16.1.9 Documentation of Statistical Methods

Statistical Analysis Plan

Sponsor Name:	Marinus Pharmaceuticals, Inc.
Protocol Number and Title:	1042-0603 A Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial to Determine the Efficacy and Safety of Ganaxolone as Adjunctive Therapy for Adults with Drug-Resistant Partial-Onset Seizures Followed by Long-term Open-Label Treatment.
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SAP Version:	3.0
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Statistical Analysis Plan Approval

Version: 3.0 **Version Date:** 24-May-2016

confirm that I have reviewed this document and agree with the content.

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1 GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AE	adverse event
AEDs	anti-epilepsy drugs
ALT	alanine transferase (SGPT)
ANCOVA	analysis of covariance
AST	aspartate transferase (SGOT)
BID	bis in die; two times per day
BMI	body mass index
C-SSRS	Columbia-Suicide Severity Rating Scale
CPS	complex partial seizures
CRF	case report form
DB	double-blind
DC	discontinuation
DSM-V	Diagnostic and Statistical Manual of mental disorders, 5th edition
EEG	electroencephalogram
ECG	electrocardiogram
eCRF	electronic case report form
HCG	human chorionic growth hormone
IWRS	interactive web randomization system
MedDRA	Medical Dictionary for Regulatory Activities
MITT	modified intent to treat
MRI	magnetic resonance imaging
OL	open label
POS	partial-onset seizure
PP	per protocol
PT	preferred term
QC	quality control
ROW	Rest of World
SAE	serious adverse event
SAP	statistical analysis plan
SPS	simple partial seizure
SPS-motor	simple partial seizure with motor/observable component
SGTC	secondarily generalized tonic-clonic (seizures)
SI	standard international system of units
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment emergent adverse event
TLF	Table, Listing and Figure

Abbreviation	Description
ULN	upper limits of normal
VAS	visual analogue scale
VNS	vagal nerve stimulator
WHO	World Health Organization

2 PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are completely specified and appropriate to allow valid conclusions regarding the study objectives.

2.1 Responsibilities

FMD K&L Inc. will perform the statistical analyses and is responsible for the production and quality control of all tables, figures and listings as specified in the SAP. Data Management will be conducted by Numoda, based in Philadelphia, PA. Pharmacokinetic analysis of the study drug will be performed by QPS LLC and NMS, a sub-contractor for ACM will conduct the ConAED PK analysis. The results of ConAED and study drug PK levels will be included in the listing.

2.2 Timings of Analyses

The primary analysis of efficacy, safety, and tolerability is planned after all subjects in Cohort 2 complete the 14-week double-blind (DB) phase of the study. Unless otherwise specified, the analysis includes all DB phase of Cohort 2 data collected in the database through database lock for the DB phase of the study for all subjects randomized.

A follow-up analysis will be conducted when all subjects complete the final visit of the study, which includes a 1-year open-label (OL) phase that follows the 14-week DB phase of the study. Analyses that include data collected after the DB phase database lock from the primary analysis of the study will be issued as an addendum to the study report.

3 STUDY OBJECTIVES

3.1 Primary Objective

To evaluate efficacy of ganaxolone compared to placebo as adjunctive therapy in adults with partial-onset seizures (POS), with or without secondary generalization.

3.2 Secondary Objectives

To evaluate the safety and tolerability of ganaxolone compared to placebo as adjunctive therapy in adults with POS, with or without secondary generalization.

To evaluate pharmacokinetics of ganaxolone at 1200 mg/d and 1800 mg/d after chronic dosing.

To evaluate the safety and tolerability of ganaxolone when administered as adjunctive therapy in adults with POS, with or without secondary generalization, over a 12-month period.

3.3 Brief Description

This is a 2-cohort study with each cohort comprised of 2 phases, a DB phase (Phase 1) followed by an OL phase (Phase 2). Cohort 1 will provide efficacy, tolerability, safety, and PK

information for ganaxolone 1200 mg/d, 1800 mg/d compared to placebo. Cohort 2 will investigate the efficacy, tolerability and safety of ganaxolone 1800 mg/d compared to placebo. Cohort 1 (N = approximately 50) will enroll into a 67-week protocol comprising a 4-week retrospective and 4-week prospective baseline period and 2 treatment phases: a 9-week DB phase followed by a 52-week OL phase. Cohort 2 (N = 292) will enroll into a 76-week study comprising an 8-week prospective baseline period and 2 phases: a 14-week DB phase followed by a 52-week OL phase. In each cohort, the final safety assessment will be conducted 2 weeks following the end of the OL phase.

Baseline seizure activity will be determined by 8 weeks of recording in subject daily seizure calendars. In Cohort 1, the 8 weeks are obtained from a 4-week retrospective baseline period and a 4-week prospective baseline. The baseline for Cohort 2 is an 8-week prospective baseline, though some subjects randomized into Cohort 2, under Protocol version Amendment 2, will have baseline comprised of 4 weeks retrospective and 4 weeks prospective data. After completing the 8-week baseline period, eligible subjects will be randomized to receive either ganaxolone or placebo.

Cohort 1, Phase 1 of treatment includes a 9-week DB placebo-controlled phase to evaluate oral study medication as add-on therapy in adults with epilepsy consisting of POS, with or without secondary generalization. Study subjects will be randomized to one of the 2 study treatment arms: ganaxolone (1200 mg/day (mg/d) followed by 1800 mg/d), or placebo. Phase 1 (DB phase) is comprised of a Baseline period (8 weeks; 4 weeks retrospective and 4 weeks prospective seizure calendar data to be used for baseline assessment), followed by 2 treatment periods: Titration (1 week; step titration up to 1200 mg/d) and Maintenance (8 weeks; 4 weeks on 1200 mg/d followed by 4 weeks on 1800 mg/d).

Between DB (Phase 1) and OL (Phase 2) study phases, Cohort 1 has a 1-week, double-blinded, step transition for placebo subjects to 900 mg/d followed by 1800 mg/d while ganaxolone subjects are maintained on their current dose. For the purpose of entering dosing information on the eCRFs, the sites are instructed to assume that all patients transitioning to the OL phase are on placebo and will enter dose-escalation information accordingly. After unblinding K&L will correct the actual dosing, and the patients who were on ganaxolone during the DB phase will be changed to have received 1800 mg/day during the transition period.

Cohort 1, Phase 2 is the OL phase, consisting of 2 treatment phases: Flexible Dosing (51-week flexible dosing during which time the dose may be adjusted based on efficacy and tolerability guidelines), and De-escalation (2 weeks, at study termination). Subjects discontinued during the study will be de-escalated over 2 weeks based on dose, duration, and tolerability in the opinion of the investigator.

Cohort 2, Phase 1 of treatment includes a 14-week DB phase placebo-controlled treatment period to evaluate oral study medication as add-on therapy in adults with epilepsy consisting of POS, with or without secondary generalization. Study subjects will be randomized to one of the 2 study treatment arms: ganaxolone at 1800 mg/d or placebo. Phase 1 (DB phase) is comprised of a Baseline period (8 weeks), followed by 2 treatment periods: Titration (2 weeks up to 1800 mg/d) and Maintenance (12 weeks on 1800 mg/d). Subjects entered into Cohort 2, under

Protocol Amendment 2, will have a baseline assessment based on 4 weeks retrospective and 4 weeks prospective seizure data.

Between the study phases, Cohort 2 has a 2-week, blinded, step transition for placebo subjects to ganaxolone, starting at 900 mg/d to 1800 mg/d, while ganaxolone subjects are maintained on their current dose. For the purpose of entering dosing information on the eCRFs, the sites are instructed to assume that all patients transitioning to the OL phase are on placebo and will enter dose-escalation information accordingly. After unblinding K&L will correct the actual dosing, and the patients who were on ganaxolone during the DB phase will be changed to have received 1800 mg/day during the transition period.

Cohort 2, Phase 2 is the OL Phase consisting of 2 treatment periods: Flexible Dosing (50-week flexible dosing during which time the dose may be adjusted between 900 – 1800 mg/day based on efficacy and tolerability), and De-escalation (2 weeks, at study termination). Subjects discontinued during study will be de-escalated over 2 weeks based on dose, duration, and tolerability in the opinion of the investigator.

At all dose levels, ganaxolone capsules or matching placebo will be administered BID in divided doses. Subjects will maintain seizure calendars to record the number and type of seizures throughout the entire study. Subjects will also record concomitant medications and any errors in study medication dosing in their seizure calendars.

A graphic representation of the design of this study is provided in SAP Section 3.8, Figure 1 and Figure 2.

3.4 Subject Selection

The study will randomize approximately 50 subjects into Cohort 1 and approximately 356 subjects into Cohort 2 at a 1:1 ratio of ganaxolone to placebo. It is estimated that approximately 320 subjects will complete the 14-week DB Phase of Cohort 2, which assumes approximately 10% discontinuation rate.

3.4.1 Inclusion Criteria

Subjects must meet all inclusion criteria to be eligible for entry in the study. The option for re-screening of subjects who do not meet all criteria must be discussed with the medical monitor.

1. Able to give informed consent in writing, or have a legally authorized representative able to do so, after being properly informed of the nature and risks of the study and prior to engaging in any study-related procedures.
2. Willing to enter and participate for the full term of either the 9 or 14-week DB phase and willing to enter into the 52-week OL phase.
3. Male or female outpatients ≥18 years of age at time of consent.
4. Have a confident diagnosis of drug-resistant epilepsy with POS with or without secondary generalization (classified according to International League Against Epilepsy Guidelines [Guy, 1981] and as determined by secondary review by the Epilepsy Consortium) for ≥2 years and is having POS, with or without secondary generalization despite having been treated in the past with ≥2 approved anti-epilepsy drugs (AEDs) either alone or in

combination at adequate doses for a sufficient length of time in the opinion of the investigator. Diagnosis should have been established by clinical history, electroencephalogram (EEG) or video EEG with results consistent with partial-onset epilepsy, and computerized tomography (CT) or magnetic resonance imaging (MRI) of the brain to rule out progressive structural lesions within the last 10 years.

5. Based on documented history of POS, the investigator judges that the subject is likely to have 3 or more POS*, with or without secondary generalization, during any 4-week period prior to study treatment, i.e, rarely falls below that threshold with usual fluctuations. Further, the pattern of seizures makes it unlikely the subject will have 21 seizure-free days in any 4-week period prior to study treatment.

   * POS includes complex partial seizures [CPS], and simple partial seizures [SPS] with motor expression. Partial seizures may be seizures secondarily generalized [SGTC]. Subjects who only have simple partial seizures without any observable motor component will NOT be eligible to participate in this study.
6. Currently being treated and maintained with a stable regimen of 1, 2, or 3 AEDs for ≥1 month prior to the screening visit, without a foreseeable change in dosing for the duration of the DB phase of the study.

Barbituates: If the subject is taking barbiturates (e.g, phenobarbital), the dose of the barbiturate must have been stable for ≥3 months prior to the screening visit.

Vagus Nerve Stimulator (VNS): VNS will not be counted towards the number of concomitant AEDs. Subjects with surgically implanted VNS will be allowed to enter the study provided that all of the following conditions are met:

- The VNS has been in place for ≥1 year prior to the screening visit
- The settings must have remained constant for ≥3 months prior to the screening visit and remain constant throughout the study
- The battery is expected to last for the duration of DB Phase 1 (9 or 14 weeks) of the study

Benzodiazepines: The chronic use of a benzodiazepine as a concurrent AED is permitted as long as the dose has been stable for ≥1 month prior to the screening visit and remains constant throughout the study. See Protocol Section 9.4.10 for use of benzodiazepines for seizure rescue or for other indications.

Felbamate: The use of felbamate is allowed provided that the subject has been maintained on a stable dose of felbamate for greater than 18 months, and has had stable liver function (AST/ALT) and hematology during the course of treatment, and is expected to remain constant throughout the study.

Perampanel: The use of perampanel is allowed provided that the subject has been maintained on a stable dose of perampanel for greater than 3 months and has not experienced any serious psychiatric and behavioral reactions such as hostility- and aggression- related adverse reactions.

7. Able and willing to maintain an accurate and complete daily written seizure calendar or has a caregiver who is able and willing to maintain an accurate and complete daily written seizure calendar.
8. Able and willing to take drug with food twice daily. Ganaxolone must be administered with food.
9. Sexually active women of childbearing potential must be using a medically acceptable method of birth control and have a negative qualitative serum β- human chorionic growth

hormone (HCG) pregnancy test from a blood sample collected at the screening visit and negative urine pregnancy tests at baseline line and subsequent visits. A woman of childbearing potential is defined as a female who is biologically capable of becoming pregnant. A medically acceptable method of birth control includes intrauterine devices in place for at least 3 months, surgical sterilization, or adequate barrier methods (e.g, diaphragm and foam). An oral contraceptive alone is not considered adequate for the purpose of this study. Use of oral contraceptives in combination with another method (e.g, a spermicidal cream) is acceptable. In subjects who are not sexually active, abstinence is an acceptable form of birth control and β-HCG will be tested per protocol. Birth control should be continued for a minimum of 3 days after the last dose of study drug.

3.4.2 Exclusion Criteria

1. Have had previous exposure to ganaxolone.
2. Known sensitivity or allergy to any component in the study drug, progesterone, or other related steroid compounds.
3. Exposure to any investigational drug or device less than 30 days prior to screening, or plans to take another investigational drug at any time during the study.
4. Time of onset of epilepsy treatment less than 2 years prior to enrollment.
5. Have generalized epilepsy, such as Lennox-Gastaut syndrome, juvenile myoclonic epilepsy, absence epilepsy, or non-epileptic seizures within the last 12-month period prior to study entry.
6. Have less than 3 POS seizures, with or without secondary generalization, in a 28-day period or more than 21 consecutive seizure-free days during the 8-week baseline period.
7. Have only simple partial seizures without any observable motor component.
8. Have innumerable seizures or status epilepticus within the last 12-months prior to screening.
9. Have more than 100 POS total (complex partial seizures [CPS] only + simple partial seizures [SPS] with motor (both types with or without secondary generalized tonic-clonic seizures [SGTC]) per each 4-week baseline period.
10. Seizures secondary to illicit drug or alcohol use, infection, neoplasm, demyelinating disease, degenerative neurological disease, or central nervous system (CNS) disease deemed progressive, metabolic illness, or progressive degenerative disease.
11. Current use of vigabatrin is not permitted, as well as prior use of vigabatrin without stable visual fields tested twice over the 12 months after the last dose of vigabatrin.
12. Current use of ezogabine (retigabine; Potiga; Trobalt) is not permitted. Subjects who may have used this agent in the past should have been off this medication for at least 3 months prior to screening and should have had a documented normal fundoscopic exam by an ophthalmologist.
13. Are planning surgery, or to be evaluated for surgery, during the 9 or 14-week DB phase to control seizures including those subjects who are considering implantation of a VNS device.
14. Are suffering from acute or progressive neurological disease, moderate or severe psychiatric disease, or severe mental abnormalities that are likely to require changes in pharmacotherapy during the 9 or 14-week DB portion of the study or interfere with the objectives of the study or the ability to adhere to the protocol requirements.
15. Have active suicidal plan/intent, or have had active suicidal thoughts in the past 6 months.

16. Have a history of an actual suicide attempt in the last 5 years or more than 1 lifetime actual suicide attempt as classified by the Columbia-Suicide Severity Rating Scale (C-SSRS).
17. Have a positive urine drug screen at Screening or meet criteria for current or historical Substance Use Disorder (DSM-V criteria) within the past 5 years. As with other AEDs, the use of alcohol is not advised.
18. Have any medical condition that, in the investigator's judgment, is considered to be clinically significant and could potentially affect subject safety or study outcome, including but not limited to: clinically significant cardiac, renal, pulmonary, gastrointestinal, hematologic or hepatic conditions; or a condition that affects the absorption, distribution, metabolism or excretion of drugs.
19. Have Alanine transferase (ALT; SGPT) or Aspartate transferase (AST; SGOT) levels greater than 3 times upper limits of normal (ULN), or total bilirubin greater than 1.5 time ULN at the screening and baseline visits.
20. Have a history of malignancy within the past 2 years, with the exception of basal cell carcinoma.
21. Are currently following or planning to follow a ketogenic diet.
22. Use of dietary supplements or herbal preparations are not permitted if subject has been using them consistently for less than 6 months prior to screening, or does not plan on remaining on stable doses for the duration of the DB phase. Use of St. John's Wort is not permitted (See Protocol Section 9.4.10: Excluded, Prior, and Concomitant Medications).
23. Females who are pregnant, currently breastfeeding or planning to become pregnant during the duration of the study.
24. A history of chronic noncompliance with drug regimens.
25. Inability to withhold grapefruit and grapefruit juice from diet during the entire clinical trial (See Protocol Section 9.4.10: Excluded, Prior, and Concomitant Medications).

3.5 Determination of Sample Size

Using a medium dose (1500 mg/day oral suspension,) the Marinus study 1042-0600 found a mean difference in percentage change in seizure frequency from BL of -19.58%, with a standard deviation of 54.019%. This is equivalent to an effect size of 0.3625. Because a higher dose of ganaxolone (1800 mg/day oral capsule) is used in study 1042-0603, we have assumed an effect size of at least 0.30 can be achieved in Cohort 2. A sample size of 178 in each group has approximately 0.8 power to detect a treatment difference, where the effect size is 0.30, based on Wilcoxon rank sum test with two-sided alpha = 0.05 by using PASS 11 software. Assuming a dropout of 10%, the sample size (160 in each group) will still have a power of approximately 85% to detect an effect size of 0.35. The sample size (178 per group) also provides approximately 88% power when the 50% responder rates are assumed to be 26% for ganaxolone and 13% for placebo, and a large 2 sample Z test is used with the two-sided alpha of 0.05.

3.6 Treatment Assignment & Blinding

Subjects will be randomized to receive ganaxolone or placebo during Phase 1 in a 1:1 ratio by the interactive web response system (IWRS) system. Randomization for Cohort 2 will be stratified by country.

All study medication will be provided as identically appearing gelatin capsules. The contents of each bottle will be blinded using labels that contain a unique bottle number and a manuracturing lot code. The randomization schedule will match a subject number to a bottle number. Upon completion of the 8 week baseline evaluations for each subject, the Investigator, or appropriate designee, will log into the IWRS to randomize the subject to the study drug assignment and receive bottle numbers. The designated personnel at the clinical site will match the assigned bottle numbers with the correct bottles of investigational product and distribute the bottle to the Investigator or designee. Only the investigational product supplier will be unblinded to the bottle number and the contents of each bottle of investigational product. An unblinded representative of the manufacturer will have access to the manufacturing lot codes for active and placebo.

3.7 Administration of Study Medication

All study medication will be provided as identically appearing white/opaque gelatin capsules. Study drug will be packaged in bottles. Ganaxolone or placebo capsules will be administered 2 times daily (BID), following the morning and evening meals. No study-related tests or treatments, including screening, will be conducted before the subject has signed the Informed Consent Form.

3.8 Study Procedures and Flowchart

Figure 1. Cohort 1 Trial Design

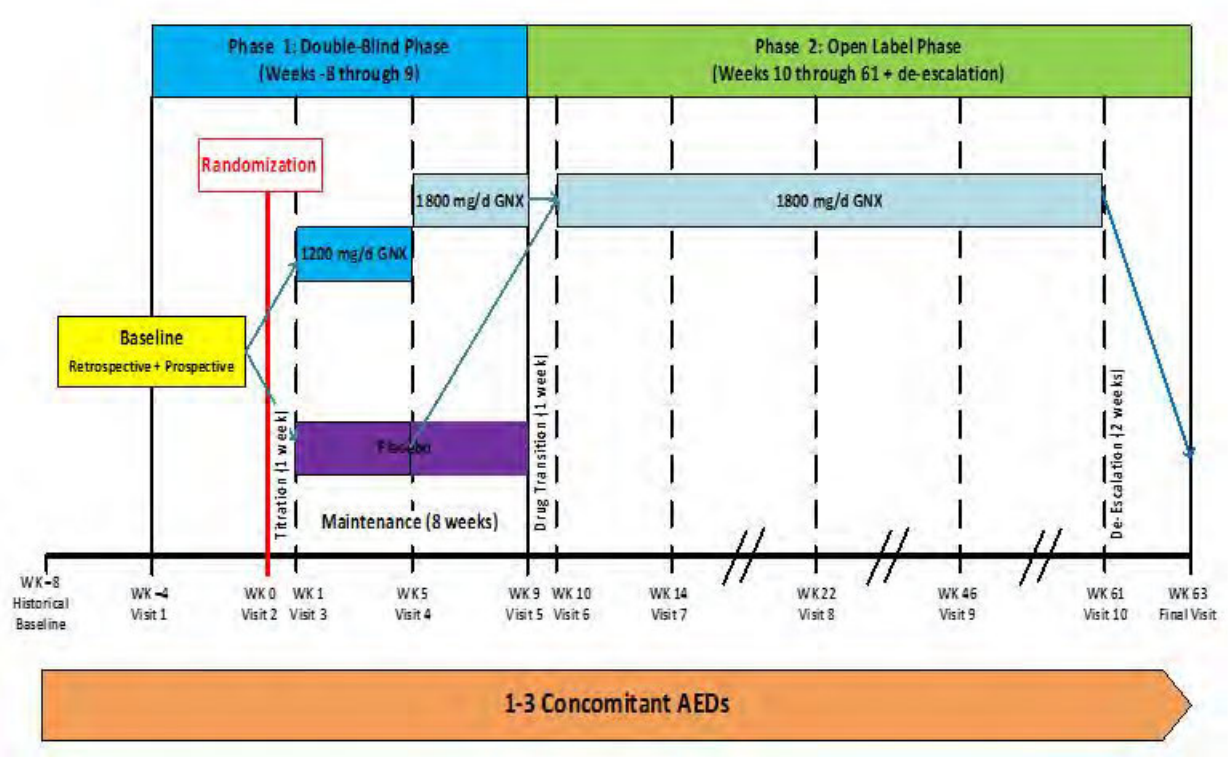
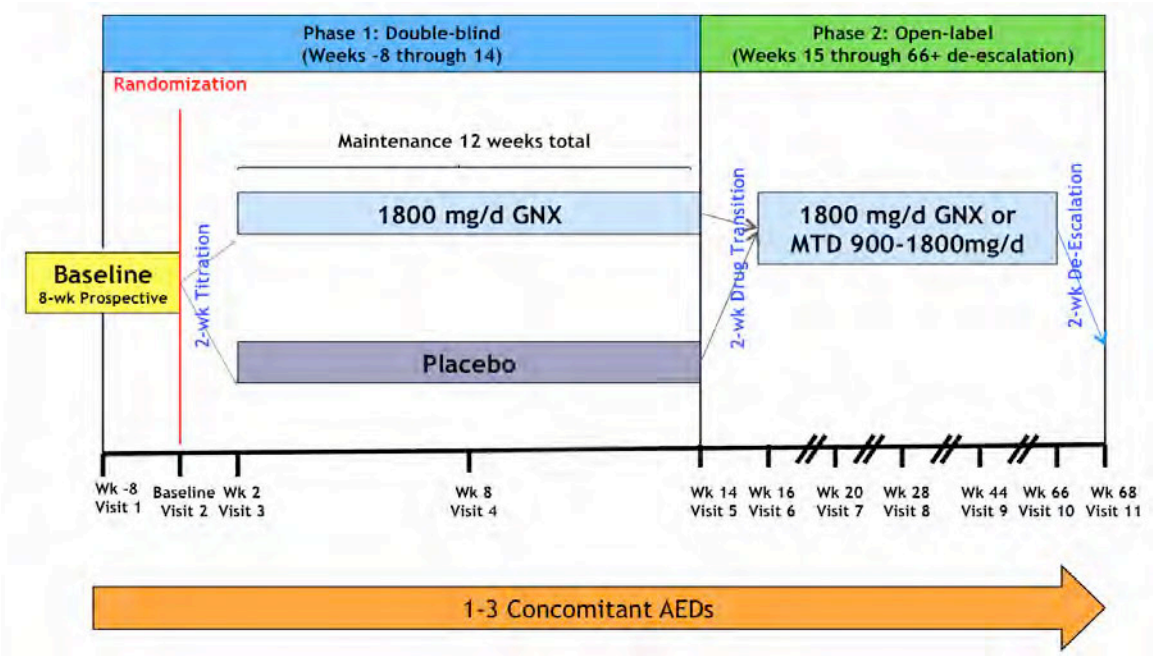


Figure 2. Cohort 2 Trial Design



See Appendix 1: Schedule of Events in the protocol for detailed information regarding the timing of all assessments.

4 ENDPOINTS

4.1 Primary Efficacy Endpoint

The primary efficacy endpoint for US Food and Drug Administration registration is the percent change in the 28-day seizure frequency (POS with or without secondary generalization) from baseline to the DB phase for Cohort 2. Frequency of POS, with or without secondary generalization, for primary and secondary efficacy endpoints only includes 3 seizure subtypes that are SPS-motor, CPS and SGTC. Per patient 28-day seizure frequency will be based on the number of seizures in the Cohort 2 14-week titration + maintenance period of the DB Phase, relative to the 8- week prospective baseline period of the Cohort 2 DB Phase, per 28 days. It will be calculated as the number of seizures over the time interval divided by the number of days with available seizure data in the interval and multiplied by 28 to obtain both the baseline 28-day seizure frequency and the post-baseline 28-day seizure frequency.

The primary efficacy endpoint for European Medicines Agency registration is 50% responder rate during the maintenance treatment period of the DB phase for Cohort 2. A 50% responder is an individual who experiences at least a 50% decrease in seizure frequency compared to baseline. This end-point is analysed independently of the US registration end-point. The key-secondary end-point analysis (below) is not predicated on the results of this end-point.

4.2 Secondary Efficacy Endpoints

Key Secondary Endpoints:

The 3 key secondary endpoints will be tested using a fixed sequence procedure to protect the familywise error rate at 0.05. If the primary outcome measure is statistically significant, the p-values of the secondary measures will be examined in the order listed below. The process stops at the first p-value above 0.05.

- Responder rate (experiencing a ≥50% reduction) during the titration + maintenance treatment periods of the DB phase for Cohort 2
- Change in the number of seizure free days per 28-day period from baseline during the titration + maintenance treatment periods of the DB phase for Cohort 2
- Clinical Global Impression of Change – Improvement (CGI-I; Investigator) at Week 14 of the double blind treatment phase relative to the baseline for Cohort 2

All remaining secondary efficacy endpoints listed in the protocol will be tested at alpha =.05 so all p-values are nominal.

Secondary efficacy outcome measures are listed below.

a) Percent change in the 28-day seizure frequency from baseline to the DB phase during the maintenance treatment period for Cohort 2
b) Change from baseline in 28-day seizure frequency during the DB phase for Cohort 2 (titration + maintenance and maintenance only).
c) Change in the number of seizure free days per 28-day period from baseline during the maintenance treatment period of the DB phase for Cohort 2
d) Proportion of responders experiencing a ≥R% reduction from baseline to the end of treatment period in 28-day seizure frequency (titration + maintenance and maintenance only) for Cohort 2. R% will be 20%, 40%, 60%, and 80%
e) Proportion of subjects who completed the DB portion of the study (Cohort 2) and did not experience any seizures during the maintenance phase of the study
f) Proportion of subjects who experienced at least one 28-day seizure free period during the DB phase of the study (titration + maintenance) for Cohort 2
g) Longest period of time seizure free (%) (longest period of seizure free days divided by number of days with available seizure data) during the double blind phase (titration + maintenance) for Cohort 2
h) Change from baseline in 28-day seizure frequency for different subtypes of seizures during the DB portion of the study (titration + maintenance) for Cohort 2 (SPS, SPS-motor, CPS, SGTC)
i) Patient Global Impression of Change – Improvement (PGI-I; Patient/Caregiver) at each assessment visit
j) Clinical Global Impression of Change – Improvement (CGI-I; Investigator) at each assessment visit

Exploratory endpoint

[redacted] except that the primary endpoint and 50% responder rate will be analyzed the same way as in Cohort 2.

The other primary and secondary efficacy outcome measures will be assessed descriptively for each of the time periods listed below in Cohort 1 DB phase ([a-e] below) and Cohort 1+Cohort 2 OL ([f below]):

a) Ganaxolone Titration + Maintenance 1200 mg/day + Maintenanace 1800 mg/day vs Placebo (Cohort 1: Weeks 1 to 9).
a) Ganaxolone Maintenance 1200 mg/day + Maintenanace 1800 mg/day (Cohort 1: Weeks 2-9) vs Placebo (Cohort 1: Weeks 1 to 9).
b) Ganaxolone Titration + Maintenance 1200 mg/d (Cohort 1: Weeks 1-5) vs placebo (Cohort 1: Weeks 1 to 9).
c) Ganaxolone Maintenance 1800 mg/d vs (Cohort 1: Weeks 6-9) placebo (Cohort 1: Weeks 1 to 9).
d) Ganaxolone maintenance 1200 mg/d vs placebo (Cohort 1: Weeks 2 to 5).
e) OL (Cohort 1: Weeks 10 to 61; Cohort 2: Weeks 16 to 66).

4.3 Safety Endpoints

Planned safety assessments include:

- Neurological and physical examinations
- Clinical laboratory tests
- 12-lead ECG
- Vital signs: temperature, blood pressure, pulse rate, respiration rate, height, weight and BMI
- AEs: incidence, frequency, severity, duration, causality, outcome

See Protocol Appendix 1 for a Schedule of Events for timing of safety assessments.

Additional safety outcome measures include those listed below:

- Number of subjects at each dose
- Change from baseline in vital signs (blood pressure, respiration rate and heart rate), body weight and ECG
- Assessment of suicidality via the Columbia Suicide C-SSRS

In addition, tolerability of ganaxolone during the up-titration periods of the study will be compared between the 2 cohorts. Cohort 1 went through a 1-week titration period, followed by a 4-week period at 1200 mg/day, before the start of a 4-week treatment with 1800 mg/day. In comparison, Cohort 2 was treated with a 2-week titration period followed by maintenance treatment with 1800 mg/day. AEs with onset during the titration period in Cohort 2 will be compared to AEs with onset during the weeks 1-5 in Cohort 1 (1 week titration + 4 week treatment with 1200 mg/day). In addition, in Cohort 2, AEs with onset during the titration period will be compared to AEs with onset during the maintenance period. AEs that emerge during the de-escalation period will also be tabulated to investigate whether discontinuation of ganaxolone is associated with withdrawal symptoms.

5 ANALYSIS POPULATIONS

5.1 Randomized Population

All subjects randomized will be used for summaries of subject disposition.

5.2 Safety Population

The safety population includes all randomized subjects who received at least 1 dose of study medication. This population is defined for safety analysis. Subjects will be analyzed based on the actual treatment received. The safety population will be used for all analyses of safety endpoints.

5.3 Modified Intent To Treat Population

The modified intent to treat (MITT) population (full analysis population in protocol) includes all randomized subjects who received at least 1 dose of study medication and provided any post baseline seizure outcome data. The MITT population is the primary population for efficacy analysis. Subjects will be analyzed based on their randomized treatment assignment.

5.4 Per Protocol Population

The per protocol (PP) population includes all MITT subjects who received at least 1 dose of treatment without major protocol violations that would potentially impact efficacy. The PP population is used for supportive efficacy analyses. PP population will be finalized by the study team prior to database lock. Per protocol analysis will be conducted on the primary and key-secondary end-points only.

5.5 Protocol Deviations

Major protocol violations leading to exclusion from the per protocol population will be determined prior to unblinding.

6 GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1 General Methods

- All analyses and summaries will be produced using SAS version 9.2 or above.
- Unless otherwise specified, summaries will be presented by cohort, treatment and overall.
- Continuous variables will be summarized by number of subjects, mean, standard deviation, median, minimum, and maximum.
- Categorical variables will be summarized by counts and percentages.

6.2 Key Definitions

Calculation of Baseline:

For the primary efficacy endpoint(s):

For subjects enrolled under and prior to Amendment 2, baseline will be calculated based upon a combination of 4 weeks of prospective recording in a daily seizure calendar contiguous with 4 weeks of retrospective seizure history (seizure diary) which will be collected after obtaining informed consent. Acceptable retrospective daily seizure data include a diary record of the frequency and type of seizures by day, subjects without acceptable retrospective daily seizure data will not be randomized. After completing the 4-week prospective baseline period, eligible subjects are to be randomized to receive either ganaxolone or placebo.

For subjects enrolled under Amendment 3, baseline will be calculated based upon the 8 weeks prospective recording in a daily seizure calendar, which will be collected after obtaining informed consent.

For subjects still in the study at time of the primary analysis, last dose date will be considered the date of the most recent DB study visit in the database for that subject.

For safety endpoints, non-missing value of last assessment before first dose will be set as baseline value for both Cohort 1 and Cohort 2.

See Tables 1 and 2 in the protocol for details of the dosing regimen for each cohort/phase.

6.3 Missing Data

If a subject has missing seizure count information during the baseline or treatment periods, these days will be not be imputed or considered in the calculation of the seizure frequency (i.e., the seizure frequency will be computed only over the non-missing days of the period).

If a subject withdraws from the study before the end of the treatment period, the seizure information collected up until the time of withdrawal will be used to calculate the seizure frequency over the treatment period.

However, a set of sensitivity analyses will conducted as outlined below to understand the impact of missing data due to subject withdrawal from the study.

Imputation of Missing Diary Seizure Frequency Data

The imputation process consists of a sequence of multiple imputation (MI) steps, with each step imputing missing values at one time-point only. The approach differentiates those who withdrew for treatment-related reasons (lack of efficacy or adverse events) and those who withdrew for other reasons (e.g. withdrawal of consent due to a move).

A. Dropout Reason-based Multiple Imputation (DRMI)

The not missing at random (NMAR) model assumes that observed data obtained from the pre-specified subset of withdrawn GNX subjects who dropped out for treatment-related reasons are correlated with unobserved future visits similar to subjects in the placebo arm. This is equivalent to assuming that the unobserved trajectory of patients in the GNX arm is similar to that of the placebo subjects. Treatment related reasons include AEs, death and insufficient clinical response.

B. Dropout Missing at Random Imputation (MAR)

The missing data of the remaining GNX patients who have dropped out (due to non-treatment-related reasons) are imputed assuming MAR. Missing data for placebo patients who withdrew for any reason will always be imputed based on placebo diary seizure frequency data.

A summary of reasons for patients withdrawing from the GNX treatment arm and the corresponding treatment arm used to calculate the imputation of diary seizure frequency data under DRMI will be populated after the blind is broken as shown in the Table below.

The MNAR imputation is achieved by using prior data and previously imputed values at each stage of the imputation. Imputation will be carried out in two steps; first, the non-monotone (intermediate—having a previous and subsequent observation) missing seizure frequencies will be imputed based on a Markov chain Monte Carlo (MCMC) method using SAS PROC MI. Next, missing values in each period will be imputed using a sequential regression method using MONOTONE REG option of SAS PROC MI. The lengths of the period will be two weeks.

For example, to impute missing values in a two week period ending at time t for subjects in the GNX arms who dropped out due to one of treatment related reasons, placebo observations up to and including time t and observations from subjects in the GNX arms who dropped out due to one of the treatment related reasons, up to and including time t-1 will be used to develop the model. This is repeated sequentially for each bi-weekly time period using observed data and previously imputed values in the new model.

Ten replicate study imputations will be carried out using a seed of 123456. The analysis of each of the imputed dataset will be based on rank ANCOVA, the analytical method described in the Section 8.1 of the primary analysis; these imputations will be combined using Rubin's formula implemented in the SAS procedure PROC MIANALYZE.

Reason for withdrawal	**DRMI**
Adverse Event	Placebo
Insuff. clinical response	Placebo
Death	Placebo
Non-compliance or Protocol Violation	GNX
Ineligible Per Inclusion/Exclusion Criteria	GNX
Lost to follow up	GNX
Withdrawal of Consent By Subject	GNX
Other	GNX

6.4 Visit Windows

Subjects must have a minimum of 28 days of prospective baseline seizure charting. Visit windows are time intervals between the mid-points of 2 consecutive scheduled visits for Phase 1 DB and Phase 2 OL (Visits 2- Post taper Safety Follow up) .

6.5 Pooling of Centers

Sites will be pooled as follows: US sites and Rest of the World sites, for the analysis of the primary and secondary efficacy endpoints.

7 DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1 Subject Disposition and Withdrawals

The disposition table will include the number of subjects present at each phase, and discontinued along with the reason for discontinuation. Data will be summarized by cohort, treatment, phase, and period, as appropriate.

Additionally, duration in study will be summarized.

7.2 Demographic and Other Baseline Characteristics

Subject demographic data (age, gender, race, and ethnicity), height, weight and body mass index (BMI) will be collected at study screening and will be summarized by using descriptive statistics by cohort and overall.

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)

7.3 Medical History

Medical history will be listed. The medical history conditions will be summarized for each of the 4 periods within the 2 phases and cohorts combinations by treatment group and overall using frequencies and percentages on the body system levels and preferred term. Medical history will be sorted alphabetically by body system and preferred term. Medical history terms were coded using MedDRA version 16.0.

7.4 Epilepsy History

Epilepsy history will be documented via eCRF at screening and includes the following information: age in years and in months at first seizure, followed by the family history(Y/N) in first degree relatives (parent, sibling, and child). For each 'Y', the following are collected: seizure type (if applicable and known), IQ (with date), Neurological Dysfunction. Additionally, seizure calendars will be collected at the each visit and includes the following: date and type for each seizure. These data will be summarized via appropriate summary statistics (see Section 6.1), and will be listed. Percentage of patients with VNS will be summarized.

7.5 Medication

Subjects participating in the study must be taking 1-3 AEDs in addition to the investigational medication. Marketed medications indicated for the treatment of partial seizures are acceptable with the exceptions noted below:

Vigabatrin: Current use of vigabatrin (Sabril) is not permitted for the duration of the study due to its ophthalmologic toxicity, as well as prior use of vigabatrin without stable visual fields tested twice over the 12 months after the last dose of vigabatrin.

Ezogabine (retigabine; Potiga; Trobalt): Current use of ezogabine (retigabine) is not permitted. Subjects who may have used this agent in the past should have been off this medication for at least 3 months prior to screening and should have had a documented normal fundoscopic exam by an ophthalmologist.

Perampanel (Fycompa): Perampanel is permitted as a concomitant medication only if the subject has been on a stable dose for at least 3 months prior to screening and has not experienced any serious psychiatric and behavioral reactions and is expected to remain on a constant dose throughout the study.

Felbamate: Felbamate (Felbatol) is permitted as a concomitant medication only if the subject has been on felbamate for at least 18 months and has stable AST/ALTs and hematology laboratory tests and is expected to remain constant throughout the study.

Benzodiazepines: If a subject is taking a benzodiazepine chronically for epilepsy and/or non-epilepsy conditions, it will be counted as 1 of the 3 AEDs and the dose cannot be changed during the study.

Vagal Nerve Stimulator: Subjects receiving treatment with a VNS may be included as long as the VNS has been in place for at least 1 year prior to entry into the study, the VNS battery is not due for replacement during the DB phase (Cohort 1 weeks 1 to 9 and Cohort 2 weeks 1 to 14), and stimulation parameters have been kept constant for 3 months prior to screening. VNS will not be counted as one of the 3 concomitant AEDs.

AED medications will be coded using WHODrug Dictionary (December 2013), and will be summarized by standard medication name and medication class and sorted by descending incidence of standard medication name then alphabetical within medication class. Data listings will be sorted in the same manner.

The following table describes how missing date information regarding AED medications 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

7.5.1 Prior Medication

Prior medications will be summarized by WHO Drug Dictionary (December 2013) standard medication name, cohort, and treatment group. Prior medication will be listed. Prior AED medications will be summarized separately.

A prior medication will be defined as any drug that has a start date before the first dose date of study drug. Any medication that starts on the first dose date of study drug will not be considered prior. Medications with a completely missing start date will be considered prior.

Partial start dates will be used to determine if a medication is prior. Medications with a completely missing start date will be considered prior. If only a start month and year are present, then medications for which the month is before or the same as the first dose month will be

considered prior. If only the start year is present, then medications for which the start year is before or the same as the first dose year will be considered prior.

7.5.2 Concomitant Medication

Concomitant medications will be summarized by WHO Drug Dictionary (December 2013) standard medication name, cohort, treatment phase and treatment group. Concomitant AED medications will be summarized separately. Concomitant medication will be listed.

Concomitant medications will be defined as any drug that has a start date on or after the first dose date of study drug. A medication that starts prior to first dose and stops after first dose will be considered as both Prior and Concomitant medications. Medications with a completely missing end date will be considered concomitant.

8 EFFICACY

8.1 Primary Efficacy Endpoint and Analysis

The primary efficacy endpoint for US FDA registration is the percent change in 28-day seizure frequency (POS with or without secondary generalization) in Cohort 2 DB phase (14-week titration + maintenance treatment periods) relative to the baseline in the MITTP, frequency of POS seizures only includes 3 seizure subtypes which are SPS-motor, CPS and SGTC. Post-baseline 28-day seizure frequency will be calculated as the number of seizures in the entire treatment phase divided by the number of days with available seizure data in the treatment phase, multiplied by 28. Baseline 28-day seizure frequency will be calculated as the number of seizures in the baseline period 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 group using descriptive statistics.

The null hypothesis is that there is no difference in the medians between the 2 treatment groups with respect to percent change in seizure frequency.

A rank analysis of covariance (ranked ANCOVA) will be used as primary analysis. A nonparametric rank analysis of covariance will be used to analyze rank of percent change data from baseline, with treatment and pooled center (either US or ROW) as factors and the rank of baseline 28-day seizure frequency as a covariate in the model. The baseline, post-baseline, and percent change from baseline in 28-day seizure frequency will be summarized by treatment group by using descriptive statistics. The 2-sided significance level of 0.05 will be used for comparison. Hodges−Lehmann estimator and 95% confidence interval (CI) for the estimator will be calculated.

An analysis of covariance (ANCOVA) as a sensitivity analysis will be conducted on the rank of percent change data from baseline, with treatment and pooled center (either US or ROW) as factors and the rank of baseline seizure frequency as a covariate. *P*-value to test treatment effect will be determined by permutation test with seed = 123456 and 2000 iterations. To deal with the missing data after subjects dropout, the multiple imputation method described in Section 6.3 will be utilized to perform additional sensitivity analyses. These analyses provide a robustness assessment of the results.

The MITT population of Cohort 2 is the primary population for efficacy analysis. The PP population of Cohort 2 will be considered as supportive.

There are 2 different types of baselines in the study; Cohort 1 has a baseline composed of 4 weeks retrospective + 4 weeks prospective data collection, while subjects in Cohort 2, randomized under protocol amendment 3, has a baseline composed of 8 weeks of prospective data collection; however subjects randomized under protocol amendment 2 will have baseline data that is collected in the same fashion as Cohort 1 subjects. Summary statistics will be generated by type of baseline to provide information regarding the robustness of the endpoint with respect to the choice of baseline. Wilcoxon rank sum test will be used to test if there is difference between these 2 types of baseline. Hodges−Lehmann estimator and 95% confidence interval (CI) for the estimator will be calculated.

For European (EMA) Registration

The primary efficacy endpoint for EMA registration is 50% responder rate during the maintenance treatment phase of DB phase for Cohort 2. A 50% responder is an individual who experiences at least a 50% decrease in seizure frequency compared to baseline. This end-point is analysed independently of the FDA registration end-point, and analysis of the key secondary end-points (below) is not predicated on the results of this end-point.

The responder rates between ganaxolone and placebo will be compared using a logistic regression model, with terms for treatment, pooled center (either US or ROW), and baseline 28-day seizure frequency in the model. The number and percentage of responders will be summarized by treatment, odds ratio and associated 95% confidence interval and p-values will be reported.

8.2 Secondary, Exploratory Efficacy Endpoints and Analyses

Key Secondary Endpoints:

The 3 endpoints immediately following this paragraph will be tested by using a fixed sequence procedure to protect the familywise error rate at 0.05. If the primary outcome measure is statistically significant, the p-values of the secondary measures will be examined in the order listed below. The process stops at the first p-value above 0.05.

- Responder rate (experiencing a ≥ 50% reduction) during the titration + maintenance treatment periods of the DB phase for Cohort 2
- Change in the number of seizure free days per 28-day period from baseline during the titration + maintenance treatment phases of the DB phase for Cohort 2

Clinical Global Impression of Change – Improvement (CGI-I; Investigator) at Week 14 of the double blind treatment phase relative to the baseline for Cohort 2. All remaining secondary efficacy endpoints listed in the protocol will be tested at alpha =.05 so all p-values are nominal.

Secondary efficacy outcome measures are listed below.

a) Percent change in the 28-day seizure frequency from baseline to the DB phase during the maintenance treatment phase for Cohort 2
b) Change from baseline in 28-day seizure frequency during the DB phase for Cohort 2 (titration + maintenance and maintenance only)
c) Change in the number of seizure free days per 28-day period from baseline during the maintenance treatment phase of the DB phase for Cohort 2
d) Proportion of responders experiencing a ≥R% reduction from baseline to the end of treatment period in 28-day seizure frequency (titration + maintenance and maintenance only) for Cohort 2. R% will be 20%, 40%, 60%, and 80%
e) Proportion of subjects who completed the DB portion of the study (Cohort 2) and did not experience any seizures during the maintenance phase of the study
f) Proportion of subjects who experienced at least one 28-day seizure free period during the DB phase of the study (titration + maintenance) for Cohort 2
g) Longest period of time seizure free (%) (longest period of seizure free days divided by number of days with available seizure data) during the double blind phase (titration + maintenance) for Cohort 2
h) Change from baseline in 28-day seizure frequency for different subtypes of seizures during the DB portion of the study (titration + maintenance) for Cohort 2 (SPS, SPS-motor, CPS, SGTC)
i) Patient Global Impression of Change – Improvement (PGI-I; Patient/Caregiver) at each assessment visit
j) Clinical Global Impression of Change – Improvement (CGI-I; Investigator) at each assessment visit

Exploratory endpoint

[redacted]

[redacted] except that the primary endpoint and 50% responder rate will be analyzed the same way as in Cohort 2.

The other primary and secondary efficacy outcome measures will be assessed descriptively for the time periods listed below in Cohort 1 DB phase ([a-e] below) and Cohort 1 + Cohort 2 OL ([f below]):

a) Ganaxolone Titration + Maintenance 1200 mg/day + Maintenanace 1800 mg/day vs Placebo (Cohort 1: Weeks 1 to 9).

b) Ganaxolone Maintenance 1200 mg/day + Maintenanace 1800 mg/day (Cohort 1: Weeks 2-9) vs Placebo (Cohort 1: Weeks 1 to 9).
c) Ganaxolone Titration + Maintenance 1200 mg/d (Cohort 1: Weeks 1-5) vs placebo (Cohort 1: Weeks 1 to 9).
d) Ganaxolone Maintenance 1800 mg/d (Cohort 1: Weeks 6-9) vs placebo (Cohort 1: Weeks 1 to 9).
e) Ganaxolone maintenance 1200 mg/d vs placebo (Cohort 1: Weeks 2 to 5).
f) OL (Cohort 1: Weeks 10 to 61; Cohort 2: Weeks 16 to 66).

8.2.2 Change from Baseline in 28-day Seizure Frequency and Change from Baseline in 28-day Seizure Frequency for different subtypes of seizures (SPS, SPS-motor, CPS, SGTC)

A rank analysis of covariance (ranked ANCOVA) will be performed. A nonparametric rank analysis of covariance will be used to analyze rank of change from baseline in 28-day seizure frequency, with treatment and pooled center (either US or ROW) as factors and the rank of baseline 28-day seizure frequency as a covariate in the model. The baseline, post-baseline, and change from baseline in 28-day seizure frequency will be summarized by treatment group by using descriptive statistics. The 95% confidence interval of the median by treatment group will also be presented. The 2-sided significance level of 0.05 will be used for comparison. Hodges−Lehmann estimator of the difference in medians together with 95% confidence interval (CI) will be calculated.

Summary table with descriptive statistics will be provided in OL phase for Cohort 1,2, and the combined 2 cohorts. The baseline is the same as for the DB phase.

8.2.3 Responder Rate

An R% responder is an individual whose reduction of percent change from baseline in seizure frequency is greater than or equal to R%. R% will 20%, 40%, 60%, 80% for one of the secondary points, and 50% for the first key secondary endpoint.

The responder rates between ganaxolone and placebo will be compared using a Logistic Regression Model, with terms for treatment, pooled center (either US or ROW), and baseline 28-day seizure frequency in the model. The test for treatment effect is a test of whether the

coefficient of the treatment term is equal to zero. The number and percentage of responders will be summarized, odds ratio and associated 95% confidence interval and p-values will be reported.

Summary table with descriptive statistics also will be provided in OL phase for both Cohort 1 and Cohort 2, the baseline is the same as for the DB phase.

Summary table of subjects by treatment in each following category for each phase and each cohort will be provided, the cut off of reduction of percent change from baseline will be classified in the following categories: ≤0%, ≤20%, ≤40%, ≤60%, ≤80%, and ≤100% in the summary table, and the corresponding graph will be displayed also.

8.2.4 Change in the Number of Seizure Free Days per 28-day Period from Baseline

Post-baseline number of seizure free days per 28-day period will be calculated as: (the number of seizure free days in the maintenance treatment period during the double blind phase) divided by the number of days with available seizure data in the treatment phase and multiplied by 28.

Baseline number of seizure free days per 28-day period will be calculated as: the number of seizure free days in the entire baseline phase divided by the number of days with available seizure data in the baseline phase, multiplied by 28.

The calculation of change in number of seizure free days per 28-day period from baseline will be done as follows for each subject:

Post-baseline number of seizure free days per 28-day period – Baseline number of seizure free days per 28-day period.

Change in number of seizure free days between ganaxolone and placebo will be analyzed using a rank ANCOVA, with treatment and pooled center (either US or ROW) as factors and the rank of baseline number of seizure free days per 28-day period as a covariate in the model. The baseline, post-baseline, and change in number of seizure free days per 28-day period from baseline will be summarized by using descriptive statistics. The 95% confidence interval of the median by treatment group will be presented also. The 2-sided significance level of 0.05 will be used for comparison. Hodges−Lehmann estimator of the difference in medians together with 95% confidence interval (CI) will be calculated.

Summary table with descriptive statistics also will be provided in OL phase for both Cohort 1 and Cohort 2, the baseline is same as DB phase.

8.2.5 Proportion of Seizure Free Subjects

Proportion of subjects who completed the DB portion of the study and did not experience any seizures during the maintenance period of the study, and proportion of subjects who experienced at least one 28-day seizure free period anytime during the DB phase of the study (titration + maintenance) will be calculated.

A frequency table will summarize the responses for each treatment in DB phase for Cohort 1 and Cohort 2. The proportions of seizure free subjects between treatment groups will be compared

using a Logistic Regression Model, with terms for treatment, pooled center (either US or ROW) and baseline number of seizure free days per 28-day period in the model. The numbers and percentage of seizure free subjects will be summarized descriptively. The test for treatment effect is a test of whether the coefficient of the treatment term is equal to zero. The odds ratio and its associated 95% confidence interval and p-value according to the Logistic Regression Model will be reported.

Summary table with descriptive statistics also will be provided in OL phase in both Cohort 1 and Cohort 2.

8.2.6 Longest period of time seizure free (%)

Longest period of time seizure-free is defined as the percent of the longest seizure free period days divided by the days with available seizure data during double blind phase for Cohort 2 (titration + maintenance), and then multiplied by 100%.

The longest period of time seizure-free will be summarized by treatment group by using descriptive statistics. The 95% confidence interval of the median by treatment group will be presented also.

In addition, a rank analysis of covariance (rank ANCOVA) will be conducted on the longest period of time seizure-free during DB (titration + maintenance), with treatment and pooled center (either US or ROW) as factors and the rank of baseline number of seizure free days per 28-day period as a covariate. The 2-sided significance level of 0.05 will be used for comparison. p-values will be reported. Hodges–Lehmann estimator of the difference in medians together with 95% confidence interval (CI) will be calculated.

8.2.8 Clinical Global Impression of Change

Clinicial Global Impression of Improvement (CGI-I): A 7-point Likert scale completed by the Clinician representing the degree to which the subject's epilepsy symptoms have changed relative to baseline. On the CGI-I, 1 = very much improved and 7 = very much worse.

A frequency table will summarize the responses for each treatment by visit, separately for each cohort in each phase. To take into account the ordinal nature of the response, the Row Mean Score Difference, p-value based on Cochran-Mantel-Haenszel test adjusting for pooled center (either US or ROW) will be reported. Clinical Global Impression data will be listed.

8.2.9 Patient/Caregiver Global Impression of Change

Patient/Caregiver Global Impression of Improvement (PGI-I): A 7-point Likert scale completed by the Patient or Caregiver representing the degree to which the subject's epilepsy symptoms have changed relative to baseline. On the PGI-I, 1 = very much improved and 7 = very much worse.

A frequency table will summarize the responses for each treatment by visit, separately for each cohort in each phase. To take into account the ordinal nature of the response, the Row Mean Score Difference, p-value based on Cochran-Mantel-Haenszel statistics adjusting for pooled center (either US or ROW), will be reported. Patient Global Impression data will be listed.

8.3 Subgroup analysis

8.3.1 Subgroup Analysis of Subjects Stratified by Inducer/ Non-inducer

Efficacy endpoints of subgroup analysis include:

Inducers are subjects who have taken carbamazepine, phenytoin, oxcarbazepine, primidone or phenobarbital.

Non-inducer subjects are subjects who have not taken any one of the above but may have taken topiramate, levetiracetam, lorazepam, valproic acid, zonisamide, pregabalin, lamotrigine, felbamate, clonazepam, lacosamide or gabapentin. The inducers and non-inducers will be identified from the current AED data.

8.3.2 Subgroup Analysis of Seizure Subtypes

Efficacy endpoints of subgroup analysis include:

- Percent change in 28-day seizure frequency from baseline.
- Change in 28-day seizure frequency.

Descriptive statistics for the efficacy endpoints listed above will be produced for the titration+ maintenance period in the DB phase and the OL phase for both Cohort 1 and Cohort 2 by seizure subtype: CPS, SGTC, SPS-motor and SPS (without motor).

8.3.3 Other Subgroup Analyses

Subgroup analyses on age group (<65, ≥65), gender, ethnicity and geographical region will be conducted also. For each of the subgroups, a separate rank ANCOVA model will be fitted using the same model terms as used for the primary analysis, with additional terms for the subgroup main effect and the treatment by subgroup interaction. The p value to test if the treatment by subgroup interaction is 0 will be presented. Similar output will be displayed for each subgroup as for the primary analysis in Cohort 2. Descriptive summaries only will be displayed for all subgroup analyses in Cohort 1.

Results (Hodge-Lehman estimator and its 95% CI) for all subgroups will be presented in tabular form and forest plots.

9 SAFETY

The population used for safety analyses will be the Safety Population (SP).

9.1 Extent of Exposure

Exposure information will be calculated from the study drug log. Capsule level accountability is not being collected, so 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. Doses should be taken just before or up to 2 hours after a meal or snack, with 240 mL (8 oz.) of water. Each dose should be separated by a minimum of 8 hours and a maximum of 12 hours. 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. Exposure data will be summarized using the Safety population for both cohorts.

See tables below for the titration schedules for the transition from DB to OL for both cohorts:

Cohort 1, Phase 2 - Open-Label					
DB Transition to OL					
				Bottle A 225 mg or PBO cap/day	**Bottle B 225 mg or PBO cap/day**
		Dose (mg)/day		**GNX: 225mg**	**GNX: 225mg**
Visit	**Study Day**	**GNX/GNX**	**PBO/PBO**	**PBO: 225mg**	**PBO: PBO**
Visit 5	64	1800	900	4	4
	65	1800	900	4	4
	66	1800	1350	6	2
	67	1800	1350	6	2
	68	1800	1350	6	2
	69	1800	1800	8	0
	70	1800	1800	8	0

Cohort 2, Phase 2 - Open-Label					
DB Transition to OL					
				Bottle A 225 mg or PBO cap/day	**Bottle B 225 mg or PBO cap/day**
		Dose (mg)/day		**GNX: 225mg**	**GNX: 225mg**
Visit	**Study Day**	**GNX/GNX**	**PBO/PBO**	**PBO: 225mg**	**PBO: PBO**
Visit 5	99	1800	450	2	6
	100	1800	450	2	6
	101	1800	450	2	6
	102	1800	900	4	4
	103	1800	900	4	4
	104	1800	900	4	4
	105	1800	1350	6	2
	106	1800	1350	6	2
	107	1800	1350	6	2
	108	1800	1350	6	2
	109	1800	1800	8	0
	110	1800	1800	8	0
	111	1800	1800	8	0
	112	1800	1800	8	0

These schedules will be used to calculate the exposure for placebo subjects.

Exposure to study medication and cumulative number of days on study medication will be summarized in the DB phase and OL phase for both Cohort 1 and Cohort 2. A summary table of overall exposure to study medication combining the DB phase with OL phase in both Cohort 1

and Cohort 2 will be provided. Ganaxolone group in Cohort 1 will be separated into 2 groups by dose level which are Ganaxolone 1200 mg and Ganaxolone 1800 mg.

A summary table of subjects who reached and maintained maintenance dose of 1800 mg will be provided in each treatment phase for both cohorts. Study drug dosing will be listed.

9.2 Treatment Compliance

A record of all investigational products used will be maintained at each clinical site. This record will include the date the investigational product is dispensed to a subject, initials of the individual dispensing investigational product, quantity dispensed (by unit and strength), the date unused investigational product and empty investigational product containers are returned from the subject, and the quantity returned during Visits 3 through 10 and final post-taper safety assessment. Investigational product and associated accountability forms that are maintained at the clinical site will be present for review by Clinical Research Monitors at each monitoring visit.

At each visit all subjects will receive monthly Subject Seizure Calendars. Each day subjects are to record administration of study drug and background AEDs on the Seizure Calendar.

Compliance with study drug treatment will be assessed by inspecting the Subjects'.

Seizure Calendars and returned supplies with queries as necessary. The Study Drug compliance is a variable in the database calculated using the following formula: (Stop date-Start date) + 1-number of day's drug not taken divided by (Stop date-Start Date) + 1 multiplied 100. This value is calculated for visits 3, 5, 7, 9, 10, 12, 15, and 16. If value is not calculated, a reason should be provided. Per protocol, compliance with background AED medication will be accessed using data from the PK analysis of the AED medication, per SAP Section 2.1 this should be described and issued under a separate analysis plan.

Study treatment compliance will be summarized in DB phase and OL phase for both Cohort 1 and Cohort 2. The ganaxolone group in Cohort 1 will be separated into 2 groups by dose level which are Ganaxolone 1200 mg and Ganaxolone 1800 mg. Study treatment compliance will be listed.

9.3 Adverse Events

The summary of AEs (or SAEs) will be limited to treatment emergent adverse events (TEAEs). A TEAE is any AE (or SAE) occurring on or after administration of the first dose of study medication and before the end of study. An existing AE which worsens on or after administration of the first dose of study medication is also considered a TEAE. AEs will be tabulated by treatment and Overall, system organ class (SOC), and Preferred Term using the MedDRA v.16.0 coding system. The number and percentage of subjects with adverse events will be calculated for each cohort in each phase of the study, by treatment and overall, and in Cohort 1 DB phase, by dose and overall. Additional tables with AEs subset by severity and by relationship to drug as assessed by the investigator will also be presented. Subset listings will be

produced for adverse events that cause withdrawal and for SAEs. Any AE with completely missing start and end dates will be considered a TEAE.

All necessary information about an AE (onset, duration, severity, seriousness, causality to study drug, action taken, and outcome) should be documented by the investigator on the adverse event eCRFs (AE eCRFs). Minimum information required for each AE includes type of event, duration (start and end dates), severity, seriousness, causality to study drug, action taken, and outcome.

Severity of AEs will be graded by the Investigator using the following criteria as guidelines:

1. Mild: Nuisance, barely noticeable.
2. Moderate: Uncomfortable, troublesome symptoms not significantly interfering with daily activities or sleep.
3. Severe: Symptoms significantly interfere with daily activities or sleep.

The relationship of the AE to the study drug should be specified by the Investigator, using the following definitions:

1. Not Related: Concomitant illness, accident or event with no reasonable association with study drug.
2. Unlikely Related: The event has little or no temporal sequence from administration of the study drug, and/or a more likely alternative etiology exists.
3. Possibly Related: The event follows a reasonable temporal sequence from administration of study drug but which could also be explained by concurrent disease or other factors or medications.
4. Probably Related: The event follows a reasonable temporal sequence from administration of study drug, unlikely to be attributed to concurrent disease or other factors or medications. A clinically reasonable response may be observed if the study drug is withdrawn or dose reduced.
5. Definitely Related: The event follows a reasonable temporal sequence from administration of study drug and is definitive pharmacologically; cannot to be attributed to concurrent disease or other factors or medications. A clinically reasonable response should be observed if the study drug is withdrawn or dose reduced.

If discernible at the time of completing an AE eCRF, a specific disease or syndrome rather than individual associated signs and symptoms should be recorded. However, if an observed or reported sign, symptom, or clinically significant laboratory anomaly is not considered by the Investigator to be a component of a specific disease or syndrome, then it should be recorded as a separate AE on the AE eCRF (clinically significant laboratory abnormalities are those that are identified as such by the Investigator and/or those that require intervention).

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose (including overdose) that meets 1 or more of the following criteria:

- Is fatal, as a direct outcome of the AE
- Is life threatening

- Requires or prolongs inpatient hospitalization
- Results in permanent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

Any SAEs, including death due to any cause, which occurs to any subject who has signed Informed Consent (personally or by legally authorized representative) in this study or within 30 days following cessation of the last dose of treatment with the study drug, whether or not considered related to the investigational product, must be reported within 24 hours to the Sponsor or their designee. SAEs that occur more than 30 days after the last dose of study drug and are suspected to be related to study treatment should also be reported. All subjects with SAEs must be followed up for outcome.

Adverse events will be summarized by treatment group and overall for each cohort and phase separately for subjects in the Safety Population. In Cohort 1 tables, AE's will be summarized by treatment, dose level, and overall for subjects in the Safety Population, adverse events of subjects pooled in Cohort 1 and Cohort 2 for each treatment phase will be summarized. The following AE tables will be generated:

- An overall summary of the number and percentage of subjects reporting AEs, serious SAEs, treatment-related AEs, AEs leading to treatment discontinuation and AEs leading to death
- AEs overall and by system organ class and preferred term
- AEs by maximum severity, overall and by system organ class and preferred term
- AEs by relationship to study treatment, overall and by system organ class and preferred term
- AEs with onset (or worsening) during titration + 1200 mg/day dose (weeks 1 to 5) and 1800 mg/d (weeks 6 to 9) by preferred term in Cohort 1 DB phase
- AEs with onset (or worsening) during titration phase and maintenance phase by preferred term in Cohort 2 DB phase
- AEs with onset (or worsening) during the de-escalation phase (time interval between Pre-Taper/Early Termination visit and Post-Taper Safety Follow Up visit) by preferred term in Cohort 1 and 2 OL phase

All AEs, SAEs, AEs leading to drug discontinuation and AEs leading to death will be listed.

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

9.4 Laboratory Evaluations

Laboratory data (including change from baseline) will be summarized using descriptive statistics by treatment and overall for each cohort and phase separately for subjects in the Safety Population. Laboratory data of subjects pooled in Cohort 1 and Cohort 2 for each treatment phase will be summarized. SI units will be used for both summarization and data listings.

Separate summary tables and listings will be produced for each laboratory test group (Hematology, Serum Chemistry, Urinalysis, and other tests: See Protocol Appendix 2: Clinical Laboratory Tests).

Hematology, Serum Chemistry, Urinalysis, and other tests will be summarized for baseline, each visit assessed, and for change from baseline by treatment group using descriptive statistics.

Low, normal, and high classifications will be applied according to the central lab's definitions to determine whether the worst laboratory test value within the visit window was below (low), within (normal), or above (high) its reference range. Shifts from baseline in low/normal/high classification for each parameter will be summarized by treatment group.

If there are multiple records within a visit window the last record will be used for summary tables, all results will be used for tables that assess maximum grade or toxicity, and included in data listings.

9.5 Vital Signs

The actual values of each vital sign and change from baseline will be summarized descriptively at each visit by treatment group and overall for each cohort and phase separately for subjects in the Safety Population. Shifts from baseline in low/normal/high classification for each parameter will be summarized by treatment group. Vital sign of subjects pooled in Cohort 1 and Cohort 2 for each treatment phase will be summarized.

Listings of vital signs with abnormal flags will be provided.

9.6 ECG

The 12-lead ECG parameters including changes from baseline will be summarized using descriptive statistics by treatment and overall for each cohort and phase separately for subjects in the Safety Population. ECG data of subjects pooled in Cohort 1 and Cohort 2 for each treatment phase will be summarized. SI units will be used for both summarization and data listings. The QTc interval will be calculated using Fridericia's formula.

ECG result with Investigator comments will be listed for safety population.

The Investigator may discontinue subjects from the clinical study for any of the following reasons: Post-treatment QTc interval greater than 500 msec or uncorrected QT interval greater than 600 msec; for subjects with bundle branch block, post-treatment QTc greater than 530 msec

based on average QTc value of triplicate ECGs. A subject with a post-treatment increase in QTc of greater than 60 msec from Baseline must also be withdrawn.

If the initial electrocardiogram (ECG) indicates a QTc interval outside of these limits, then 2 additional ECGs should be collected and the average QTc value of these 3 ECGs will be used. If the average values of the triplicate ECGs exceed the stated limits, the subject must be withdrawn.

9.7 Physical and Neurological Examinations

Physical and Neurological examination data will be summarized using descriptive statistics by treatment and overall for each cohort and phase separately, and data of subjects pooled in Cohort 1 and Cohort 2 for each treatment phase will be summarized. Listings for both physical and neurological examinations will be provided.

9.8 Other Safety

Columbia-Suicide Severity Rating Scale data will be summarized and listed for each question each visit by treatment and overall, cohort and study phase for safety population.

Pregnancy test result will be listed.

Urine drug screen test result will be listed.

10 CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

10.1 Primary efficacy analysis will use only Cohort 2 data

Primary efficacy analysis will be done when last subject in Cohort 2 completes the DB Phase of the study. Analyses performed after last subject has completed the entire study, will be considered follow-up analyses.

Rationale:

Amendments to the original protocol changed the baseline seizure frequency from a combination of 4-week retrospective + 4-week prospective to 8-weeks prospective baseline period, which is more consistent with regulatory standards for registration studies, thus the desire to focus on Cohort 2 for the primary efficacy analysis. The OL phase focuses on acquiring more safety data, specifically those that may appear with long term use.

11 REFERENCE LIST

1. Jacqueline AF, et al. (2012) Adjunctive perampanel for refractory partial-onset seizures: Randomized phase III study 304. Neurology 79 August 7, 2012.

2. Hodges J. L., Jr. and Lehmann E. L. (1983). "Hodges-Lehmann Estimators," in *Encyclopedia of Statistical Sciences*, vol. 3, ed. S. Kotz, N. L. Johnson, and C. B. Read, New York: John Wiley & Sons, 463–465.

12 PROGRAMMING CONSIDERATIONS

All tables, data listings, figures (TLFs), and statistical analyses will be generated using SAS® for Windows, Release 9.2 or above (SAS® Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

12.1 General Considerations

- A separate SAS program will be created for each output.
- Each output will be stored in a separate file.
- Output files will be delivered in Word (RTF) format/pdf format.
- Numbering of TLFs will follow ICH E3 guidance.

12.2 Table, Listing, and Figure Format

Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values.

Mock-up's can be found in a separate document.

12.3 Special Consideration Regarding Site 463

Eight subjects participating in the 1042-0603 study in Bulgaria at site 463 ran out of drug supplies during the double-blind phase of the study due insufficient drug supplies available at the European drug depot. Seven of the 8 patients had a break-in dosing up to 21 days and 1 patient lowered her study drug dose in order to sustain the drug supplies until the new supplies arrived. After the supplies arrived at the site the subjects were allowed to re-start or re-titrate the study drug under the same patient identification number and treatment assignment. All 8 patients were re-titrated to 1800-mg/day dose and allowed to complete another 12 weeks of the study. Seven patients have a gap period when they were not receiving the double-blind treatment. The patients continued to record seizures in their diaries during the gap period.

For the statistical analysis these subject's titration periods and maintenance periods will be combined. For example, a subject who had two 2-week titration period, a 4-week maintenance period, a 10-day gap, a 2-week re-titration period, and another 12-week maintenance phase would have a 4-week titration period and a 16-week maintenance period. The 10 day gap without dosing would be counted towards the maintenance phase in keeping with the principles of mITT. All diary data will be included in the mITT analysis irrespective of whether the patient was receiving treatment or whether the patient's treatment was on hold due to lack of drug supplies. All 8 patients will be excluded from the per protocol analysis population. A table explaining the handling of each subject's titration and maintenance phases and the gap is included in the appendix of this document.

13 QUALITY CONTROL

SAS programs are developed to produce clinical trial output such as analysis data sets, summary tables, data listings, figures or statistical analyses.

14 MOCK-UPS

All Mock-ups will be provided in a separate file.

15 APPENDICIES

USUBJID	DOSE	DOSEST	DOSE END	DAYS MISSD	PHASE	TRPHASE	TRPHOTH	PHASSPEC	HARD CODING TO PHASE:
[redacted]	450	[redacted]	[redacted]	0	DB	TITRATION			TITRATION
	900			0	DB	TITRATION			TITRATION
	1350			0	DB	TITRATION			TITRATION
	1800			0	DB	TITRATION			TITRATION
	1800			0	DB	MAINTENANCE			MAINTENANCE
	0			16	DB	OTHER	STUDY DRUG STOPPED BECAUSE OF INSUFFICIENT MEDICATION IN THE SITE	MAINTENANCE	MAINTENANCE
	450			0	DB	OTHER	SECOND UP - TITRATION AFTER STOPPED STUDY DRUG INTAKE	TITRATION	TITRATION
	900			0	DB	OTHER	SECOND UP-TITRATION	TITRATION	TITRATION
	1350			0	DB	OTHER	SECOND UP-TITRATION	TITRATION	TITRATION
	1800			0	DB	OTHER	SECOND UP-TITRATION	TITRATION	TITRATION
	1800			0	DB	MAINTENANCE			MAINTENANCE
	450			0	DB	TITRATION			TITRATION

USUBJID	DOSE	DOSEST	DOSE END	DAYS MISSD	PHASE	TRPHASE	TRPHOTH	PHASSPEC	HARD CODING TO PHASE:
[redacted]		[redacted]	[redacted]						
	900			0	DB	TITRATION			TITRATION
	1350			0	DB	TITRATION			TITRATION
	1800			0	DB	TITRATION			TITRATION
	1800			0	DB	MAINTENANCE			MAINTENANCE
	0			17	DB	OTHER	STOPPED STUDY DRUG INTAKE BECAUSE OF IRREGULAR SUPPLY OF THE SITE	MAINTENANCE	MAINTENANCE
	450			0	DB	OTHER	SECOND TITRATION AFTER UNSUFFICIENT DRUG DELIVERIES.	TITRATION	TITRATION
	900			0	DB	OTHER	SECOND TITRATION AFTER STOPPED STUDYB DRUG INTAKE BECAUSE OF IRREGULAR SUPPLY OF THE SITE	TITRATION	TITRATION
	1350			0	DB	OTHER	SECOND TITRATION AFTER STOPPED STUDY DRUG INTAKE	TITRATION	TITRATION

USUBJID	DOSE	DOSEST	DOSE END	DAYS MISSD	PHASE	TRPHASE	TRPHOTH	PHASSPEC	HARD CODING TO PHASE:
							BECAUSE OF IRREGULAR SUPPLY OF THE SITE		
[redacted]	1800	[redacted]		0	DB	OTHER	SECOND TITRATION AFTER STOPPED STUDY DRUG INTAKE BECAUSE OF IRREGULAR SUPPLY OF THE SITE	TITRATION	TITRATION
	1800			0	DB	MAINTENANCE			MAINTENANCE
	450			0	DB	TITRATION			TITRATION
	900			0	DB	TITRATION			TITRATION
	1350			0	DB	TITRATION			TITRATION
	1800			0	DB	TITRATION			TITRATION
	1800			0	DB	MAINTENANCE			MAINTENANCE
	0			2	DB	OTHER	STUDY DRUG STOPPED BECAUSE OF INSUFFICIENT MEDICATION IN THE SITE	MAINTENANCE	MAINTENANCE
	450			0	DB	OTHER	SECOND UP-TITRATION	TITRATION	TITRATION
	900			0	DB	OTHER	SECOND UP-TITRATION	TITRATION	TITRATION
	1350			0	DB	OTHER	SECOND UP-	TITRATION	TITRATION

USUBJID	DOSE	DOSEST	DOSE END	DAYS MISSD	PHASE	TRPHASE	TRPHOTH	PHASSPEC	HARD CODING TO PHASE:
[redacted]		[redacted]	[redacted]				TITRATION		
	1800			0	DB	OTHER	SECOND UP-TITRATION	TITRATION	TITRATION
	1800			0	DB	MAINTENANCE			MAINTENANCE
	450			0	DB	TITRATION			TITRATION
	900			0	DB	TITRATION			TITRATION
	1350			0	DB	TITRATION			TITRATION
	1800			0	DB	TITRATION			TITRATION
	1800			0	DB	MAINTENANCE			MAINTENANCE
	0			12	DB	OTHER	STUDY DRUG STOPPED BECAUSE OF IRREGULAR SUPPLY OF THE SITE	TITRATION	MAINTENANCE
	1800			0	DB	MAINTENANCE			MAINTENANCE
	1800			0	DB	MAINTENANCE			MAINTENANCE
	450			0	DB	TITRATION			TITRATION
	900			0	DB	TITRATION			TITRATION
	1350			0	DB	TITRATION			TITRATION
	1800			0	DB	TITRATION			TITRATION
	0			21	DB	OTHER	MEDICATION INTAKE STOPPED BECAUSE OF	TITRATION	MAINTENANCE

USUBJID	DOSE	DOSEST	DOSE END	DAYS MISSD	PHASE	TRPHASE	TRPHOTH	PHASSPEC	HARD CODING TO PHASE:
							IRRREGULAR SUPPLY OF THE SITE		
[redacted]	450	[redacted]		0	DB	OTHER	SECOND TITRATION AFTER STOPPING STUDY DRUG INTAKE BECAUSE OF IRREGULAR SUPPLY OF THE SITE	TITRATION	TITRATION
	900			0	DB	OTHER	SECOND TITRATION AFTER STOPPED STUDY DRUG INTAKE	TITRATION	TITRATION
	1350			0	DB	OTHER	SECOND TITRATION AFTER STOPPED MEDICATION INTAKE	TITRATION	TITRATION
	1800			0	DB	OTHER	NEW TITRATION AFTER STOPPED MEDICATION INTAKE BECAUSE OF IRREGULAR SUPPLY OF THE SITE	TITRATION	TITRATION
	1800			0	DB	MAINTENANCE			MAINTENANCE

USUBJID	DOSE	DOSEST	DOSE END	DAYS MISSD	PHASE	TRPHASE	TRPHOTH	PHASSPEC	HARD CODING TO PHASE:
[redacted]	450	[redacted]	[redacted]	0	DB	TITRATION			TITRATION
	1350			0	DB	TITRATION			TITRATION
	1800			0	DB	TITRATION			TITRATION
	0			18	DB	OTHER	STUDY DRUG STOPPED BECAUSE OF IRREGULAR SUPPLY OF THE SITE	MAINTENANCE	MAINTENANCE
	450			0	DB	OTHER	SECOND TITRATION BECAUSE OF INTERRUPED STUDY DRUG INTAKE DUE TO IRREGULAR SUPPLY OF THE SITE	TITRATION	TITRATION
	900			0	DB	OTHER	SECOND TITRATION BECAUSE OF INTERRUPED STUDY DRUG INTAKE	TITRATION	TITRATION
	1350			0	DB	OTHER	SECOND TITRATION AFTER STOPPED IP INTAKE DUE TO IRREGULAR SUPPLY OF THE SITE	TITRATION	TITRATION

USUBJID	DOSE	DOSEST	DOSE END	DAYS MISSD	PHASE	TRPHASE	TRPHOTH	PHASSPEC	HARD CODING TO PHASE:
[redacted]	1800	[redacted]	[redacted]	0	DB	OTHER	SECOND TITRATION AFTER STOPPED IP INTAKE	TITRATION	TITRATION
	1800			0	DB	MAINTENANCE			MAINTENANCE
	450			0	DB	TITRATION			TITRATION
	900			0	DB	TITRATION			TITRATION
	1350			0	DB	TITRATION			TITRATION
	1800			0	DB	TITRATION			TITRATION
	0			13	DB	OTHER	STUDY DRUG SOPPED BECAUSE OF INSUFFICIENT SUPPLY OF THE SITE	MAINTENANCE	MAINTENANCE
	450			0	DB	OTHER	SECOND UP-TITRATION	TITRATION	TITRATION
	900			0	DB	OTHER	SECOND UP-TITRATION	TITRATION	TITRATION
	1350			0	DB	OTHER	SECOND UP-TITRATION	TITRATION	TITRATION
	1800			0	DB	OTHER	SECOND UP-TITRATION	TITRATION	TITRATION
	1800			0	DB	MAINTENANCE			MAINTENANCE
	450			0	DB	TITRATION			TITRATION
	900			0	DB	TITRATION			TITRATION
	1350			0	DB	TITRATION			TITRATION

USUBJID	DOSE	DOSEST	DOSE END	DAYS MISSD	PHASE	TRPHASE	TRPHOTH	PHASSPEC	HARD CODING TO PHASE:
[redacted]	1800	[redacted]	[redacted]	0	DB	TITRATION			TITRATION
	1800			0	DB	OTHER	DE-ESCALATION DUE TO INSUFFICIENT MEDICATION IN THE SITE	MAINTENANCE	MAINTENANCE
	1350			0	DB	OTHER	DE-ESCATION DUE TO INSUFFICIENT MEDICATION IN THE SITE	MAINTENANCE	MAINTENANCE
	900			0	DB	OTHER	DE-ESCALATION DUE TO INSUFFICIENT MEDICATION IN THE SITE	MAINTENANCE	MAINTENANCE
	450			0	DB	OTHER	DE-ESCALATION DUE TO INSUFFICIENT MEDICATION INN THE SITE	MAINTENANCE	MAINTENANCE
	450			0	DB	OTHER	SECOND UP-TITRATION	TITRATION	TITRATION
	900			0	DB	OTHER	SECOND UP-TITRACION	TITRATION	TITRATION
	1350			0	DB	OTHER	SECOND UP-TITRACION	TITRATION	TITRATION
	1800			0	DB	OTHER	SECOND UP-TITRATION	TITRATION	TITRATION
	1800			0	DB	MAINTENANCE			MAINTENANCE