is then followed by a long-term open-label phase.

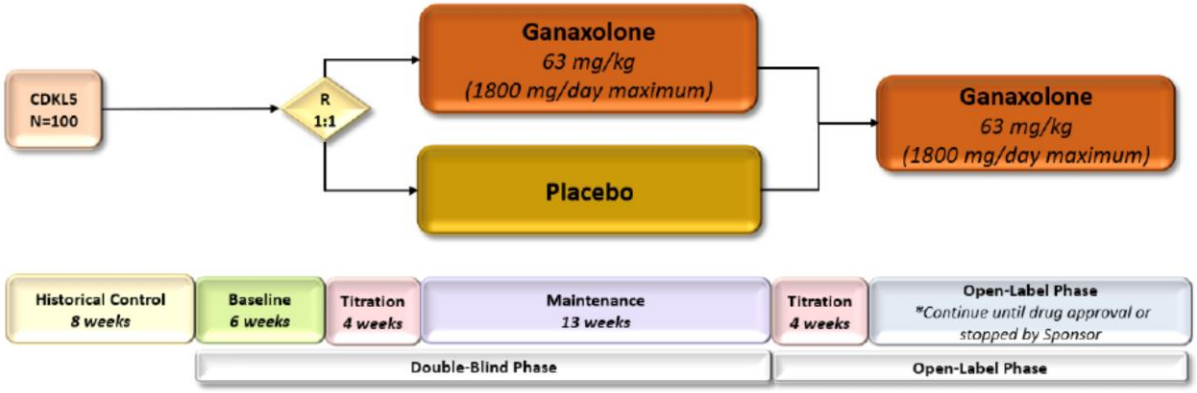
The double blind phase includes 6 weeks prospective baseline, 4 weeks of titration followed by 13 weeks of dose maintenance. After meeting the eligibility criteria, children and young adults

aged 2-21 years (inclusive) with CDD will be randomly assigned to receive GNX or PBO (1:1 ratio) for 17 weeks in addition to their standard anti-seizure treatment. Recruitment will stop after approximately 100 children and young adults have been enrolled. Participants 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 after discussion with the Sponsor. A minimum dose of 33 mg/kg/day or 900 mg/day is required during the DB phase.

After completing the initial 17-week, DB, PBO-controlled phase, all subjects will be treated with GNX in the open-label phase of the study. GNX subjects will continue GNX treatment and PBO subjects will titrate onto GNX. To maintain the blind, subjects initially randomized to GNX will undergo a false titration (increasing PBO doses) for 4 weeks, while PBO subjects will titrate up to 63 mg/kg/day GNX (1800 mg/day maximum) during the same time phase (Figure 1). The open-label phase is estimated to take an additional 3 years. It will continue until the sponsor terminates the program or GNX has been approved and marketed the investigational product in the subjects' respective country.

Participants who complete the study or discontinue investigational product treatment before the end of the study will undergo a 2-week taper phase after which he/she will return to the site 2 weeks postdose for a safety follow up visit. Subjects who discontinue investigational product treatment before the completion of the DB phase will continue to be followed per protocol and at minimum maintain daily seizure diary entry until the DB phase is completed. These subjects will also return to the site 2 weeks after the taper for safety follow-up assessments.

Figure 1. Study Design



Participants will be required to complete a daily seizure calendar noting seizure type and frequency in an electronic seizure diary calendar to determine GNX's effect on drug resistant seizures.

The Schedule of Events for the 17-week pre-randomization and double-treatment phase is presented in Table 1. The Schedule of Events for the OLE is presented in Table 2.

Table 1: Schedule of Assessment for the 17-week, Double-blind Treatment Phase of the Study

	Screen/Baseline			DB Titration + Maintenance					Final DB Visit
WEEK	**-14**	**-6 (Screening)**	**0 Baseline (Randomization)**	**3 days**	**1, 2, 3, 4**	**5**	**9**	**11, 13**	**17**
Visit Windows			**+6 days[n]**	**± 1 day**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**
	Historical Seizure frequency	**Visit 1**	**Visit 2**	**Phone Follow-up**	**Phone Follow-up**	**Visit 3**	**Visit 4**	**Phone Follow-up**	**Visit 5**
Screening and Diagnosis									
Informed Consent[a]	X[b]	X							
Demographics & Medical History		X	X[c]						
Historical Seizure Calendar Review		X							
Inclusion/Exclusion Criteria		X	X						
Genetic testing[d]		X							
Seizure Identification and Diagnostic Review Form (Epilepsy Study Consortium)		X	X						
Safety Assessments									
Vital signs (BP, HR, RR, and body temperature)		X[e]	X			X	X		X[f]
Physical/Neurological/ Developmental Exam		X				X			X
Physical/Neurological/ Developmental Exam Follow-up			X				X		

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Visit Windows			**+6 days[n]**	**± 1 day**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**
	Historical Seizure frequency	**Visit 1**	**Visit 2**	**Phone Follow-up**	**Phone Follow-up**	**Visit 3**	**Visit 4**	**Phone Follow-up**	**Visit 5**
ECG		X	X			X			X
Clinical Laboratory Tests[g]		X	X			X	X		X
Urinalysis		X[h]	X[h]						X
Drug screen[i]		X							
Pregnancy Test (WCBP)[j]		X	X						
Tanner Staging		X							
Investigational Product PK						X[k]	X[k]		X
Concomitant AED Review and levels if per standard of care[l]		X	X			X	X		X
Neurosteroid levels		X							X
Adverse Event		X	X	X	X	X	X	X	X
Efficacy Assessments									
Seizure eDiary review		X	X	X	X	X	X	X	X
Caregiver Global Impression of Change in Attention (CGICA)		X[m]				X	X		X
Caregiver Global		X[m]				X	X		X

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Visit Windows			**+6 days[n]**	**± 1 day**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**
	Historical Seizure frequency	**Visit 1**	**Visit 2**	**Phone Follow-up**	**Phone Follow-up**	**Visit 3**	**Visit 4**	**Phone Follow-up**	**Visit 5**
Impression of Change in parent/caregiver identified behavioral target (CGI-C)									
Caregiver Global Impression of Change in Seizure Intensity/Duration (CGI-CSID)						X	X		X
Clinical Global Impression Improvement (CGI-I) by parent/caregiver & clinician		X[m]				X	X		X
[redacted]									
[redacted]			[redacted]						[redacted]
[redacted]			[redacted]			[redacted]	[redacted]		[redacted]
[redacted]			[redacted]			[redacted]	[redacted]		[redacted]
[redacted]			[redacted]			[redacted]	[redacted]		[redacted]

Table 1: Schedule of Assessment for the 17-week, Double-blind Treatment Phase of the Study

	Screen/Baseline			DB Titration + Maintenance					Final DB Visit
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Visit Windows			**+6 days[n]**	**± 1 day**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**
	Historical Seizure frequency	**Visit 1**	**Visit 2**	**Phone Follow-up**	**Phone Follow-up**	**Visit 3**	**Visit 4**	**Phone Follow-up**	**Visit 5**
[redacted]			[redacted]			[redacted]	[redacted]		[redacted]
Dispense Investigational Product			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. Written informed consent/assent must be obtained from subject, parent or LAR before any study assessments are performed.

b. Written informed consent/assent from subject, parent or LAR needed if 8-week historical control is not available and need to chart prospectively.

c. Review of medical history only.

d. Genetic testing to be performed to confirm pathogenic or likely pathogenic CDKL5 variant.

e. In addition, height and weight will be measured. If weight unable to be collected at Visit 1, may be collected at Visit 2.

f. In addition, weight will be measured.

g. Chemistry & Hematology (Section 12.2).

h. 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.

i. A drug screen (urine or plasma) will be performed to test for THC and CBD at screening. A negative drug test at screening meets the protocol eligibility criteria. If the screening drug test is positive, a plasma drug screen will be performed to test for THC and CBD at baseline. A positive drug test at baseline will exclude the subject from the study.

j. Serum pregnancy test is required for all girls/women of childbearing potential.

k. 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 IP dosing).

l. Concomitant AEDs or their dose 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.

m. During the Screening visit, the investigator and parent/caregiver/LAR will decide on a specific behavior that the patient exhibits that denotes assessment measured. This behavior will be used at subsequent visits to assess change after the initiation of investigational product.

n. Visit 2 to occur minimum of 6 weeks (42 days) after Visit 1 and maximum of 6 weeks + 6 days (48 days)

Table 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 after 52 weeks)						Final OL Visit or Taper	Safety Follow-up post
WEEK	**17**	**3 Days Post Visit 5**	**18**	**19**	**20**	**21**	**28**	**34**	**43**	**52**	**60**	**68 and X visit**	**X/ or early D/C**	**2 weeks post last**
Visit Windows		**± 1**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 3 days**
	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**	**Phone follow-up**	**Visit 10 and Visit X**	**Visit X**	**Visit X**
Safety Assessments														
Vital signs (BP, HR, RR, and body temperature)[a]	X [a]			X		X		X [a b]		X [a b]		X [a]	X [a b]	X
Physical/Neurological/ Developmental Exam	X					X		X		X		X	X	
Physical/Neurological/ Developmental Exam Follow-up				X										X
ECG	X					X		X		X		X	X	
Clinical Laboratory Tests[c]	X			X		X		X		X		X	X	X
Urinalysis	X									X[e]			X	X[e]
Pregnancy Test (WCBP)[d]													X	X
Tanner Staging[e]										X			X	

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WEEK	**17**	**3 Days Post Visit 5**	**18**	**19**	**20**	**21**	**28**	**34**	**43**	**52**	**60**	**68 and X visit**	**X/ or early D/C**	**2 weeks post last**
Visit Windows		**± 1**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 3 days**
	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**	**Phone follow-up**	**Visit 10 and Visit X**	**Visit X**	**Visit X**
Investigational Product PK	X			X		X[f]		X		X[f]		X	X	X
Concomitant AED Review and levels if per standard of care	X			X		X		X		X		X	X	X
Neurosteroid Levels	X												X	
Adverse Event	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Assessments														
Seizure eDiary review	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Caregiver Global Impression of Change in Attention (CGICA)	X					X		X		X		X	X	

Table 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 after 52 weeks)**						**Final OL Visit or Taper**	**Safety Follow-up post**
WEEK	**17**	**3 Days Post Visit 5**	**18**	**19**	**20**	**21**	**28**	**34**	**43**	**52**	**60**	**68 and X visit**	**X/ or early D/C**	**2 weeks post last**
Visit Windows		**± 1**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 3 days**
	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**	**Phone follow-up**	**Visit 10 and Visit X**	**Visit X**	**Visit X**
Caregiver Global Impression of Change (CGI-C) in parent/caregiver identified behavioral target	X					X		X		X		X	X	
Clinical Global Impression of Improvement (CGI-I) by parent/ caregiver & clinician)	X			X		X		X		X		X	X	
Caregiver Global Impression of Change in Seizure Intensity/Duration Severity (CGI-CSID)	X					X		X		X		X	X	
[redacted]														
[redacted]	[redacted]												[redacted]	

Table 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 after 52 weeks)						Final OL Visit or Taper	Safety Follow-up post
WEEK	**17**	**3 Days Post Visit 5**	**18**	**19**	**20**	**21**	**28**	**34**	**43**	**52**	**60**	**68 and X visit**	**X/ or early D/C**	**2 weeks post last**
Visit Windows		**± 1**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 3 days**
	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**	**Phone follow-up**	**Visit 10 and Visit X**	**Visit X**	**Visit X**
[redacted]	[redacted]					[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	
[redacted]	[redacted]					[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	
[redacted]	[redacted]					[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	
[redacted]	[redacted]					[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	
Dispense Investigational Product	X			X		X		X		X		X	X	

Table 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 after 52 weeks)						Final OL Visit or Taper	Safety Follow-up post
WEEK	**17**	**3 Days Post Visit 5**	**18**	**19**	**20**	**21**	**28**	**34**	**43**	**52**	**60**	**68 and X visit**	**X/ or early D/C**	**2 weeks post last**
Visit Windows		**± 1**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 3 days**
	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**	**Phone follow-up**	**Visit 10 and Visit X**	**Visit X**	**Visit 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.

a. In addition, weight will be measured at every visit, except the safety follow-up visit.

b. In addition, height will be measured. Height will be measured annually after Visit 9 (Week 52), except the safety follow-up visit.

c. Chemistry & Hematology (Section 12.2).

d. Serum pregnancy test is required for all girls/women of childbearing potential.

e. Conduct annually and at the final open-label visit.

f. Population PK will be conducted at these visits: Visit 7: between 1-5 hours since last IP dosing and Visit 9: between 1-5 hours since last IP dosing

1.3.2 Sample Size and Statistical Power Considerations

Based on data from the 7 patients in Study 1042-0900 evaluating GNX in CDKL5 patients, the standard deviation for the percent change in 28-day seizure frequency for seizure types tonic (sustained motor activity ≥ 3 seconds), tonic-clonic, atonic/drop, epileptic spasms, or clonic (generalized or unilateral) is estimated to be 44.5. Therefore, when the percent change in 28-day seizure frequency on GNX minus that on PBO truly is 30%, then a trial with 100 subjects randomized in a 1:1 manner will have 92% power to detect this effect when using an ANOVA that preserves a (one-sided) 2.5% false positive error rate. If the true difference in the percent changes is 35%, then the study will have 97.5% power.

The threshold for achieving statistical significance at the final analysis when 100 subjects have completed their 17-week DB treatment phase would be an estimate of the difference that is approximately 17.5%. (The actual analysis will use a Wilcoxon rank-sum test, which has approximately the same power as the ANOVA.)

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 OLE phases of the study. Only events occurring before entry into the OLE phase will be included in the DB phase outputs, and except where indicated, only pre-treatment events and events occurring after entry into the OLE phase will included in the OLE phase outputs. 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 OLE phase will show the results for each DB treatment group (all subjects will be receiving GNX in the OLE phase) and combined over them. For the efficacy endpoints, the results will be derived according to the randomized treatment group; for the other endpoints, they will be derived according to the treatment actually received.

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

Baseline seizure activity will be determined by 6 weeks of prospective recording in subject daily seizure calendars, which are provided after signing informed consent. Within the DB phase of the study, post-baseline seizure activity will be determined by the days following the first day after the first DB treatment. (The first day of DB treatment is included in neither the baseline nor DB phase since seizures could occur both before and after the initiation of treatment.) Within the OLE phase, post-baseline seizure activity will be determined by the first day of OLE treatment.

Baselines 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 OLE 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 following degree of precision, unless otherwise specified:

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 Safety and Intention-to-Treat (ITT) Population

This population comprises all randomized subjects who received at least one dose of study drug. In addition to being the population for the safety analyses, it is the primary population for the efficacy and neurosteroid level analyses.

2.2.2 Per-Protocol Population (PP)

This population consists of ITT subjects who received study drug for at least 6 weeks, provided at least 5 weeks of post-baseline seizure data, and had no major protocol violations. There will be no PP population for the OLE phase of the study.

2.3 Time Windows for Analysis

For by-visit safety or efficacy summaries, only scheduled visits will be analyzed. But if subjects prematurely discontinue from the study and complete assessments at the Taper Visit, then that visit may be reassigned to another visit for analysis purposes, as described in subsequent sections, including Section 7.1.1.

2.4 Pooling of Centers

Data of all sites will be pooled together 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 7.1.7.

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 extension phases of the study.

The disposition will include the following:

- Subjects screened (DB phase only)
- Screen failures (DB phase only)
- Subjects enrolled (randomized)
- Subjects in the Safety Population
- Subjects in the ITT Population
- Subjects in the PP Population
- Ongoing subjects (OLE phase only)
- Subjects who completed the phase
- Subjects who discontinued study drug before the end of the phase (DB phase only)
- Reasons for study drug discontinuation before the end of the phase (DB phase only)

- Subjects who discontinued study before the end of the phase
- Reasons for study discontinuation before the end of the phase (OLE phase only)

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

3.2 Eligibility Criteria and Protocol Deviations

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

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, gender, race, height, weight and body mass index (BMI), country, and ethnicity) and the Tanner staging collected prior to the first dose; and the number of prior medications taken and stopped prior to the first dose will be summarized using descriptive statistics in the safety population and, if it differs substantially from the safety population, the PP population as well. (The safety population is also the ITT population.) The statistics will be shown within each DB treatment group and combined over them.

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

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

BMI (kg/m2) = Weight (kg)/[Height(m)^2]

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

5. MEDICAL HISTORY AND GENETIC TESTING

Medical history will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) Terminology version 16.0 or higher. 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) by treatment and overall in the safety population and, if it differs substantially from the safety population, the PP population as well.

The number and percent of subject replies to each question of the genetic testing done at Screening 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.

6. PRIOR AND CONCOMITANT MEDICATIONS AND THERAPIES

Prior medications 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, 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 OLE phase.

The summary of concomitant medications/therapies for the OLE phase will include all medications/therapies, other than study drug, administered on or after the first dosing day of the phase. (There will be no summary of prior medications/therapies for the OLE 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). The number (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. The tables of prior and concomitant medications will be provided separately for non-AED and AED medications, as will subject data listings of them.

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 in a subject data listing.

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

Partial Missing Start or Stop Date	Imputed Start Date	Imputed Stop Date
Missing year, month, and day	First dose date	
Missing month and day, and the year is present	First dose date if the year is the same as the year of first dose date, else first dose date of the OLE if the year is the same as the year of the first OLE dose date, else January 1 of the start year.	December 31 of that year

Missing day, but year and month are present	First dose date if the year and month are the same as the year and month of first dose date, else first dose date of the OLE if the year and month are the same as the year and month of the first OLE dose date, else the 1st of the 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 with 95% distribution-free confidence intervals for the median and Hodges-Lehmann point estimates and asymptotic 95% confidence limits for the location shifts. Section 12.2 contains SAS code for obtaining the distribution-free confidence limits for the median and the Hodges-Lehmann estimates and confidence intervals.

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

7.1 Double-Blind Phase

All efficacy analyses will be conducted in the ITT population. A supportive analysis of the primary and secondary efficacy endpoints also will be conducted in the PP population.

The estimand that is most clinically relevant as well as estimable in a manner that protects the integrity of randomization is the outcome measure (e.g., the percent change in 28-day seizure frequency), where ALL randomized subjects would be included in this analysis throughout the study period. Hence, all available data will be used, 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 6 weeks 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 OLE and up to the day before the first dose of OLE treatment for those who do. The first day of treatment is not in either phase since the seizures could occur both before and after the first treatment.

Tests of significance between the 2 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 the post-baseline DB phase intervals will be calculated as:
100 x (Number of Days with Available Seizure Diary) / (Last Available Seizure Diary Date – First Day of the Phase + 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.

The compliances 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 to nearly zero, but despite these efforts, some missing data may still arise. Thus a sensitivity analysis, in which the missing data will be replaced, will be performed on the primary efficacy endpoint; see Section 7.1.8.

When an item from a secondary or efficacy endpoint is missing, then so will any subscales or totals that include it.

When subjects prematurely discontinue from the study they are asked to complete the non-seizure assessments at the Taper Visit. For analysis purposes, their data from the Taper Visit will be reassigned to the first visit at which the assessment is scheduled subsequent to the discontinuation and the scheduled day is within 32 days of the Taper visit. For example if a subject completed Visit 3 and then prematurely discontinued and completed assessments at the Taper Visit on Study Day 100, then the Taper visit would be reassigned to Visit 5 (Week 17) for analysis purposes since Visit 5 is scheduled for Study Day 120, 20 days after the assessments were actually completed. (Although the first visit after Visit 3 is Visit 4 (Week 9), that visit is scheduled on Study Day 64, which is not within 32 days of Study Day 100.) But if the Taper Visit assessments were completed on Study Day 28 then the Taper visit would not be reassigned to a regular study visit since Study Day 28 is not within the 32-day window of any scheduled visit. Taper Visit assessments that are not reassigned will not be included in the tabulations but will be included in the data listings.

7.1.2 Primary Efficacy Endpoint

The primary efficacy endpoint is the percent change from baseline in 28-day primary seizure frequency during the 17-week DB treatment phase. Primary seizure types include bilateral tonic, generalized tonic-clonic, atonic/drop, bilateral clonic, or focal to bilateral tonic-clonic seizures. 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. 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 and post-baseline values and the changes and percent changes from baseline in 28-day seizure frequency will be summarized using descriptive statistics.

The difference between the treatment groups in the percent changes from baseline will be tested for statistical significance. Since the percent differences are anticipated to display skewness and/or outliers, the tests will be performed using the Wilcoxon Rank-Sum statistic.

7.1.3 Secondary Efficacy Endpoints

All secondary efficacy endpoints will compare GNX and PBO at the end of the 17-week DB treatment phase relative to the 6-week prospective baseline phase. If any endpoint value at baseline is zero, then any percentage changes from baseline for that endpoint will be missing.

All secondary analyses will be done primarily in the ITT population and secondarily in the PP population.

7.1.3.1 Change from baseline in the Percentage of Seizure-Free Days Based on the Primary Seizure Types

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 17-week DB 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 6-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.

7.1.3.2 Percentage of Subjects Experiencing ≥ 50% Reduction from Baseline in 28-day Seizure Frequency Based on the Primary Seizure Types

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.

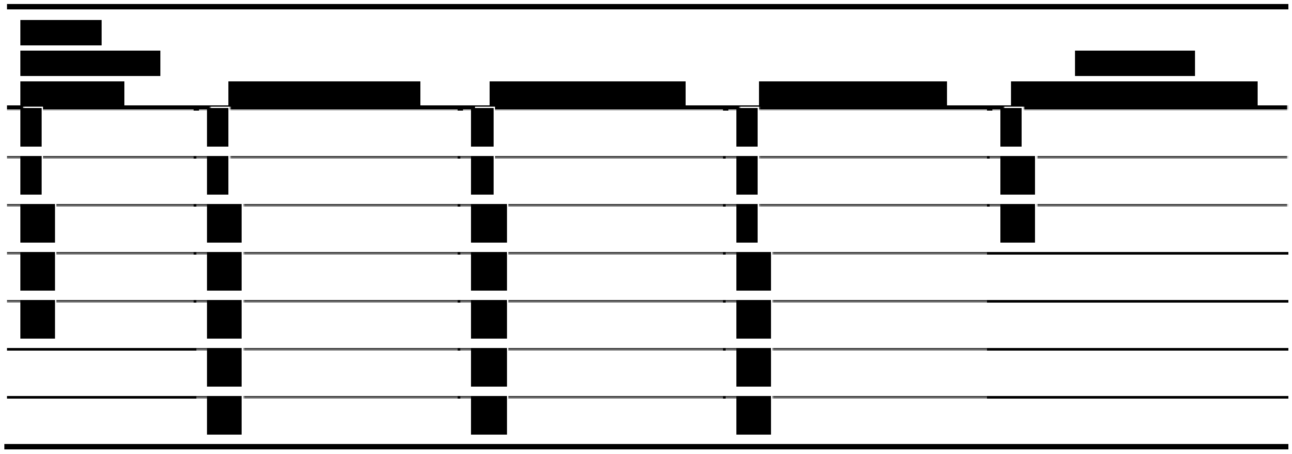
7.1.3.3 Change in Seizure Intensity/Duration

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.

7.1.3.4 Behavioral/Neuropsychiatric Endpoints

The CGICA, CGI-C, and the CGI-I are all 7-point scales, 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.)

[redacted]



[redacted]

7.1.5 Subgroup Analyses

Two subgroup summarizations of the primary efficacy parameter are planned. The first one is by Allo_S levels [(low (≤ 2.5 ng/mL), middle (> 2.5 ng/mL and < 6.0 ng/mL) or high (≥ 6.0 ng/mL)], and since there may be a potentially greater treatment effect among subjects with low levels the subgroup with low levels will be analyzed as a sensitivity analysis; see Section 7.1.8 for additional details. The second subgroup is by gender.

7.1.6 Analysis of Weeks 5 and 9

In order to explore the time course of GNX on non-seizure endpoints, the analyses of those endpoints will be repeated using the data from the scheduled Week 5 and Week 9 visits.

7.1.7 Protections for Multiplicity

There is a single primary efficacy endpoint, and formal hypothesis testing will not be performed for the other endpoints. Hence no protections for multiplicity are needed.

7.1.8 Sensitivity Analyses

Three sensitivity analyses of the primary efficacy endpoint of change in 28-day frequency of the primary 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

minimal in occurrence) prior to the end of the 17-week DB phase: for those missing days, the corresponding median PBO data will be imputed (irrespective of treatment arm) as follows:

- Partition the subjects in the PBO arm into quartiles, where the quartile equals Floor[Rank*4/(n+1)], where Floor[.] is the integer floor function, Rank is the rank of the 28-day seizure frequency in the PBO arm based on all available PBO measurements during the 6-week baseline phase (tied scores receive tied ranks), and n is the number of subjects in the PBO arm.
- Assign each subject for whom imputation is needed into the quartile that covers the 28-day seizure frequency based on that subject's available measurements during the 6-week baseline phase. If a frequency is lower than the lower bound of the lowest quartile (which could happen only in the GNX arm), then assign that subject to the lowest frequency quartile; likewise if a frequency is higher than the upper bound of the highest quartile, then assign that subject to the highest frequency quartile. If a frequency falls between two quartiles (which, again, could happen only in the GNX arm), then based on the distances between the frequency and the upper and lower bounds of the lower and higher quartiles, respectively, assign the subject to the closer quartile (in case of a tie, assign to the lower quartile).
- Within each quartile, 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 DB phase).
- For any days (whether they be on the PBO or GNX arm) with missing counts due to a subject stopping recording measurements permanently, impute 'A' from the corresponding quartile 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 in the 3rd and 4th bullets above, except that quartiles are not used, will be modified to use the median of the 5 highest counts (equivalent to the 3rd highest count) among all the PBO subjects with data.

The third sensitivity analysis is to examine the effect of GNX compared to PBO among subjects with low Allo-S levels. The open-label phase 2 study 1042-0900 enrolled 30 subjects who were treated for up to six months. In these subjects with various pediatric epilepsies, including 11 with PCDH19 genetic epilepsy and 7 with CDKL5 Deficiency Disorder, Allo-S levels and 28-day seizure rates were assessed. A GNX responder was specified, by post-hoc definition, as having at least a 25% reduction in 28-day seizure rate. In the PCDH19 cohort, responders (n=6) and non-responders (n=5) had plasma Allo-S concentrations of 501 ± 430 pg mL-1 and 9,829 ± 6,638 pg mL-1, respectively (mean ± SD). When performing a retrospective separation of the PCDH19 cohort according to their Allo-S levels, the 7 subjects with Allo-S levels below 2,500 pg mL-1 had a 53.9% reduction in seizure rates while the 4 subjects with Allo-S levels above 2,500 pg mL-1 had a 247% increase.

All 7 of the subjects with CDKL5 Deficiency Disorder in the 1042-0900 study had low Allo-S levels (below 1000 pg/mL), and their median 28-day seizure reduction was 31%.

The PCDH19 cohort results were based on only 11 subjects and were from an uncontrolled study. Even if low Allo-S levels are indeed associated with increased efficacy of GNX relative to PBO among patients with PCDH19 seizures, this effect modification by baseline Allo-S levels will not necessarily hold among subjects with CDKL5 seizures; it does nevertheless suggest that among patients suffering with CDKL5 seizures the benefit of GNX compared to PBO could be greater in patients with low Allo-S levels. As a result, most important sensitivity analysis for the effect of GNX on the primary efficacy endpoint of change in 28-day frequency of the primary seizure types will be in those subjects with low Allo-S levels at baseline. Based upon insights from the Study 1042-0900 clinical trial data, subjects in this trial will be considered to have low Allo-S levels if they have a baseline Allo-S level of less than or equal to 2500 pg/mL (Pinna Lab method).

7.2 Open-Label Extension

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

- The results will be presented overall and also classified according to the DB treatment received by the subjects
- The post-baseline seizure endpoints will be derived starting from the first dosing day of OLE treatment
- The only sensitivity analysis to be performed is the analysis of the primary endpoint among subjects with low Allo-S levels
- The seizure frequencies during the titration and maintenance phases will not be analyzed separately
- The time points for the efficacy, exploratory, and quality of life endpoints will be at Weeks 21, 34, 52, and every 16 weeks thereafter of open-label treatment relative to the 6-week prospective baseline phase. For the seizure endpoints, this corresponds to the first 4, 17, 35, 51, etc. weeks from the start of the OLE 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
- If a subject prematurely discontinues from the OLE phase, the EEG comparison to baseline at the Final OL/Taper Visit cannot be reassigned for analysis purposes since the EEG is performed only at that visit in the OLE phase; hence the tabulation at that visit will include all the subjects, regardless of whether they discontinued. (Taper Visit assessments among the subjects who prematurely discontinue from the DB phase are reassigned if possible; if they cannot be reassigned then they are not tabulated.)

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 OLE phases will be summarized separately. In both phases, the results will be summarized by the DB treatment actually received and, for the OLE phase of the study, combined over the treatment groups.

The number and percentage of days that subjects received study drug, the highest percentage of the maximum allowable daily dose (1800 mg or 63 mg/kg) that subjects received, and the total amount of study drug received will be summarized. The denominator for the percentage of days of study drug is the number of days in the phase. If the subject stops taking drug during the phase then the last day that drug was taken will be used for the last day of the phase, and if the subject is ongoing in the phase then the last known treatment date will be used. For the OLE phase, the number and percentage of days that subjects received study drug will be summarized over just the OLE phase as well as over the entire study (combined DB and OLE phases) but the classification by the DB treatment applies only for the OLE phase summary. The summarization over the entire study will include the DB data only from subjects who were in the GNX group during the DB phase, regardless of whether they entered the OLE, and all the subjects from the OLE 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 temperature, blood pressure, pulse rate, and weight
- 12-lead ECG
- Physical, neurological and developmental examinations
- Tanner staging (OLE phase only)
- Concomitant AED levels

Baseline is defined as the last non-missing value obtained before the first 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. Assessments performed at the Taper Visit for prematurely discontinued subjects will be reassigned as described in Section 7.1.1; if the assessments are not

reassigned, they will not be included in the tabulations but will be included in the data listings. Subjects who prematurely discontinue from the study are also asked to complete assessments at the Safety Follow-up Post-Taper Visit, but these will not be reassigned.

9.1 Adverse Events

Adverse events (AEs) will be coded by System Organ Class (SOC) and Preferred Term (PT) using the MedDRA®, version 16.0 or higher. The verbatim term will be included in the AE listings. Except where indicated, the summary tables will include only TEAEs. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

A treatment-emergent adverse event (TEAE) is defined as an AE that starts or worsens on or after the first dosing day of study drug. The AE analyses for the main 17-week 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 OLE phase; ie, they will not include any AEs starting or worsening on or after the first dosing day of the OLE phase.

For the OLE phase of the study, the AEs will be summarized over just the OLE phase as well as over the entire study (combined DB and OLE phases) but the classification by the DB treatment applies only for the OLE phase summary. The summarization over the entire study will include AEs in the DB phase only from subjects who were in the GNX group during the DB phase, regardless of whether they entered the OLE, and all the subjects from the OLE phase; i.e., it will include only the AEs following GNX exposure. The summarizations over just the OLE phase will include TEAEs that start or worsen after the first day of the OLE 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 > unrelated) to study drug when summarized by relationship. TEAEs with missing relationships will be considered as related.

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.

Pre-treatment emergent AEs by will be summarized by SOC and PT (only for the DB period summary).

TEAEs will be summarized as below.

- An overview table of TEAEs, including number of events and number (%) of subjects with
    - TEAEs

  - serious TEAEs (Treatment-emergent SAEs)
  - treatment related TEAEs
  - TEAEs by severity
  - TEAEs leading to study drug discontinuation
  - TEAEs leading to dose reduction or temporary study drug discontinuation
  - TEAEs leading to death
- TEAEs by SOC and PT
- TEAE by SOC, PT, and Severity
- Study drug related TEAEs by SOC, PT
- Treatment-emergent SAEs by SOC and PT
- TEAEs leading to study drug discontinuation by SOC and PT
- TEAEs leading to dose reduction or temporary study drug discontinuation by SOC and PT
- TEAEs of special interest: rashes and the reproductive system and breast disorders system organ class
- TEAEs by PT

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 OLE summaries; in case of tied frequencies, the sorting will be alphabetical.

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

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

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

9.1.1 Deaths, Serious and Adverse Events Leading to Early Study Drug Termination

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

9.2 Clinical Laboratory Parameters

Laboratory assessments include hematology, clinical chemistry, and urinalysis:

- Hematology: Hemoglobin, Hematocrit, Erythrocytes, Leukocytes + differential, Thrombocytes (platelet count).
- 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), eGFR.
- Urinalysis: pH, Color, Clarity, Specific Gravity, Urobilinogen, Ketones, Protein, Glucose, Bilirubin, Blood, Leukocyte esterase, Nitrite

All laboratory parameters will be presented in SI units. Quantitative results (including actual value, and change from baseline) will be summarized using descriptive statistics by baseline and post-baseline visit for each laboratory test group above. Laboratory test results will be assigned an LNH classification according to whether the value was below (L), within (N), or above (H) the normal reference range (some urinalysis labs are assigned only normal and abnormal classifications). Values outside the normal range are also classified as to whether they were potentially clinically significant (PCS). The number and percentage of subjects in each category will be summarized by baseline and post-baseline visit for each lab test. In addition, shift tables cross-tabulating the baseline and post-baseline LNH classifications, by visit, will be provided. The PCS criteria are:

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)		

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.

Vital sign test results will be assigned an LNH classification according to whether the value was below (L), within (N), or above (H) the normal reference range. Values outside the normal range will also be classified as to whether they were potentially clinically significant (PCS). Vital signs normal ranges are:

Age	**SBP (mm Hg)**	**DBP (mm Hg)**	**Pulse (beats/min)**	**Respiration Rate (breaths/min)**
1 – 3 yrs	90-105	55-70	80-125	20-30

> 3 – 6 yrs	95-110	60-75	70-115	20-25
> 6 – 12 yrs	100-120	60-75	60-100	14-22
> 12 yrs	100-120	70-80	60-100	12-18

The subjects' age categories will be determined by their age at the time of the vital signs collection. Since only the birth years of the subjects are available, the month and day of birth will be assumed July 1st. The subjects' age at the time of the collection will then be derived as: Floor((Collection Date – Birth Date + 1) / 365.25).

PCS abnormalities are defined as:

SBP:
High: ≥1.5 x ULN; or a ≥ 20 mmHg increase from baseline if clinically significant at baseline
Low: ≤0.75 x LLN; or a ≥ 20 mmHg decrease from baseline if clinically significant at baseline

DBP:
High: ≥1.3 x ULN; or a ≥ 15 mmHg increase from baseline if clinically significant at baseline
Low: ≤0.70 x LLN; or a ≥ 15 mmHg decrease from baseline if clinically significant at baseline

Pulse:
High: ≥1.20x ULN; or a ≥ 15 bpm increase from baseline if clinically significant at baseline
Low: ≤0.80x LLN; or a ≥ 15 bpm decrease from baseline if clinically significant at baseline

Respiratory Rate
Low: ≤0.80 x LLN
High ≥1.25 x ULN

The number and percentage of subjects with abnormalities will be summarized by baseline and post-baseline time point for each parameter.

A subject listings of vital signs, including out of the normal range and PCS flags, will be provided.

9.3.2 ECG

The 12-lead ECG parameters including value and change from baseline will be summarized using descriptive statistics by baseline and post-baseline visit. Except for QTc, the parameters will be assigned an LNH classification according to whether the value was below (L), within (N), or above (H) the normal reference range. Values outside the normal range, and the QTc parameters, will also be classified as to whether they were potentially clinically significant (PCS).

ECG normal ranges and PCS criteria are:

HR: Same as in Vital Signs
PR interval: PCS: < 0.9xLLN or >1.1 x ULN
QRS: PCS: >1.1x ULN
QTc B/FN interval: PCS: ≥ 470 msec (females), ≥ 450 msec (males), or increase ≥ 60 msec from baseline

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

Overall ECG results were 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, and shift tables cross-tabulating the baseline and post-baseline ECG interpretations, by visit, will be provided.

A subject listing of the ECG parameters and overall interpretation, including out of the normal range and PCS flags, will be provided.

9.3.3 Physical, Neurological, and Developmental Examinations

Physical examination results are interpreted as normal, abnormal (not clinically significant) or abnormal (clinically significant). Neurological examination results were interpreted as normal or abnormal. The number and percentage of subjects in each category for these examinations will be summarized. The developmental examination consists of several questions and the number and percentage of subject replies to each question will be summarized. Listings for all the examinations will be provided.

9.3.4 Tanner Staging

This endpoint is a safety endpoint for only the OLE period of the study.

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 9 (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 OLE visit.

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

9.3.5 Concomitant AED Levels

Concomitant AED levels are not mandatory but will be collected per sites' standard of care. A subject listing, including date and time of last AED dose and date and time of AED PK sample, will be provided.

10. INTERIM ANALYSES AND DATA AND MONITORING COMMITTEE (DMC)

Up to two formal interim analyses are planned, in addition to the final analysis, of treatment effect on the primary endpoint. They will be conducted when 50 subjects and 75 subjects are at least 17 weeks post randomization. The interim analyses will include only those subjects, and will be based on use of O'Brien-Fleming monitoring boundaries regarding benefit and lack of benefit. If the trial is not terminated at the interim analyses, the sample size at the final analysis will be approximately 100 participants.

(Note that while the boundaries discussed in the remainder of this section will be illustrated for the setting in which 50 (75) subjects would be at least 17 weeks post randomization at the interim analysis, these boundaries will be computed based on the actual number 'X' of subjects at the times of the interim analyses.)

In addition, two supportive analyses will be performed, for informational purposes only, at each interim analysis:

- For those subjects who stop recording measurements permanently (anticipated to be minimal in occurrence) prior to the end of the 17-week DB phase, the imputation procedure for the first sensitivity analysis described in Section 7.1.8 will be applied.

- All randomized subjects who are at least 4 weeks post randomization at the time of the interim analyses will be included.

10.1 Termination Based on Reliable Evidence of Lack of Benefit

An O'Brien-Fleming boundary that rules out benefit will be used, protecting an experimental (one-sided) 0.025 false negative error rate, under an assumed maximum sample size of 100 participants, and under the alternative hypothesis that the percent change in 28-day seizure frequency on ganaxolone minus that on placebo truly is 0.5618 times the standard deviation for the percent change in 28-day seizure frequency; when that standard deviation is 44.5, this alternative hypothesis for the percent change in 28-day seizure frequency on ganaxolone minus

that on placebo would be 25%. (This reduction is the effect the trial has 80% power to detect at the final analysis when 100 subjects have completed their 17-week DB treatment phase.)

If the standard deviation for the percent change in 28-day seizure frequency is 44.5, then the estimate of the percent change in 28-day seizure frequency on ganaxolone minus that on placebo that would be at the boundary for early termination due to lack of benefit at 50 subjects would be approximately an estimated 10% increase, and at 75 subjects would be approximately an estimated 1% decrease.

The proposed boundary for termination based on reliable evidence of lack of benefit is somewhat conservative, in part due to the recognition that statistical significance might not be required for this trial to be sufficiently favorable to justify regulatory approval.

10.2 Termination Based on Definitive Evidence of Benefit

An O'Brien-Fleming boundary for definitive evidence of benefit will be used, protecting an experimental (one-sided) 0.005 false positive error rate, under an assumed maximum sample size of 100 participants, and under the null hypothesis of no effect on the percent change in 28-day seizure frequency on ganaxolone minus that on placebo.

This boundary for termination based on definitive evidence of benefit would be crossed only if the statistical strength of evidence is midway between that of one and two trials, (i.e., one in 200 under the null hypothesis), even when adjustment is made for multiplicity due to interim monitoring. It is proposed that two interim 'efficacy' analyses be performed, specifically at the times when 50% and 75% of the 100 subjects have completed the 17 week double blind period. The Z-values at the interim analyses conducted at the times of 50% and 75% information are:

$2.64\ (100/50)^{1/2} = 3.73$ (at 50 subjects)

and

$2.64\ (100/75)^{1/2} = 3.03$ (at 75 subjects)

The (one-sided) nominal p-value corresponding to the Z-value of 3.73 is 0.0001; and corresponding to the Z-value of 3.03 is 0.0012.

If the standard deviation for the percent change in 28-day seizure frequency is 44.5, then the estimate of the percent change in 28-day seizure frequency on ganaxolone minus that on placebo that would be at the boundary for early termination due to definitive evidence of benefit at 50 subjects would be an estimated 47% decrease, and at 75 subjects would be an estimated 32% decrease.

Nearly all of the experimental (one-sided) 0.025 false positive error rate will be spent at the time of the final analysis of the primary endpoint, conducted when all 100 study participants have completed their double-blind period, because the interim analyses were conducted using an O'Brien-Fleming boundary that, during the interim analyses, preserved the (one-sided) 0.005 false positive error rate. To be specific, at least 0.0250 - 0.0013 = 0.0237 of the (one-sided) false

positive error remains for this final analysis. Hence, the two-sided p-value at the final analysis will be approximately 0.048.

10.3 Data Monitoring Committee

The emerging study data will be reviewed on a regular basis by an independent Data Monitoring Committee (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.

11. SUMMARY OF MAJOR CHANGES IN THE PLANNED ANALYSES

Any major changes in the planned analyses will appear in updated versions of this SAP. In the event of discrepancies between the SAP and the protocol, the SAP will take precedence.

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, Inc.
      Study No 1042-CDD-3001
      ```

    - Header with page number at the upper right margin:

      ```
      PAGE: X of N
      ```

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

    - Footer with the date the output was generated:

      ```
      ddMMMyyyy: hh:mm
      ```

2. Each 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 (eg, 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

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

5. All data listings should be sorted by treatment group (PBO first) 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 (eg, Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject 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 (eg, 0.12, 0.3).
9. Missing descriptive statistics or p-values due to non-estimability in tables, as well as missing data in subject 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; eg, 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 95% distribution-free confidence interval of the median:

```
proc univariate data=dataset(where=(specify analysis population,
 endpoint, study phase, and time point) ciquandf;
  class trtp;  *trtp is the name of the randomized treatment
    variable;
  var pchg;  *pchg is the name of the percent change variable;
run;
```

The following code will provide the Wilcoxon rank-sum test along with the Hodges-Lehmann estimate and its asymptotic 95% confidence interval:

```
proc npar1way data=dataset (where=(specify analysis population,
 endpoint, study phase, and time point) wilcoxon
 HL(refclass='formatted value of PBO group');
  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

Rothmann MD, Zhang JJ, Lu L, Fleming TR(2012). Testing in a prespecified subgroup and the intent-to-treat population. Drug Info Journ 46: 175-179