16.1.9 Documentation of Statistical Methods

Statistical Analysis Plan

Protocol No.: 1042-0604

A follow-on, two-year open-label extension study of ganaxolone as add-on therapy in adult patients with drug-resistant partial-onset seizures

Sponsor:	Marinus Pharmaceuticals, Inc.
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STATISTICAL ANALYSIS PLAN APPROVAL

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ABBREVIATIONS

Abbreviation	Term
AEs	Adverse Events
AEDs	Anti-Epilepsy Drugs
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BID	Two Times Daily
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
cm	Centimeter
CO_2	Carbon Dioxide
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
eCRF	Electronic Case Report Form
CPS	Complex Partial Seizures
°C	Degrees Centigrade
°F	Degrees Fahrenheit
ECG	Electrocardiography
FAP	Full Analysis Population
FDA	Food And Drug Administration
kg	Kilogram
kg/m^2	Kilogram Per Square Meter
lb	Pound
m	Meter
MedDRA	Medical Dictionary For Regulatory Activities
POS	Partial-Onset Seizure
PT	Preferred Term
SAEs	Serious Adverse Events
SAP	Statistical Analysis Plan
SD	Standard Deviation
SI	Système International
SOC	System Organ Class
SPS-motor	Simple Partial Seizure with Motor/Observable Component

Abbreviation	Term
SGTC	Secondarily Generalized Tonic-Clonic (seizures)
TEAE	Treatment-Emergent Adverse Event
WHO	World Health Organization

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for Protocol 1042-0604 (Amendment 1 V1.0, 29 February, 2016).

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

To assess the safety and tolerability of adjunctive ganaxolone during two-year open label treatment in adult subjects with drug-resistant partial-onset seizures.

1.1.2 Secondary Objective

To assess efficacy of adjunctive ganaxolone during a two-year open-label treatment in adult subjects with drug-resistant partial-onset seizures.

1.2 STUDY ENDPOINTS

1.2.1 Safety Endpoints

Safety endpoints include:

- Adverse events (AEs)
- Clinical laboratory tests
- Vital signs
- 12-lead ECG
- Physical and neurological examinations
- Columbia-Suicide Severity Rating Scale (C-SSRS)

1.2.2 Main Efficacy Endpoint

Percentage change in seizure (partial-onset seizure (POS) with or without secondary generalization) frequency per 28-days relative to baseline in study 1042-0603. POS seizures only includes three seizure subtypes which are simple partial seizure with motor/observable component (SPS-motor), complex partial seizures (CPS) and secondarily generalized tonic-clonic seizures (SGTC).

1.2.3 Other Efficacy Endpoints

Responder rate (experiencing a ≥ 50% reduction at the end of the study compared with Study 1042-0603 baseline

1.3 SUMMARY OF THE STUDY DESIGN

1.3.1 General Study Design and Plan

Study 1042-0604 is an open-label extension of Study 1042-0603, providing a two-year adjunctive ganaxolone treatment (900-1800 mg/d) to adult subjects with epilepsy consisting of partial-onset seizure (POS). Subjects who have completed all scheduled clinical study visits in the previous protocol 1042-0603 and have shown a minimum 35% improvement in mean seizure frequency per 28-days vs. baseline over the three 28-day periods preceding study entry, and acceptable tolerability, are eligible to participate.

Subjects will enter the study at their current dose of ganaxolone from study 1042-0603. The dose of ganaxolone may be adjusted for tolerability and response. Safety and tolerability will be assessed by diary record and at clinic visits approximately every four months. During the study if the patient fails to continue to meet the minimum improvement criteria (mean 28-day seizure frequency over the past three 28-day periods before the study visit showing 35% improvement over baseline) at any study visit the investigator should consider discontinuing the patient from the study. Efficacy will primarily be assessed based on daily seizure calendar entries.

Baseline for safety and efficacy evaluations will be each subject's baseline from Study 1042-0603.

The Schedule of Events is presented in Table 1.

Table 1 Schedule of Events

WEEK	0	17	34	52	69	86	104 (Study completion/ET)	106 (Post-Taper Safety Follow-Up)	Unscheduled Visit[4]
Visit Windows (Weeks)	±2	±2	±2	±2	±2	±2	±2	±2	
VISIT	**V1 / Study 1042-0603 Visit 10**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	
Informed consent	X								
Demographics & Medical HX[1]	X								
Inclusion/Exclusion criteria	X								
Concomitant AEDs[2] Review	X	X	X	X	X	X	X	X	X
Safety Assessments									
Physical examination	X[3]			X			X		
Physical brief exam		X	X		X	X		X	
Vital signs	X[3]	X	X	X	X	X	X	X	X
Neurological examination	X[3]			X			X		
Neurological brief exam		X	X		X	X		X	
ECG (12 lead)[5]	X[3]			X			X		
Safety Labs	X[3]	X	X	X	X	X	X	X	X
Urine Pregnancy test (WCBP)	X[3]	X	X	X	X	X	X	X	
Columbia Suicide Scale (C-SSRS)	X[3]	X	X	X	X	X	X	X	
Review safety and record AEs	X[3]	X	X	X	X	X	X	X	X
Efficacy Assessments									
Subject Calendar Review	X[3]	X	X	X	X	X	X	X	
Clinician's Global Impression of Improvement	X[3]	X	X	X	X	X	X		
Patient / Caregiver Global Impression of Improvement	X[3]	X	X	X	X	X	X		
Study Medication									
Dispense study medication	X	X	X	X	X	X	X		
Study medication compliance check		X	X	X	X	X	X	X	
Visit Windows (Weeks)	±2	±2	±2	±2	±2	±2	±2	±2	

1 Any Adverse Event that occurred in 1042-0603 which is not resolved at the time of enrollment into 1042-0604 or is deemed significant by the Principal Investigator is to be captured in the subject's 1042-0604 medical history
2 Concomitant AEDs and their dose and VNS settings should be stable for 1 month prior to entry into the study
3 These procedures will be captured in Study 1042-0603 database as part of the Visit 10
4 Check Vital Signs at all unscheduled visits. Other procedures performed as needed
5 ECGs will be done locally
ET = Early Term; AED = antiepileptic drug; AEs = adverse events; ECG = electrocardiogram; WCBP = women; C-SSRS = Columbia-Suicide Severity Rating Scale

1.3.2 Randomization and Blinding

This is an open-label extension study and no randomization was planned.

1.3.3 Sample Size and Statistical Power Considerations

This is an open-label, long-term continuation study. Sample size will be determined by those eligible after successful completion of Study 1042-0603.

2. STATISTICAL METHODS

2.1 GENERAL CONSIDERATIONS

In general, continuous variables will be summarized by number of subjects, mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables will be summarized by counts and percentage of subjects in each category. If data is sparse, no summary table will be presented. Summary tables will present data by treatment received during the this study, i.e. Ganaxolone. 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 variables for all enrolled subjects.

Baseline seizure activity will be determined by 8 weeks of retrospective recording in subject daily seizure calendars in Study 1042-0603.

Baselines for safety assessments are defined as the last non-missing value of the assessment before the first dose of treatment in Study 1042-0603.

2.1.1 Reporting Precision

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

Statistics	Degree of Precision
Mean, Geometric mean, Median, Quartiles, Confidence limit boundaries	One decimal place more than the raw data.
Standard deviation, Standard error	Two decimal places more than the raw data.
Minimum, Maximum	The same as the raw data.
p-value	Rounded to 4 decimal places and therefore presented as 0.xxxx; p-values smaller than 0.0001 as ‘<0.0001’; p-values greater than 0.9999 as

	'>0.9999'.
Percentage	One decimal place. A percentage of 100% will be reported as 100%. Percentages of zero will be reported as 0.

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

2.2 DEFINITIONS OF ANALYSIS POPULATIONS (ANALYSIS SETS)

2.2.1 Safety Population

All subjects who signed informed consent and took one dose of study medication in this study. In protocol, it is termed ITT Safety population.

2.2.2 Full Analysis Population (FAP)

Subjects who returned at least 25 days of seizure calendar data.

2.3 TIME WINDOWS FOR ANALYSIS

No visit window will be constructed for the analysis. Summary table will present data of scheduled visits. Data of unscheduled visits will only be reported in listings.

2.4 POOLING OF CENTERS

Data of all sites will be pooled together for analysis.

2.5 HANDLING OF MISSING DATA

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

2.6 ANALYSIS SOFTWARE

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

3. STUDY SUBJECTS

3.1 DISPOSITION OF SUBJECTS

Disposition will be summarized by treatment, i.e. Ganaxolone, in all enrolled subjects to this study.

The disposition will include the following:

- Subjects enrolled to Study 1042-0604
- Subjects in the Safety Population
- Subjects in the FAP
- Subjects completed study
- Subjects discontinued study
- Reasons for discontinuation

A listing of dispositions will be provided for all subjects.

3.2 PROTOCOL DEVIATIONS

The clinical team will identify deviations and the deviations will be recorded into the database.

A subject data listing will be provided.

4. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

4.1 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic data (age, gender, race, and ethnicity) and baseline characteristics (including height, weight and body mass index (BMI)) collected at study screening will be summarized using descriptive statistics by treatment, i.e. Ganaxolone, in the safety population and FAP, separately.

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

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

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

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

4.2 MEDICAL HISTORY

Medical history will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) Terminology version 16.0. The number and percent of subjects with clinically significant medical history at screening will be summarized by system organ class (SOC) and preferred term (PT) by treatment, i.e. Ganaxolone, in safety population.

5. STUDY DRUG AND EXPOSURE

5.1 EXTENT OF EXPOSURE

Exposure to study medication will be summarized as a continuous variable, via the number of days of drug taken. Ganaxolone will be administered BID following the morning and evening meals. A missed dose of study medication may be taken later up to 8 hours before the next scheduled dose; otherwise, the missed dose should not be given. Treatment exposure and treatment compliance will be summarized using the Safety population.

- Treatment Exposure = the number of days of drug taken = drug stop date – start date + 1
- Treatment Compliance %= [(drug stop date – start date) + 1 – number of days drug not taken] / [(drug stop date – start date) +1] x 100%.

A subject data listing will be provided for study drug dispense and return.

5.2 PRIOR AND CONCOMITANT THERAPY

Prior medications are defined as medications that started prior to the first dose of study drug in study 1042-0604. Concomitant medications are defined as medications (other than the study drug) taken on or after the first does of the study drug during the study. 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. Medications with complete missing start/end date are considered both prior and concomitant medications.

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, i.e. Ganaxolone, in safety population, by ATC Classification and WHO Drug PT.
A subject data listing of prior and concomitant therapy will be provided.

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

Partial Missing Start or Stop Date	**Imputed Start Date**	**Imputed Stop Date**
Missing month and day, and the year is present	January 1 of that year or first dose date if the year is the same as the year of first dose date	December 31 of that year
Missing day, but year and month are present	First day of that month or first dose date if the year and month are the same as the year and month of first dose date	Last day of that month
Missing month, but year and day are present	Missing month imputed as January	Missing month imputed as December

6. EFFICACY ANALYSES

All efficacy analyses will be performed for partial-onset seizure (POS) with or without secondary generalization only. POS seizures includes three seizure subtypes which are SPS-motor, CPS and SGTC.

All efficacy data will be summarized by treatment, i.e. Ganaxolone, in FAP.

6.1 MAIN EFFICACY ANALYSIS

The primary efficacy endpoint is the percentage change in POS seizure frequency per 28-days relative to baseline in study 1042-0603. Post-baseline 28-day seizure frequency will be calculated as the total number of seizures in this open-label extension study (Study 1042-0604) divided by the number of days with available seizure data in the post-baseline period, multiplied by 28. Baseline 28-day seizure frequency will be calculated as the total number of seizures in the baseline period of Study 1042-0603 (≤ 56 days) divided by the number of days with available seizure data in the baseline period, 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, post-baseline, and percent change from baseline in 28-day seizure frequency will be summarized by treatment, i.e. Ganaxolone, in FAP.

A subject data listing will be provided.

6.2 OTHER EFFICACY ANALYSIS

6.2.1 Responder rate, Proportion of subjects with >=50% reduction in 28-day seizure frequency compared with baseline.

A 50% responder is an individual whose reduction of percent change from baseline to the end of the open label extension period in 28-day POS seizure frequency is greater than or equal to 50%. The number and percentage of responders will be summarized.

A subject data listing will be provided.

6.3 SUBGROUP ANALYSIS

No subgroup analysis planned.

7. SAFETY ANALYSIS

All safety analyses will be performed by treatment, i.e. Ganaxolone, in the Safety Population. Safety assessments include:

- AE
- Clinical laboratory tests
- Vital signs including temperature, blood pressure, pulse rate, and weight
- 12-lead ECG
- Physical and neurological examinations
- Columbia-Suicide Severity Rating Scale (C-SSRS)

Baseline is defined as the last non-missing value obtained before the first treatment in the preceding Study 1042-0603.

7.1 ADVERSE EVENTS

Adverse events (AEs) will be coded by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA®, version 16.0/AECODE). The verbatim term will be included in the AE listings.

A treatment-emergent adverse event (TEAE) is defined as an AE that occur or worsen on or after the first dose of study drug in Study 1042-0604 and before the end of the study (including the safety follow-up period). Only TEAEs will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized as the number (percentage) of subjects with TEAEs within SOC and PT. 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 > probably related > possibly related > unlikely related > Not related) to study drug when summarized by relationship. If a subject reports multiple PT for a SOC, the subject will be counted only once for that SOC. Treatment related AEs are defined as those events recorded on the CRF as ‘Related’, ‘Probably Related’ or ‘Possibly Related’, others will not be related AEs.

TEAEs will be summarized as below.

- An overview table, including number of subjects with
    - TEAEs
    - serious AEs (SAEs)
    - study drug related TEAEs
    - TEAEs by severity

  - TEAEs leading to study discontinuation
  - TEAEs leading to death
- TEAE by SOC and PT
- TEAE by SOC, PT, and Severity
- TEAE by PT
- TEAEs by SOC, PT, and Relationship to Study Drug

All AE tables will be sorted by SOC and PT in decreasing frequency of the number and percentage of subjects.

Missing date will be imputed followed table describes how missing date information will be handled:

Partial Missing Start or Stop Date	**Imputed Start Date**	**Imputed Stop Date**
Missing month and day, and the year is present	January 1 of that year or first dose date if the year is the same as the year of first dose date	December 31 of that year
Missing day, but year and month are present	First day of that month or first dose date if the year and month are the same as the year and month of first dose date	Last day of that month
Missing month, but year and day are present	Missing month imputed as January	Missing month imputed as December

7.1.1 Deaths, Serious and Other Significant Adverse Events

The listings of serious AEs, AE leading to study discontinuation, and subjects who died during the study will be provided.

7.2 CLINICAL LABORATORY PARAMETERS

Laboratory assessments include hematology, clinical chemistry, and urinalysis as in Table 2:

Table 2: Clinical laboratory parameters:

Clinical Chemistry	**Hematology**	**Urinalysis**
Total Bilirubin	Hemoglobin	pH
AST (SGOT)	Hematocrit	Color
ALT (SGPT)	Erythrocytes	Transparency

BUN	Leukocytes + differential	Specific Gravity
Glucose	Thrombocytes (platelet count)	Urobilinogen
Potassium		Ketones
Sodium		Protein
Calcium		Glucose
Alkaline Phosphatase		Hemoglobin
Chloride		
Creatinine		
CO_2		
Total Protein		
Serum Albumin		

ALT = alanine transferase; AST = aspartate transferase; BUN = blood urea nitrogen

All laboratory parameters will be presented in Système International (SI) units. Quantitative results (including actual value, and change from baseline) for hematology and chemistry will be summarized using descriptive statistics by visit. The number (and percentage) of subjects with urine abnormalities will be summarized by visit.

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

7.3 VITAL SIGNS, 12-LEAD ECG, PHYSICAL AND NEUROLOGICAL EXAMINATIONS, AND C-SSRS

7.3.1 Vital Signs

Vital signs include temperature, blood pressure, pulse rate, respiration rate, height, weight and BMI.

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

Listings of vital signs with abnormal flags will be provided.

7.3.2 12-Lead ECG

12-lead ECG data will be reported in listing.

7.3.3 Physical and Neurological Examinations

Physical examination data will be summarized using descriptive statistics by post-baseline visit, for each component. Listings for physical examination will be provided.

Neurological examination data will be reported in listing.

7.3.4 C-SSRS

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

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

8.1 INTERIM ANALYSES

No formal interim analyses are planned.

8.2 DATA AND SAFETY MONITORING BOARD (DSMB)

DSMB is N/A.

9. SUMMARY OF MAJOR CHANGES IN THE PLANNED ANALYSES

Below changes from protocol have been made in the SAP.

Safety Endpoints:
Due to early termination of the study and low patient numbers 12-lead ECG and Neurological Examination results will only be reported in listings. C-SSRS data were collected in eCRF and will be reported as one of the safety endpoints.

Efficacy Endpoints:
Due to early termination of the study and low patient numbers seizure free intervals and seizure free days will not be derived and the Clinician's Global Impression of Improvement, and the Patient/Caregiver Global Impression of Improvement results will only be reported in listings

To avoid confusion, protocol defined primary and secondary efficacy endpoints are re-named as main and other efficacy endpoints, respectively, to clarify that the primary objective of the study is to assess the safety and tolerability of adjunctive ganaxolone during two-year open-label treatment in adult subjects with drug-resistant partial-onset seizures.