16.1 STUDY INFORMATION

16.1.1 Protocol

MARINUS
PHARMACEUTICALS, INC.

CLINICAL STUDY PROTOCOL

STUDY TITLE: 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

PROTOCOL NUMBER: 1042-0603

STUDY PHASE: 3

STUDY DRUG(S): Ganaxolone (CCD 1042:3α-hydroxy-3β-methyl-5α-pregnan-20-one)

IND NUMBER: 44,020

INDICATION: Epilepsy with uncontrolled partial-onset seizures

SPONSOR: Marinus Pharmaceuticals, Inc.
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INITITAL VERSION:	September 9, 2013
AMENDMENT 1:	December 3, 2013
AMENDMENT 2:	March 10, 2014
AMENDMENT 3:	September 23, 2014
AMENDMENT 4:	April 8, 2016

1. SIGNATURE PAGE

Sponsor Approval

Signature: [redacted] **Date:** [redacted]

Name (print) [redacted]

Investigator Agreement: I have read the protocol and agree to conduct the study as outlined herein.

Signature: _____ **Date:** _____

Name (print): _____

Institution (print) _____

2. SYNOPSIS

Name of Sponsor/Company: Marinus Pharmaceuticals, Inc.	
Protocol Number: 1042-0603	**Phase of Development:** 3
Title of Protocol: 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	
Primary Objectives: To evaluate efficacy of ganaxolone compared to placebo as adjunctive therapy in adults with partial-onset seizures (POS), with or without secondary generalizations.	
Secondary Objectives: • To evaluate the safety and tolerability of ganaxolone compared to placebo as adjunctive therapy in adults with POS • To evaluate serum levels 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 over a 12-month period.	
Study Design and Methodology: This is a 2-cohort study comprised of 2 phases in each cohort. Phase 1 is a double-blind phase followed by Phase 2, an open-label phase. Cohort 1 will provide tolerability, safety, and PK information for ganaxolone 1200 mg/d, 1800 mg/d and placebo. Cohort 2 will investigate the efficacy, tolerability and safety of ganaxolone 1800 mg/d compared to placebo. Cohort 1 (N=approximately 46) will enroll into a 67-week study comprised of a 4-week prospective baseline period plus 4 week retrospective baseline followed by two treatment phases: a 9-week randomized double-blind (DB) placebo-controlled treatment phase followed by a 52-week open-label (OL) treatment phase. Cohort 2 (approximately N=359) will enroll into a 76-week study comprised of an 8-week prospective baseline period followed by two treatment phases: a 14-week randomized DB placebo-controlled treatment phase followed by a 52-week open-label (OL) treatment phase. A final safety assessment will be conducted two weeks following the end of each OL treatment phase. The Schedule of Events is contained in Appendix 1.	
Study Population and Main Criteria for Inclusion/Exclusion: Male and female subjects 18 years of age and older able to provide written informed consent with a confident diagnosis of epilepsy with POS with or without secondary generalization with a POS frequency rate of ≥3 POS per 28-day who are currently treated on a stable regimen of AEDs. Subjects must not have previous exposure to ganaxolone, generalized epilepsy, have less than 3 POS seizures per 28-day period or ≥21 seizure-free days. Subject should not have innumerable seizures, more than 100 POS total per each 4-week baseline period. No subjects will be admitted who have an active central nervous system (CNS) infection, demyelinating disease, degenerative neurological disease, CNS disease	

deemed progressive, clinically unstable psychiatric disorder, suicide attempt within the last 5 years, or current significant suicidal ideation.
Number of Subjects: Approximately 525 subjects will be screened to randomize approximately 46 subjects into Cohort 1 and 359 subjects into Cohort 2 at 1:1 ganaxolone or placebo.
Test Product, Dose and Mode of Administration: Ganaxolone 200 mg or 225 mg capsules or matching placebo, administered in BID up to a total of 1800 mg/day.
Duration of Treatment: Cohort 1: Four weeks prospective baseline plus 63 weeks treatment: 1 week titration, 4 weeks at 1200 mg/day, 4 weeks at 1800 mg/day for double-blind phase, 1 week transition to OL, 51 weeks at 1800 mg/day for open-label phase. Cohort 2: Eight weeks prospective baseline plus 68 weeks treatment: 2 week titration, 12 weeks at 1800 mg/day for double-blind phase, 2 week transition to OL, 50 weeks at 1800 mg/day for open-label phase. Subjects will de-escalate treatment over 2 weeks at end of the OL phase or at discontinuation.
Reference Therapy, Dose and Mode of Administration: Orally-administered placebo capsules administered BID.
Criteria for Efficacy Evaluation: 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. The primary endpoint analysis will consist of rank analysis of covariance (ANCOVA) conducted on the percent change data, with treatment and pooled countries as factors and the rank baseline seizure frequency per 28 days as a covariate The primary efficacy endpoint for European registration is 50% responder rate during the maintenance treatment phase of the double-blind phase for Cohort 2. A 50% responder is an individual who experiences at least a 50% decrease in seizure frequency compared to baseline. Key secondary end-points The three 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]

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

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

b) Ganaxolone Maintenance 1200 mg/day + Maintenance 1800 mg/day vs Placebo (Cohort 1: Weeks 2-9).

c) Ganaxolone Titration + Maintenance 1200 mg/d vs placebo (Cohort 1: Weeks 1-5).

d) Ganaxolone Maintenance 1800 mg/d vs placebo (Cohort 1: Weeks 6-9).

e) Ganaxolone maintenance 1200 mg/d vs placebo (Cohort 1: Weeks 2-5).

f) OL (Cohort 1: Weeks 10-61; Cohort 2: Weeks 16-66).

Safety: Neurological and physical examinations, clinical laboratory tests, Columbia Suicide Severity Rating Scale (C-SSRS), seizure severity, electrocardiogram (ECG), vital signs, and spontaneously reported adverse events (AEs).

Pharmacokinetic Data: Blood samples for concomitant AEDs will be drawn at Visits 1, 2, 3, 4, 5, 7, 8, 9 and 10. Blood samples for ganaxolone will be drawn at Visits 4, 5, 7, 8, 9 and 10.
Pharmacokinetic evaluation will be conducted if needed and reported separately. Levels of ganaxolone and of concomitant AEDs are not considered a safety assessment within this protocol.

Statistical Methods: The primary endpoint analysis will consist of rank analysis of covariance (ANCOVA) conducted on the percent change data, with treatment and pooled countries as factors and the rank baseline seizure frequency per 28 days as a covariate.

The responder rates and seizure-free rates between ganaxolone and placebo will be compared using a logistic regression analysis. To take into account the ordinal nature of the response to Clinical Global Impression of Change and Patient Global Impression of Change scales (CGI-I, PGI-I), the Row Mean Score Difference, and the p-value based on Cochran-Mantel-Haenszel test adjusting for pooled center (either US or ROW), will be used to test if there is a treatment effect.

Adverse events (AEs) will be tabulated by Overall, system organ class (SOC), and Preferred Term using the MedDRA v.16.1 coding system. Frequency 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 double blind phase, by dose level and overall. Additional tables, with AEs subset by severity and by relationship to drug as assessed by the investigator will be presented. Subset listings will be produced for adverse events that cause withdrawal and for SAEs.

Laboratory data, vital signs and ECGs will be summarized using descriptive statistics by treatment including changes from baseline. Critically significant changes in laboratory and ECG values and vital signs will be flagged in data listings. Listings of most abnormal changes will be provided.

3. TABLE OF CONTENTS

LIST OF WITHIN TEXT FIGURES AND TABLES

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4. LIST OF ACRONYMS, ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Definition
3α,5α-P	3α-hydroxy-5α-pregnan-20-one; allopregnanolone
AE	adverse event
AE eCRF	adverse event electronic case report form
AED	antiepileptic drug
ALT	alanine transferase (SGPT)
ARS	acute repetitive seizures
AST	aspartate transferase (SGOT)
ANCOVA	analysis of covariance
BID	bis in die; two times per day
CFR	Code of Federal Regulations
β-HCG	β-human chorionic growth hormone
°C	degrees centigrade
CNS	central nervous system
CPS	complex partial seizures
eCRF	electronic case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
DB	double-blind
DDI	drug-drug interaction
ECG	electrocardiogram
EEG	electroencephalogram
ET	Early Termination
°F	degrees Fahrenheit
FAP	full analysis population
FDA	Food and Drug Administration
POS	Partial-onset seizure
FS	Focal seizure
FPFV	first patient, first visit
$GABA_A$	γ-aminobutyric $acid_A$
GCP	Good Clinical Practice
GTCS	generalized tonic-clonic seizure
Hz	Hertz
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
ILAE	International League Against Epilepsy
IPIN	Investigational Product Identification Number
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	interactive web response system
kg	kilogram
LOCF	last observation carried forward
LPLV	last patient, last visit
m	meter
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mg/d	milligram per day

Term	Definition
Min	minutes
mITT	modified intent to treat
mL	millilitre
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
n	number of subjects
OL	open-label
OLE	open-label extension
oz	ounces
PK	pharmacokinetics
POS	partial-onset seizure
PTZ	pentylenetetrazol
POP-PK	population pharmacokinetics
PP	per-protocol
SAE	serious adverse event
SAE CRF	serious adverse event case report form
SOC	system organ class
SP	safety population
SPS	simple partial seizure
t.i.d.	three times daily
T_{max}	time to maximum concentration
ULN	upper limits of normal
USA	United States of America
VNS	vagal nerve stimulator
WCBP	women of child bearing potential

5. ETHICS

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

This study will be conducted in compliance with current Good Clinical Practices (GCP) and Title 21 Part 56 of the United States of America (USA) Code of Federal Regulations (CFR) relating to IRBs and the International Conference on Harmonisation (ICH) E6 guidelines for Good Clinical Practice.

5.2 Ethical Conduct of Study

The study will be conducted in accordance with GCP as described in the USA Food and Drug Administration (FDA) CFR (21 CFR § 50, 56, 312), and the International Conference on Harmonisation (ICH) and the ethical principles of the Declaration of Helsinki.

5.3 Subject Information and Consent

This study will be conducted in compliance with Title 21 Part 50 of the USA CFR and ICH E6(RI) (Section 4.8) pertaining to informed consent. At the first visit, prior to initiation of any study-related procedures, will give their written consent to in the study after having been informed about the nature and purpose of the study, conditions for study participation/termination, and potential risks and benefits.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This will be a multi-center study with approximately 55 investigational sites in the USA, the Russian Federation (Russia), Australia, Bulgaria, Germany and Poland with approximately 6 subjects enrolled at each site. Study enrollment is planned for 26 months from the time of first subject visit. Duration of subject participation in Cohort 1 is up to 67 weeks: 4 weeks prospective seizure recording, 1 week titration, 8 weeks double-blind maintenance (total 9 weeks of double-blind [DB] treatment), 52 weeks of additional open-label (OL) treatment ± 2 weeks of dose de-escalation at study end. Duration of subject participation in Cohort 2 is up to 76 weeks: 8 weeks prospective seizure recording, 2 week titration, 12 weeks double-blind maintenance (total 14 weeks of double-blind [DB] treatment), 52 weeks of additional open-label (OL) treatment ± 2 weeks of dose de-escalation at study end.

7. INTRODUCTION

Approximately 2 million people in the United States of America (USA) have epilepsy. As many as 30% of epilepsy subjects may not be well controlled on treatment with a single or multiple existing antiepileptic drugs (AEDs; French et al., 2004). The approach of adding on an experimental AED to an existing non-optimal therapeutic regimen has proven to be a useful technique for demonstrating efficacy of novel compounds. The present study is designed to evaluate the safety, tolerability and efficacy of ganaxolone when used as an add-on therapy in adult subjects with epilepsy consisting of partial-onset (focal) seizures that are uncontrolled on their present AED regimen.

Ganaxolone is the 3β-methylated synthetic analog of allopregnanolone, which is synthesized *in vivo* when progesterone undergoes 5α-reduction and loses all progestational activity. Ganaxolone is a positive allosteric modulator of γ-aminobutyric acid A ($GABA_A$) receptors with potency and efficacy comparable to its endogenous analog allopregnanolone (Carter et al., 1997). As with allopregnanolone, ganaxolone potentiation of the $GABA_A$ receptor occurs at a site distinct from the benzodiazepine site. Ganaxolone has protective activity in diverse rodent seizure models, including clonic seizures induced by pentylenetetrazol (PTZ) and bicuculline, limbic seizures in the 6 Hz model, and amygdala kindled seizures (Carter et al., 1997; Kaminski et al., 2004; Reddy et al., 2004). Unlike allopregnanolone, ganaxolone cannot be converted to an active steroid; it is currently under study for treatment of chronic neuropsychiatric conditions such as epilepsy, Posttraumatic Stress Disorder and behaviors in Fragile X Syndrome. Human trials indicate that ganaxolone is well tolerated and that it may be efficacious in the treatment of diverse forms of epilepsy in children and adults (Bialer et al. 2010).

As of May 31, 2013, 986 subjects have received and completed treatment with ganaxolone in 35 studies, ranging in duration from 1 day to more than 2 years. Two hundred and eighty-nine subjects received ganaxolone in Phase 1 studies, including 22 subjects in Study 1042-0404 which was an open-label, ascending multiple-dose safety and tolerability study of 1200, 1600 and 2000 mg/day. Subjects were maintained at each dose level for 3-5 days; the doses were safe and generally well-tolerated. Pharmacokinetics were assessed at steady state after each dose level. Results showed that both Cmax and levels increased with increasing dose over the range of 600 to 1000 mg

BID under fed conditions, though not in proportion to increases in dose. The incidence of adverse events (AEs) was dose-related and most AEs were classified as mild and possibly related to study drug. The most common AEs affecting more than 20% of subjects (n, %) were somnolence (19, 86%), euphoric mood (13, 59%), nausea (8, 36%), headache (6, 27%), and tremor, flatulence and muscle spasms (each 5, 23%). There were no clinically significant findings for laboratory safety values, vital signs or ECG data. There were no positive findings on the Columbia-Suicide Severity Rating Scale (C-SSRS) during the study.

In Phase 2 adult trials in the ganaxolone program, 697 adults received ganaxolone in 9 studies, 6 of which were in epilepsy. To date, the largest placebo-controlled study (N=147) of ganaxolone in epilepsy was 10-week, double-blind Study 1042-0600 followed by an open-label extension of up to two years duration. Study 1042-0600 showed ganaxolone (500 mg t.i.d.) adjunctive therapy significantly reduced partial onset seizures, with or without secondary generalizations, compared to placebo (p= 0.014). Ganaxolone-treated subjects experienced a median decrease of 26% (17.6% mean) compared to a 10.2% (+2.0% mean) decrease in placebo.

Most of the adverse events reported in the clinical development program were mild or moderate in severity, dose-related, and resolved upon treatment discontinuation. Adult and pediatric subjects in open label extension studies to the epilepsy trials have been dosed with ganaxolone for >2 years with no new adverse events reported as compared to the controlled trials. Three deaths have been reported in the program, none related to ganaxolone.

Adverse events reported from Study 1042-0600 in at least 5% of subjects and >1.5 times more frequent in the ganaxolone group than the placebo group were dizziness (16.3 v. 8.3%), fatigue (16.3 v. 8.3%) and somnolence (13.3 v. 2.0%). The discontinuation rates due to adverse events between the ganaxolone and placebo groups in Study 1042-0600 were comparable, 7.1% and 6.1% respectively.

In Study 1042-0600 and in the ganaxolone development program overall, no clinically significant trends in changes from baseline electrocardiogram (ECG) recordings, vital signs, or physical or neurological examinations have been noted in the clinical studies,

and no mean changes from baseline in clinical labs have been identified. Transient increases in LFTs (>3xULN) have been noted in less than 1% of subjects treated with ganaxolone. Serious adverse events (SAEs) reported in the ganaxolone epilepsy trials were considered by a Scientific Advisory Board to be usual for the population without any pattern attributable to ganaxolone. Profiles of the most frequently reported AEs have been consistent with the predicted pharmacology of the drug.

Due to the favorable tolerability profile of ganaxolone in Study 1042-0600 and its open-label extension, the current study is designed to further examine the safety, tolerability and efficacy of ganaxolone as adjunctive treatment of POS when administered BID at doses up to 1800 mg/day in a capsule formulation.

8. STUDY OBJECTIVES

8.1 Primary Objectives

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

8.2 Secondary Objectives

1. To evaluate the safety and tolerability of ganaxolone compared to placebo as adjunctive therapy in adults with POS.
2. To evaluate serum levels of ganaxolone at 1200 mg/d and 1800 mg/d after chronic dosing.
3. To evaluate the safety and tolerability of ganaxolone when administered as adjunctive therapy in adults with POS over a 12-month period.

9. INVESTIGATION PLAN

9.1 Overall Study Design and Plan

This is a 2-cohort study with each cohort comprised of 2 treatment phases. Phase 1 is a double-blind phase followed by Phase 2, an open-label phase. Cohort 1 will provide tolerability, safety, and PK information for ganaxolone 1200 mg/d, 1800 mg/d and placebo. Cohort 2 will investigate the efficacy, tolerability and safety of ganaxolone 1800 mg/d compared to placebo. Cohort 1 (N=approximately 46) will enroll into a 67-week protocol comprising a 4-week prospective baseline period and two treatment phases: a 9-week double-blind treatment phase followed by a 52-week open label treatment phase. Cohort 2 (N=359) will enroll into a 76-week study comprising an 8-week baseline phase and two treatment phases: a 14-week double-blind treatment phase followed by a 52-week open label treatment phase. A final safety assessment will be conducted two weeks following the end of each OL treatment phase.

Baseline seizure activity will be determined by 8 weeks of recording in a daily seizure calendar. 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 double-blind placebo-controlled treatment period to evaluate oral study medication as add-on therapy in adults with epilepsy consisting of uncontrolled partial-onset seizures (POS) with or without secondary generalizations. Study subjects will be randomized to one of the two study treatment arms: ganaxolone at 1200 mg/day (mg/d) and 1800 mg/d, or placebo. Phase 1 is comprised of 3 periods: Baseline (4 weeks), 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). Subjects in Cohort 1 are to provide 4 weeks of retrospective seizure calendar data to be used for baseline assessment.

Cohort 1, Phase 2 is the open-label treatment period consisting 3 periods: Transition (1 week, step titration for placebo subjects from 900 mg/d to 1800 mg/d while ganaxolone subjects are maintained on their current dose), 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 study will be de-escalated over 1-2 weeks based on dose, duration, and tolerability in the opinion of the investigator.

Cohort 2, Phase 1 of treatment includes a 14-week double-blind placebo-controlled treatment period to evaluate oral study medication as add-on therapy in adults with epilepsy consisting of uncontrolled POS with or without secondary generalizations. Study subjects will be randomized to one of the two study treatment arms: ganaxolone at 1800 mg/d or placebo. Phase 1 is comprised of 3 periods: Baseline (8 weeks), 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, collected 4 weeks retrospective and 4 weeks prospective baseline data.

Cohort 2, Phase 2 is the open-label treatment period consisting 3 periods: Transition (2 week, step titration for placebo subjects from 900 mg/d to 1800 mg/d while ganaxolone subjects are maintained on their current dose), Flexible Dosing (50-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 study will be de-escalated over 1-2 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 Figure 1. The complete list of tasks per visit is described in Section 9.5.5 Schedule of Study Procedures and the visit schedule may be found in Appendix 1 Schedule of Events.

Figure 1. Cohort 1 Trial Design

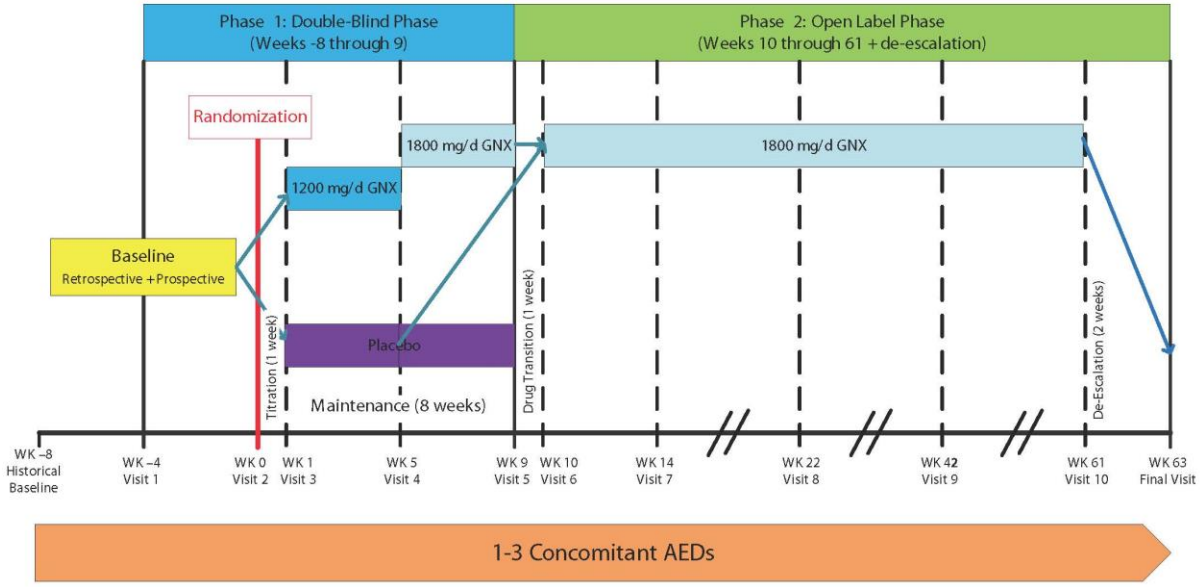
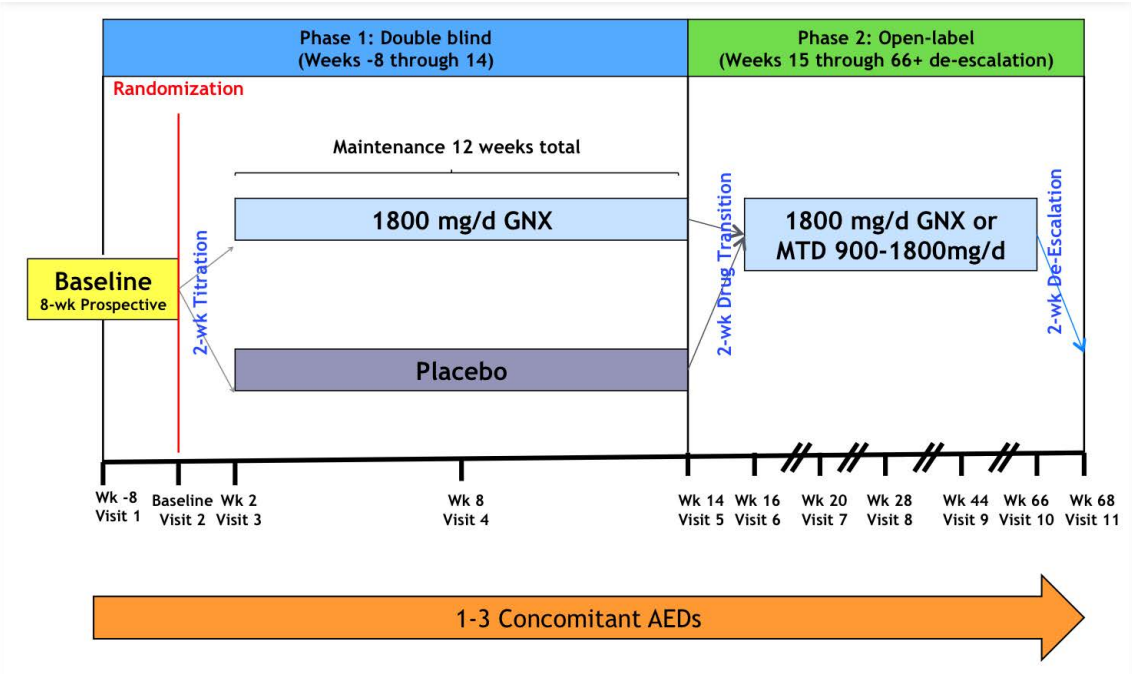


Figure 2. Cohort 2 Trial Design



9.2 Discussion of Study Design, including the Choice of Control Group

The study is designed to investigate the efficacy, safety, and tolerability of a capsule formulation of ganaxolone administered as 1800 mg per day in divided (BID) doses in

the adult epilepsy population with drug-resistant epilepsy consisting of POS, compared to placebo. A secondary goal is to evaluate blood levels, efficacy and tolerability of ganaxolone 1200 mg/d and 1800 mg/d in a separate cohort of subjects. Completers in both cohorts are eligible to enter into a one year, open-label, flexible dose continuation phase.

The two-cohort design permits evaluation of the relative blood levels of 1200 mg/d and 1800 mg/d doses of ganaxolone in Cohort 1, and while Cohort 2, evaluates efficacy, tolerability and safety of the 1800 mg/d dose in an appropriately powered sample size for a 12 week duration that is consistent with regulatory standards for registration studies.

Administration of study drug as adjunctive therapy to background AEDs permits comparison with placebo while maintaining the subjects on prior anticonvulsant therapy.

9.3 Selection of study population

9.3.1 Number of Subjects

Approximately 525 subjects will be screened to randomize approximately 46 subjects into Cohort 1 and approximately 359 subjects into Cohort 2 at a 1:1 ratio of ganaxolone to placebo, assuming a screen-failure rate of 15%. It is estimated that approximately 320 subjects will complete the 14-week double-blind phase of Cohort 2, which assumes approximately 10% discontinuation rate.

9.3.2 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 (if permitted in your country/region), 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 9 or 14-week double-blind phase and willing to enter into the open-label 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 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. For Poland, a CT or MRI of the brain to rule out progressive structural lesions should be performed within 2 years prior to screening visit.

5. Based on documented history of POS, the investigator judges that the subject is likely to have 3 or more POS* 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 double-blind phase of the study (AEDs may be adjusted during the open-label phase of the study).

a. 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.
b. 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:
    i. The VNS has been in place for ≥1 year prior to the screening visit
    ii. The settings must have remained constant for ≥3 months prior to the screening visit and remain constant throughout the study
    iii. The battery is expected to last for the duration of DB Phase I (9 or 14 weeks) of the study
c. 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 Section 9.4.10 for use of benzodiazepines for seizure rescue or for other indications.
d. Felbamate: The use of felbamate is allowed provided that the subject has been maintained on a stable dose of felbamate for ≥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.
e. Perampanel: The use of perampanel is allowed provided that the subject has been maintained on a stable dose of perampanel for >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 (WCBP) must be using a medically acceptable method of birth control and have a negative qualitative serum β-human chorionic growth hormone (β-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.

9.3.3 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 ≤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 <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 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 prior to screening. If used during the last 12 months two visual fields tests are required.

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 double-blind 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 double-blind 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 >3 times upper limits of normal (ULN), or total bilirubin >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 double-blind phase. Use of St. John's Wort is not permitted (See 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 Section 9.4.11: Excluded, Prior, and Concomitant Medications).

9.3.4 Removal of Subjects from the Study

9.3.4.1 Criteria for Withdrawal

All subjects reserve the right to withdraw from the clinical study at any time, as stated in the informed consent form (ICF). The Investigator may discontinue subjects from the clinical study for any of the following reasons:

1. Post-treatment QTc interval >500 msec or uncorrected QT interval >600 msec; for subjects with bundle branch block, post-treatment QTc >530 msec based on average QTc value of triplicate ECGs. A subject with a post-treatment increase in QTc of >60 msec from Baseline must also be withdrawn.
    a. 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.
2. Subject is found to have entered the clinical investigation in violation of the protocol;

3. Subject requires the use of an unacceptable or contraindicated concomitant medication;
4. Use of benzodiazepines as rescue for innumerable seizure clusters more than two times during 9 or 14-week DB phase, or more than once in a 28-day period must be discontinued;
5. Use of benzodiazepines as rescue for innumerable seizure clusters more once in a 28-day period during the Open-Label Phase, Investigator should consider discontinuation;
6. Subject's condition changes after entering the clinical investigation so that the subject no longer meets the inclusion criteria or develops any of the exclusion criteria;
7. Subject is noncompliant with procedures set forth in the protocol in an ongoing or repeated manner;
8. Subject experiences an adverse event (AE) that warrants withdrawal from the clinical investigation;
9. It is the Investigator's opinion that it is not in the subject's best interest to continue in the study;
10. Any subject who exhibits any of the following will be immediately withdrawn from the clinical investigation:
    a. Clinically significant worsening of seizures as judged by Investigator or subject such that treatment outside of the protocol is assumed to be in the subject's best interest.
    b. Two episodes of generalized tonic-clonic seizures (GTCS) if not present at baseline.
    c. Status epilepticus at any time during the clinical investigation.
    d. Any Suicidal Behavior as classified by the Columbia Suicide-Severity Scale (C-SSRS) or a "yes" answer to question 4 and 5 in the Suicidal Ideation section of the C-SSRS. These patients should be referred to psychiatric evaluation immediately.
11. Any subject who has the following liver enzyme findings should be immediately contacted and instructed to stop the study drug or start down titration of the study drug

a. ALT or AST > 8 x ULN
b. ALT or AST >5 x ULN for more than 2 weeks
c. ALT or AST > 5 x ULN and total bilirubin >2 x ULN
d. ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia

Patients with ALT or AST > 3 x ULN but <8 x ULN and no clinical signs and symptoms indicating liver dysfunction can, at the discretion of the investigator, continue the intake of study drug with close monitoring.

All patients who fall into either category (patients who must discontinue the study drug [a, b, c and d] and who may continue the study drug with close monitoring) must be brought back to the study center without any delay, the next day if possible, but no later than 72 hours after the study results have been received, for evaluation of the underlying cause and confirmatory laboratory testing. More frequent monitoring of the liver tests should be initiated.

Discontinuation decisions will be made at each participating site by the Site Principal Investigator. If feasible, the process of discontinuation should be discussed with the Medical Monitor. The decisions regarding the discontinuation of the investigational therapy, whether the study medication should be stopped immediately or tapered should be discussed with the Medical Monitor, but final decisions about the process will remain at the discretion of the Site Principal Investigator.

Subjects who are discontinued from the clinical investigation for any reason will not be replaced.

9.3.4.2 Early Termination Procedures

Any subject who informs the site of an intention to withdraw from the study, or any subjects who are discontinued prior to the end of the study (early termination; ET), will be asked to complete the procedures for Visit 10 (pre-taper/ET) which include: physical and neurological exams, labs, ECG, pregnancy test, C-SSRS, collection of adverse events and seizure calendar review. The study drug will then be continuously tapered over one

to two weeks, if possible, based on the dose and duration of treatment. A post-taper safety follow-up visit would then be completed. Subjects who are discontinued from the clinical investigation should return to their physician's care and continue appropriate medical treatment. Any AEs that have not resolved as of discontinuation will be followed until resolution. An end-of-study letter will be provided, if requested. Any follow-up information that is available will be added to the case report form up until the time that the database is locked.

9.3.4.3 Consequences of Early Termination

The protocol specifies dose de-escalation of study medication over one to two weeks depending upon dose and duration of treatment. This recommendation is based on cumulative evidence from various classes of CNS drugs that slow taper is beneficial. It is possible that abrupt cessation of the drug might cause discontinuation symptoms. Every effort will be made to ensure implementation of the de-escalation.

9.4 Treatments

9.4.1 Treatments Administered

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 two 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 ICF.

9.4.2 Identity of Investigational Products

Ganaxolone will be provided in size 00 white/opaque gelatin capsules packaged in HDPE bottles with a foil induction seal and child resistant closure. Each bottle will contain 70 capsules. Each capsule contains either 200 mg or 225 mg ganaxolone (3α-hydroxy-3β-methyl-5α-pregnan-20-one), and hydroxypropyl methylcellulose, sucrose, polyethylene glycol 3350, polyethylene glycol 400, sodium lauryl sulfate, sodium benzoate, citric acid anhydrous, sodium methyl paraben, microcrystalline cellulose, 30% Simethicone Emulsion, gelatin capsules, polysorbate 80, and sodium chloride.

Placebo formulation is comprised of sucrose spheres of comparable size to the ganaxolone spray layered spheres encapsulated in a size 00 white/opaque gelatin capsule. The weights of placebo capsules are matched to ganaxolone capsules.

All study medication will be labeled according to regional regulatory requirements. At minimum labels will contain the study number; a blinded bottle number; contents including quantity; dose and form; route of administration; storage conditions; instructions for study drug administration; caution that this compound is an investigative drug intended for clinical trial use only; warning to keep out of reach of children; and the identity of manufacturer and Sponsor. For those regions that require it, a blinded lot number and an expiry date will also be listed.

All study medication will be stored at the research pharmacy prior to dispensing, or in a locked cabinet accessible only to members of the investigative research team after the completion of each study visit. Study medication should be stored at room temperature 15°C to 30°C (59°F to 86°F).

9.4.3 Method of Assigning Subjects to Treatment Groups

No study related tests or treatments, including screening, will be conducted until the subject has signed the ICF.

Subjects will be randomized (Visit 2, Week 0, before dosing) to receive investigational product in an active:placebo ratio of 1:1, with stratification by country. The interactive web response system (IWRS) will centrally randomize subjects. The randomization schedule will be generated using a standard, validated method and maintained by the investigational product supplier and IWRS vendor. The Investigator will be told which numbered bottle to use to dose a subject by the IWRS. The Investigator and research staff will be aware of the ascending dose design of the clinical investigation; however, the Investigator, the research staff, and the subjects will be blinded with respect to who is receiving active drug versus placebo. The maximum placebo period is 9 weeks for Cohort 1 and 14 weeks for Cohort 2.

The contents of each bottle will be blinded using labels. The randomization schedule will match a subject number to a bottle number. Upon completion of baseline evaluations for each subject, the Investigator or appropriate designee will log into the IWRS to receive a

bottle number. Complete instructions for obtaining a bottle number will be provided to the clinical sites prior to initiating the study.

The designated personnel at the clinical site will match the assigned bottle number with the correct bottle of investigational product and distribute the bottle to the Investigator or designee. Only the investigational product supplier and one investigational product manager will be unblinded as to the bottle number and the contents of each bottle of investigational product.

9.4.4 Subject Numbering

During enrollment (Visit 1, Week -4, pre-dose), each subject will be assigned a unique 6-digit subject number by the study staff. The subject number will consist of a 3-digit clinical investigational site number assigned by the Sponsor (from [redacted]), followed by a three-digit subject number (e.g., 001) assigned by the study staff. This subject number will also serve as the screening number. A separate randomization number will be assigned once the subject is randomized but the randomization number will not be used to track the subject. The unique 6-digit subject number will serve as the subject ID and be used to track the subject throughout the study. Each subject number will correspond with a treatment (active or placebo) as determined by the randomization schedule.

The clinical site is responsible for maintaining a current log of subject number assignments and bottle numbers of the investigational product administered to each subject. The subject's initials (first/middle/last) and unique subject number are required to be entered on all clinical investigation documentation (i.e., eCRFs, labeling of clinical materials and samples containers, drug accountability logs, etc.).

9.4.5 Study Dosing and Dosage Adjustments

<u>Double-blind Phase:</u>

Cohort 1: The study drug dose will be titrated from 400 mg/day to 1200 mg/day in divided doses BID by the end of Week 1 and maintained to Week 5. Dosage will be increased to 1800 mg/day Week 6 and maintained through Week 9 (Table 1).

Cohort 2: The study drug dose will be titrated from 450 mg/day to 1800 mg/day in divided doses BID by the end of Week 2 and maintained through Week 14 (Table 2).

Both titration schedules are consistent with acceptable starting doses and MTDs from previous ganaxolone studies.

Open-Label Phase: Following the completion of the double-blind (DB) phase in either cohort, subjects randomized to placebo will transition to ganaxolone while subjects randomized to ganaxolone will stay on 1800 mg/d. Cohort 1 placebo subjects will begin the 1-week dose titration to 1800 mg/d after completing their Visit 5. Subjects will receive ganaxolone 900 mg/d in divided doses BID for 2 days and step up to 1350 mg for 3 days and then increase to 1800 mg in divided doses BID for 2 days until their Visit 6 (Table 1). Titration for Cohort 2 placebo subjects will mirror the DB phase. Subjects will begin the 2-week dose titration to 1800 mg/d after completing their Visit 5. Subjects will start with 450 mg/d in divided doses BID for 3 days, 900 mg/d in divided doses BID for 3 days, 1350 mg/d in divided doses BID for 4 days, and 1800 mg/d in divided doses BID for 4 days until their Visit 6 (Table 2). At Visit 6, all subjects in both cohorts will be evaluated for tolerability and the investigator will make the determination to maintain the subject on 1800 mg/d or adjust their dose. If the patient experiences any tolerability issues during the transition to OL, such as sedation or dizziness, changes to the titration schedule (e.g., conducting the titration over 3 weeks vs. 2 weeks) may be approved after discussion with the medical monitor. Subjects may be maintained on the MTD of ganaxolone that provides adequate seizure control that is not less than 900 mg/d and not more than 1800 mg/d. Doses may be adjusted upward or downward in 225 mg/d increments every 3 days to reach an optimal dose level over the duration of the 52-week OL phase. Dose adjustments should be made with the investigator's agreement. Frequency of dosing changes may not be less than 3 days unless required for safety.

De-escalation Period: The study drug will be decreased in increments of 450mg/d in 4-day intervals over 12 days for 1800 mg. Decreases from doses less than 1800 mg will be adjusted accordingly (See Table 1 & 2). The subject will return for final post-taper safety assessment visit.

Details of the dosing regimen are provided in the table below.

Table 1. Dosing Schedule for Cohort 1 Double-blind Phase, Open-Label Phase, and De-Escalation Period

Cohort 1, Phase 1- Double-blind				
Visit	**Study Day**	**Dose (mg)/day**	**200 mg cap/day or matching placebo**	**225 mg cap/day or matching placebo**
Titration to 1200 mg/d (Visit 2)	1	400	2	0
	2	400	2	0
	3	800	4	0
	4	800	4	0
	5	1200	6	0
	6	1200	6	0
	7	1200	6	0
1200 mg/d Maintenance (Visit 3)	8- 35	1200	6	0
Step Titration to 1800 mg (Visit 4)	36	1800	0	8
1800 mg/d Maintenance	37-63	1800	0	8

Cohort 1, Phase 2- Open-label					
DB Transition to Open-Label					
Visit	**Study Day**	**Dose (mg)/day**		**Bottle A 225 mg or PBO cap/day**	**Bottle B 225 mg or PBO cap/day**
				GNX: 225 mg	**GNX: 225 mg**
		GNX/GNX	**PBO/PBO**	**PBO: 225 mg**	**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 1, Phase 2- Open-label			
All Subjects			
Visit	**Study Day**	**Dose (mg)/day**	**225 mg cap/day**
1800 mg/d Maintenance Visit 6	71	1800	8
OL Flex Dosing Visit 6-10	72-427	1800 or MTD	8
Cohort 1, De-Escalation Study Completion or Early Termination			
Visit	**Study Day**	**Dose (mg)/day**	**225 mg cap/day**
Visit10 / Taper Visit/	Last full dose 427	1800	8
	428	1350	6
	429	1350	6
	430	1350	6
	431	1350	6
	432	900	4
	433	900	4
	434	900	4
	435	900	4
	436	450	2
	437	450	2
	438	450	2
	439	450	2
	440	0	0
	441	0	0

Table 2. Dosing Schedule for Cohort 2 Double-blind Phase, Open-Label Phase, and De-Escalation Period

Cohort 2, Phase 1- Double-blind			
Visit	**Study Day**	**Dose (mg)/day**	**225 mg cap/day or matching placebo**
Titration to 1800 mg/d (Visit 2)	1	450	2
	2	450	2
	3	450	2
	4	900	4
	5	900	4
	6	900	4
	7	1350	6
	8	1350	6
	9	1350	6
	10	1350	6
	11	1800	8
	12	1800	8
	13	1800	8
	14	1800	8
1800 mg/d Maintenance (Visit 3)	15-56	1800	8
1800 mg/d Maintenance (Visit 4)	57-98	1800	8

Cohort 2, Phase 2- Open-Label					
DB Transition to Open-Label					
Visit	**Study Day**	**Dose (mg)/day**		**Bottle A 225 mg or PBO cap/day**	**Bottle B 225 mg or PBO cap/day**
				GNX: 225 mg	**GNX: 225 mg**
		GNX/GNX	**PBO/PBO**	**PBO: 225 mg**	**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

Cohort 2, Phase 2- Open-Label			
All Subjects			
Visit	**Study Day**	**Dose (mg)/day**	**225 mg cap/day**
1800 mg/d Maintenance Visit 6	113	1800	8
OL Flex Dosing Visit 6-10	114-477	1800 or MTD	8
Cohort 2, De-Escalation Study Completion or Early Termination			
Visit	**Study Day**	**Dose (mg)/day**	**225 mg cap/day**
Visit10 / Taper Visit/	Last full dose 478	1800	8
	479	1350	6
	480	1350	6
	481	1350	6
	482	1350	6
	483	900	4
	484	900	4
	485	900	4
	486	900	4
	487	450	2
	488	450	2
	489	450	2
	490	450	2
	491	0	0
	492	0	0

9.4.6 Dose Administration

Ganaxolone will be administered BID following the morning and evening meals, i.e., 1200 mg is dosed 600 mg am and 600 mg pm. 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 (See Section 9.4.7 Missing a Dose).

Subjects will be informed about possible side effects from the study medication and cautioned to avoid quick postural changes, at least until they know how the study drug affects them. Subjects will be advised not to drive, operate heavy machinery, or participate in any potentially hazardous activity that requires full mental alertness until they are sure the medication is not affecting alertness. Subjects will be reminded that the dose of study medication could change after each study visit. They will also be cautioned that non-adherence to the dosing instructions (e.g., increasing the dose, taking the study medication doses too close together, or using alcohol) could produce side effects.

Patients will be instructed to take the first dose of study drug in the morning with breakfast or a snack and 8 ounces of water. Subjects who are randomized at a morning clinic visit may take their first dose on the same day if they have a minimum of 8 hours until the evening dose. Subjects randomized later in the day will be instructed to take their first dose the following morning.

9.4.7 Missing a Dose

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 up to 8 hours before the next scheduled dose; otherwise, the missed dose should not be given. For example, if a subject usually takes their dose at 7am and 7pm and forgets to take a 7pm dose at dinnertime, that dose may be taken up to 9pm at night (2 hours after the evening meal, more than 8 hours until the next 7am dose). Alternatively, that dose could be taken until 11pm at night with a small snack.

Subjects should be instructed that if s/he misses 4 doses in a row or more, the site should be contacted to determine whether any adjustment in study medication is needed.

9.4.8 Blinding

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 code for manufacturing lot. The randomization schedule will match a subject number to a bottle number. Upon completion of baseline (retrospective and prospective) evaluations for each subject, the Investigator or appropriate designee will log into the IWRS to randomize the subject to 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.

9.4.9 Un-blinding

If it is deemed necessary to unblind a subject's treatment in order to provide medical management of an adverse event or to provide emergency treatment, unblinding will be conducted through the IWRS. Unblinding should only occur if necessary for the medical management of the subject. The Medical Monitor or the Sponsor must be contacted to initiate unblinding in the IWRS system. Subjects who are unblinded during the double-blind phase will be terminated from the study.

To initiate unblinding procedure 24/7/365 please contact:

Global Medical Monitor and Monitor for US Sites:

[redacted], [redacted]

INC Research

Telephone: [redacted]

Alternate Telephone: [redacted]

Email: [redacted]

Medical Monitor for Bulgarian Sites:

[redacted] M.D.

Global Clinical Trials (BCT Global)

Telephone: [redacted]

Email: [redacted]

[redacted] M.D.

R

[redacted]

Email: [redacted]

Medical Monitor for Russian Sites:

[redacted] M.D.

R

[redacted]

Email: [redacted]

Email: [redacted]

Medical Monitor for German and Polish Sites:

[redacted] M.D.

Prisma – CRO GmbH

Telephone: [redacted]

Email: [redacted]

Medical Monitor for Australian Sites (during business hours only; during off-duty hours contact Sponsor MM):

Prof. [redacted], M.D.

The Royal Melbourne Hospital

Telephone: [redacted]

Email: [redacted]

Investigators at Australian, Bulgarian, German, Polish and Russian sites should contact the Global Medical Monitor if their "in-country" Medical Monitor and backup cannot be reached.

If neither the Local nor Global Medical Monitor can be reached in an emergency, the site should contact:

Sponsor Medical Contact

[redacted], M.D., Ph.D.

Marinus Pharmaceuticals, Inc.

Telephone: +1 484-801-4678

Mobile Phone: [redacted]

Email: [redacted]

9.4.10 Background AED 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 prior to screening. If used in the last 12 months two visual fields tests are required.

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 through the double-blind phase of 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 through the double-blind phase of 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 double-blind phase of 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 double-blind phase (Cohort 1 weeks 1-9 and Cohort 2 weeks 1-14), 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.

9.4.11 Excluded, Prior, and Concomitant Medications

A list of medications that are **inducers or inhibitors of CYP 3A4/5** and are not permitted during the study are in Appendix 3. This list is not exhaustive so please consult with your in-country Medical Monitor if you have any questions. Note that **phenytoin** and **carbamazepine** are permitted as background AEDs though they are moderate CYP 3A4 inducers. Treatment with the 5-α-reductase inhibitor **finasteride** may not be initiated during the study.

Generally, concomitant medications including non-prescription medication can be used if medically necessary for indications that are not exclusionary in the protocol, and if the medication is not expected to interact with study medication nor to adversely impact the subject's ability to comply with protocol requirements (such as keeping seizure calendar and clinic appointments). The Investigator must make the decision to authorize the use of such a medication only after consideration of the clinical situation, the potential for masking symptoms of a more significant underlying event, and whether the use of the medication will compromise the outcome or validity of the clinical investigation. The Medical Monitor may be consulted for additional input. If medication is required, the name, strength, frequency, and reason for use will be recorded in source documents and name and reason entered in the electronic case report form (eCRF).

Benzodiazepines may be used intermittently (i.e., 1 to 2 doses over a 24-hour period) as rescue for the control of seizures. For subjects requiring benzodiazepine rescue more

than once per 28-day period, the investigator will determine and document the benefit to the subject for remaining in the trial.

Use of dietary supplements or herbal preparations are permitted if subject has been using them consistently for more than 6 months prior to screening, and does not plan changing the regimen for the duration of the double-blind phase. Use of St. John's Wort is not permitted (see Appendix 3).

As with other AEDs, the concomitant use of ganaxolone and alcohol during the course of the study is not advised. The effects of ganaxolone in combination with alcohol are not known.

Grapefruit and grapefruit juice are strictly prohibited during the clinical trial.

9.4.12 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. 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. Subjects that fall below 80% compliance at 2 consecutive visits during the double-blind phase should be withdrawn from the study.

9.5 Efficacy and Safety Variables

This is a 2-cohort study comprised of two phases: a double-blind, placebo-controlled (Phase 1) and a 52-week open-label (Phase 2). A 2-week de-escalation period prior to final safety assessment will be implemented at the end of study or at discontinuation.

9.5.1 Calculation of Baseline

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. After completing the 4-week prospective baseline period, eligible subjects will 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.

9.5.2 Efficacy Assessments

Subjects will record the type and number of seizures daily in the Subject Seizure Calendars that will be used for the primary analysis of efficacy. Cohort 1 subjects will be required to visit the clinic at screening and on Weeks -4, 0, 1, 5, and 9 (end of double-blind phase) and at Weeks 10, 14, 22, 42, and 61/ pre-taper during OL phase. Two telephone safety calls will also be conducted at Weeks 32 and 52 in Cohort 1. Cohort 2 subjects entered under Amendment 3 of the protocol will be required to visit the clinic at screening and on Weeks -8, 0, 2, 8, and 14 (end of double-blind phase) and at Weeks 16, 20, 28, 44, and 66/ pre-taper during OL phase. Four telephone safety calls will also be conducted in Cohort 2, two during double-blind Weeks 5 and 11 and two during OL Weeks 36 and 56. A final post-taper safety visit will be conducted at the end of de-escalation phase after study completion or early termination. At each visit, study coordinators will review each Subject's Seizure Calendars, classify seizure types, and calculate frequencies of seizures, and enter the information in the eCRF.

The primary outcome measure is the percentage change in seizure (POS with or without secondary generalization) frequency per 28 days in the Cohort 2 double-blind period relative to baseline. Please refer to Section 9.7 and the Statistical Analysis Plan (SAP) for further details regarding the statistical methods and derivation of key secondary and secondary end-points. Clinical Global Impression of Change – Improvement (CGI-I; Investigator) and Patient Global Impression of Change – Improvement (PGI-I; Patient or Caregiver) will be assessed at Weeks 5 and 9 for Cohort 1 during the double-blind phase and at Weeks 22, 42 and 61 during the open-label phase. PGI-I and CGI-I will be assessed at Weeks 8 and 14 during the double-blind phase and Weeks 28, 44 and 66 during the open-label phase for Cohort 2. Additional analyses may be considered as appropriate.

Additional assessments may be conducted as considered appropriate.

9.5.3 Safety Assessments

Planned safety assessments include:

Neurological and physical examinations

Clinical laboratory tests

12-lead ECG

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

Columbia Suicide Severity Rating Scale (C-SSRS)

AE monitoring: frequency, severity, duration, causality, outcome

Clinical labs, vitals and ECG measurements may be repeated if needed to corroborate or refute abnormal findings. Both the original and replicate assessments should be recorded in the eCRF.

See Appendix 1 Schedule of Events for timing of Safety Assessments.

Adverse events will be presented for these time periods for Cohorts 1 & 2: ganaxolone vs placebo Titration + Maintenance (Cohort 1: Weeks 1-9, Cohort 2: Weeks 1-14), 1200

mg/d vs placebo (Cohort 1: Weeks 2-5), and 1800 mg/d vs placebo (Cohort 2: Weeks 6-9) for the safety population; open-label (Cohort 1: Weeks 10-61, Cohort 2: 15-66). In addition, tolerability of ganaxolone during the up-titration phases of the study will be compared between the two cohorts. AEs with onset during the titration phase 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 phase will be compared to AEs with onset during the maintenance phase. AEs that emerge during the de-escalation period will be tabulated to investigate whether discontinuation of ganaxolone is associated with withdrawal symptoms. Secondary safety outcome measures include those listed below.

Secondary Safety Parameters for Cohorts 1 & 2	**Cohort 1**		**Cohort 2**		**Combine Cohorts 1 & 2**	
	DB Phase	**OL Phase**	**DB Phase**	**OL Phase**	**DB Phase**	**OL Phase**
Number of subjects at each dose	X	X	X	X		X
The frequency and proportion of subjects with AEs	X	X	X	X		X
Severity of AEs	X	X	X	X		X
AEs leading to DC	X	X	X	X		X
Incidence of subjects with early DC	X	X	X	X		X
Change from baseline in vital signs (blood pressure, respiration rate and heart rate), body weight and ECG	X	X	X	X		X
Change in clinical hematology and chemistry parameters	X	X	X	X		X
Assessment of suicidality via the Columbia Suicide Severity Rating Scale (C-SSRS)	X	X	X	X		X

Additional assessments may be conducted as considered appropriate.

9.5.4 Other Assessments

Blood samples will be obtained from subjects in both cohorts for pharmacokinetic assessment of concomitant anti-epilepsy drugs. Blood samples will be drawn at Visits 1, 2, 3, 4, 5, 7, 8, 9 and 10.

Blood samples for pharmacokinetic assessment of ganaxolone from both cohorts will be drawn at Visits 4, 5, 7, 8, 9 and 10.

The time of the blood sample collection, and the time of the most recent dose prior to the blood sample collection will be recorded. Samples of blood will be centrifuged to obtained plasma, which will be stored frozen (-20°C) until analysis.

Both sets of pharmacokinetic samples will be drawn and retained for assessment on an as-needed basis, for example, to evaluate compliance or drug-drug interactions. Procedures will be put in place to ensure maintenance of the blind should analysis occur during double-blind treatment. For the purposes of this protocol, ganaxolone and concomitant AED PK assessments will not be considered as safety assessments.

9.5.5 Schedule of Study Procedures

Refer to Appendix I. for tabular Schedule of Study Procedures.

The visit window for Phase 1 Double-blind Randomization Visit 2 is +3 days, however, subjects must have a minimum of 28 days of prospective baseline seizure charting. Visit windows are ± 3 days for Phase 1 Double-blind (Visits 3-5) and Visit 6 of Phase 2 Open-label and ± 7 days Phase 2 Open-label (Visits 7- Post taper Safety Follow up), respectively.

9.5.5.1 Visit 1 (Screening Visit)

Written informed consent (signed informed consent form) obtained; demographics and medical history obtained; inclusion/exclusion criteria reviewed; seizure identification review and diagnostic review form submission; concomitant AEDs reviewed; physical and neurological examinations performed; vital signs taken; ECG performed; blood samples drawn for hematology, chemistry, and concomitant AED levels; urine sample

obtained for urinalysis and drug screen; qualitative serum pregnancy test for WCBP; Columbia Suicide Scale assessed; retrospective seizure diary collected and reviewed; subject calendar reviewed.

9.5.5.2 Visit 2 (Randomization; Week 0)

Approval of seizure identification and diagnostic review form required.

Inclusion/exclusion criteria reviewed; concomitant AEDs reviewed; physical and neurological follow-up examinations performed; vital signs taken; blood samples drawn for hematology, chemistry, and concomitant AED levels; urine sample obtained for urinalysis and pregnancy test for WCBP; Columbia Suicide Scale assessed; AEs assessed; subject calendar reviewed; randomization; study medication dispensed.

9.5.5.3 Visit 3 (Up-Titration; Cohort 1: Week 1; Cohort 2: Week 2)

Concomitant AEDs reviewed; physical and neurological examinations performed; vital signs taken; ECG performed 2-3 hours after dosing; blood samples drawn for hematology, chemistry, and concomitant AED levels; urine sample obtained for urinalysis and pregnancy test for WCBP; Columbia Suicide Scale assessed; AEs assessed; subject calendar reviewed; study medication compliance assessed; study medication dispensed.

9.5.5.4 Telephone Follow Up (Cohort 2: Week 5)

AEs assessed; concomitant AEDs and medications reviewed. Subject queried regarding any planned or unplanned changes in dose regimen.

9.5.5.5 Visit 4 (Evaluation; Cohort 1: Week 5; Cohort 2: Week 8)

Concomitant AEDs reviewed; physical and neurological follow-up examinations performed; vital signs taken; blood samples drawn for hematology, chemistry, and study medication and concomitant AED levels; urine sample obtained for urinalysis and pregnancy test for WCBP; Columbia Suicide Scale assessed; AEs assessed; subject calendar reviewed; Clinician Global Impression of Improvement and Patient Global Impression of Improvement assessed; study medication compliance assessed; study medication dispensed.

9.5.5.6 Telephone Follow Up (Cohort 2: Week 11)

AEs assessed; concomitant AEDs and medications reviewed. Subject queried regarding any planned or unplanned changes in dose regimen.

9.5.5.7 Visit 5 (Final DB Evaluation; Cohort 1: Week 9; Cohort 2: Week 14)

Concomitant AEDs reviewed; physical and neurological examinations performed; vital signs taken; ECG performed 2-3 hours after dosing; blood samples drawn for hematology, chemistry, and study medication and concomitant AED levels; urine sample obtained for urinalysis and pregnancy test for WCBP; Columbia Suicide Scale assessed; AEs assessed; subject calendar reviewed; Clinician Global Impression of Improvement and Patient Global Impression of Improvement assessed; study medication compliance assessed; study medication dispensed.

9.5.5.8 Visit 6 (DB Conversion; Cohort 1: Week 10; Cohort 2: Week 16)

Concomitant AEDs reviewed; physical and neurological follow-up examinations performed; vital signs taken; blood samples drawn for hematology, chemistry; urine sample obtained for urinalysis and pregnancy test for WCBP; Columbia Suicide Scale assessed; AEs assessed; subject calendar reviewed; study medication compliance assessed; study medication dispensed.

9.5.5.9 Visit 7 (Cohort 1: Week 14; Cohort 2: Week 20)

Concomitant AEDs reviewed; physical and neurological examinations performed; vital signs taken; ECG performed; blood samples drawn for hematology, chemistry, and study medication and concomitant AED levels; urine sample obtained for urinalysis and pregnancy test for WCBP; Columbia Suicide Scale assessed; AEs assessed; subject calendar reviewed; study medication compliance assessed; study medication dispensed.

9.5.5.10 Visit 8 (Cohort 1: Week 22; Cohort 2: Week 28)

Concomitant AEDs reviewed; physical and neurological follow-up examinations performed; vital signs taken; blood samples drawn for hematology, chemistry, and study medication and concomitant AED levels; urine sample obtained for urinalysis and pregnancy test for WCBP; Columbia Suicide Scale assessed; AEs assessed; subject calendar reviewed; Clinician Global Impression of Improvement and Patient Global

Impression of Improvement assessed; study medication compliance assessed; study medication dispensed.

9.5.5.11 Telephone Follow Up (Cohort 1: Week 32; Cohort 2: Week 36)

AEs assessed; concomitant AEDs and medications reviewed. Subject queried regarding any planned or unplanned changes in dose regimen.

9.5.5.12 Visit 9 (Cohort 1: Week 42; Cohort 2: Week 44)

Concomitant AEDs reviewed; physical and neurological follow-up examinations performed; vital signs taken; blood samples drawn for hematology, chemistry, and study medication and concomitant AED levels; urine sample obtained for urinalysis and pregnancy test for WCBP; Columbia Suicide Scale assessed; AEs assessed; subject calendar reviewed; Clinician Global Impression of Improvement and Patient Global Impression of Improvement assessed; study medication compliance assessed; study medication dispensed.

9.5.5.13 Telephone Follow Up (Cohort 1: Week 52; Cohort 2: Week 52)

AEs assessed; concomitant AEDs and medications reviewed. Subject queried regarding any planned or unplanned changes in dose regimen.

9.5.5.14 Visit 10 Pre-Taper/ET Visit (Cohort 1: Week 61; Cohort 2: Week 66)

Concomitant AEDs reviewed; physical and neurological examinations performed; vital signs taken; ECG performed; blood samples drawn for hematology, chemistry, and study medication and concomitant AED levels; urine sample obtained for urinalysis and pregnancy test for WCBP; Columbia Suicide Scale assessed; AEs assessed; subject calendar reviewed; Clinician Global Impression of Improvement and Patient Global Impression of Improvement assessed; study medication compliance assessed; study medication dispensed.

9.5.5.15 Visit 11 Post-Taper Safety Follow-up Visit (Cohort 1: Week 63; Cohort 2: Week 68)

Concomitant AEDs reviewed; physical and neurological follow-up examinations performed; vital signs taken; urine sample obtained for pregnancy test for WCBP;

Columbia Suicide Scale assessed; AEs assessed; subject calendar reviewed; study medication compliance assessed.

9.5.6 Appropriateness of Measurements

Reduction in seizure frequency is the standard measure of antiepileptic drug efficacy.

9.6 Data Quality Assurance

Steps to be taken to assure the accuracy and reliability of data include the selection of qualified Investigators and appropriate study centers, review of protocol procedures with the Investigator and associated personnel prior to the study, and periodic monitoring and site audits by the Sponsor or their designee. Electronic case report forms will be reviewed for accuracy and completeness by the Sponsor or their designee during on-site monitoring visits and after their return to the Sponsor, and any discrepancies will be resolved with the Investigator or a designee, as appropriate. The data will be entered into the clinical trial database and verified for accuracy.

9.7 Statistical Methods Planned and Determination of Sample Size

9.7.1 Randomization

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.

9.7.2 Analysis Populations

Three populations will be evaluated in this study.

<u>Modified Intent to Treat Population (mITT)</u>

The modified intent to treat (mITT) population (Full Analysis Population in the earlier version of the 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.

Per Protocol Population (PP)

The per protocol (PP) population includes all mITT subjects without major protocol violations during the double-blind phase. The PP population is for supportive efficacy analysis. Major protocol violations will be defined prior to database lock.

Safety Population (SP)

The safety population (SP) includes all patients who received at least one dose of study medication. This population is defined for safety analysis. Subjects will be analyzed based on the actual treatment received.

9.7.3 Missing Data

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

9.7.4 Baseline and Demographic Characteristics

Subject demographic data and baseline characteristics will be summarized by cohort and overall for the mITT population. Categorical variables will be summarized by counts and percentages and continuous variables by number of subjects, mean, standard deviation, median, minimum, and maximum.

9.7.5 Analysis of the Primary Efficacy Variable

The primary efficacy measure is the percentage change in seizure (POS with or without secondary generalization) frequency per 28 days in the Cohort 2 double-blind period 14-week titration + maintenance period relative to baseline in the mITT analysis. Seizure frequency will be based on the number of seizures per 28 days, calculated as (the number of seizures over the time interval multiplied by 28) and divided by the number of days in the interval.

The hypothesis for percent change in seizure frequency per 28 days is:

H0: $\mu 1 - \mu 2 = 0$ Ha: $\mu 1 - \mu 2 \neq 0$

where $\mu 1$ and $\mu 2$ are the median percent change in seizure frequency.

A rank analysis of covariance (ANCOVA) will be conducted on ranked percent change data, with treatment and country as factors and the ranked baseline seizure frequency per

28 days as a covariate. The p-value based on the rank ANCOVA will be presented. Hodges-Lehmann estimator and its 95% confidence interval (CI) will also 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. This analysis provides a robustness assessment of the results.

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 analyzed independently of the US registration end-point. The key-secondary end-point analysis (below) is not predicated on the results of this end-point.

9.7.6 Analysis of Secondary Efficacy Variables

Key Secondary Endpoints:

The three key secondary endpoints (below) 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]

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

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

b) Ganaxolone Maintenance 1200 mg/day + Maintenance 1800 mg/day vs Placebo (Cohort 1: Weeks 2-9).

c) Ganaxolone Titration + Maintenance 1200 mg/d vs placebo (Cohort 1: Weeks 1-5).

d) Ganaxolone Maintenance 1800 mg/d vs placebo (Cohort 1: Weeks 6-9).

e) Ganaxolone maintenance 1200 mg/d vs placebo (Cohort 1: Weeks 2-5).

f) OL (Cohort 1: Weeks 10-61; Cohort 2: Weeks 16-66).

The responder rates and seizure-free rates between ganaxolone and placebo will be compared using a logistic regression analysis. To take into account the ordinal nature of the response to Clinical Global Impression of Change and Patient Global Impression of Change scales (CGI-I, PGI-I), the Row Mean Score Difference, and the p-value based on Cochran-Mantel-Haenszel test adjusting for pooled center (either US or ROW), will be used to test if there is a treatment effect.

Additional assessments may be conducted as considered appropriate. All secondary efficacy variables will also be summarized using descriptive statistics. The exploratory end-point of [redacted] will be summarized descriptively only without formal statistical analysis.

9.7.7 Analysis of Safety Variables

Adverse events (AEs) will be tabulated by Overall, system organ class (SOC), and Preferred Term using the MedDRA v.16.1 coding system. Frequency 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 double-blind phase, by dose level and overall. Additional tables, with AEs subset by severity and by relationship to drug as assessed by the investigator will be presented. Subset listings will be produced for adverse events that cause withdrawal and for SAEs.

Actual values and changes from baseline for laboratory data, vital signs and ECGs will be summarized using descriptive statistics by visit, by treatment and overall for each cohort and phase separately in safety population. Shifts from baseline in low/normal/high classification will be summarized for each laboratory and vital sign parameter. Critically significant changes in laboratory and ECG values and vital signs will be flagged in data listings. 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 and urine drug screen test results will be listed.

9.7.8 PK Analysis

Plasma samples will be collected (Cohort 1: Weeks -4, 0, 1, 5, 9, 14, 22, 42 and 61; Cohort 2: Weeks -8*, 0, 2, 8, 14, 20, 28, 44 and 66) for analysis of levels of concomitant AEDs and if analyzed will be tabulated and reported in a separate report. Plasma samples for ganaxolone levels will be collected at Weeks 5, 9, 14, 22, 42, and 61 for Cohort 1 and Weeks 8, 14, 20, 28, 44, and 66 for Cohort 2. Data from these samples may be used for evaluation of compliance or drug-drug interactions, or a population PK analysis to be conducted. Results may be issued under separate analysis plans and separate reports.

* Subjects entered in Protocol Amendment 2 or before will have the first sample collected at Week -4.

9.7.9 Determination of Sample Size

Marinus 1042-0600 study results using a medium dose (1500mg/day oral suspension) showed that mean difference of percentage change in seizure frequency was -19.58%, with standard deviation of 54.019% and thus giving an effect size of 0.3625. Assuming

an effect size of 0.30 could be achieved in Cohort 2 comparing placebo to high dose ganaxolone (1800 mg/day capsule) in a 1:1 ratio, a sample size of 178 in each group provides approximately 80% power when the estimated difference is -15% and standard deviations are approximately 50% in each group when Wilcoxon rank sum test is used with the two-sided α of 0.05.

10. INVESTIGATOR REQUIREMENTS

10.1 Prior to Study Initiation

The following documentation must be received by the Sponsor or their designee prior to initiation of the trial:

1. Completed original Form FDA 1572, signed by Principal Investigator. Investigators must also complete all regulatory documentation as required by the ICH GCP and local or national regulations.
2. Current curricula vitae of the Principal Investigator, all sub-investigators and key research personnel.
3. Institutional Review Board (IRB) or Ethics Committee (EC) membership list and/or Department of Health and Human Services number.
4. The ICF and any advertising materials must be reviewed and approved by the Sponsor or their designee.
5. Written documentation of IRB/EC approval of protocol (identified by protocol number or title and date of approval) and ICF (identified by protocol number or title and date of approval). A copy of the approved ICF must be supplied.
6. Written documentation of IRB/EC approval of any advertising materials to be used for study recruitment and a copy of approved advertising materials.
7. Current laboratory certification of any laboratories performing the analysis (issuing agency and expiration date), as well as current normal laboratory ranges for all laboratory tests.
8. A signed Clinical Research (Protocol) Agreement.
9. Certified translations of IRB/EC approval letters, pertinent correspondence, and approved ICF (when applicable).
10. Financial disclosure form for Principal Investigator and all sub-investigators.

10.2 Prior to Study Completion

The following data and materials are required by the Sponsor or their designee before the study can be considered complete or terminated:

1. All test results from screening through the end of the study (e.g., clinical data, all special test results).

2. Information properly recorded in the eCRFs by appropriate study personnel and electronically signed and dated by the Investigator.
3. Completed drug accountability records.
4. Copies of protocol or ICF amendments and IRB/EC approval/notification, if appropriate.
5. Copies of IRB/EC notification or approval for safety updates
6. A summary of the study prepared by the Principal Investigator (an IRB/EC summary close letter is acceptable).

10.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include but are not limited to the following:

1. Identification of new safety risk(s) or a change in the incidence or severity of known risk(s) of ganaxolone that indicates a potential health hazard to subjects.
2. Subject enrollment is unsatisfactory.
3. Data recording is inaccurate or incomplete, adversely affecting the ability to interpret results from the study.

10.4 Informed Consent

Template ICFs will be provided to the site. No major deviations should be made; all changes must be approved by the Sponsor. It is recommended that the Sponsor or its Designee review changes to the ICF template prior to IRB or EC submission. The final IRB-approved document must be provided to Sponsor or their designee for their records.

Each subject or the subject's legally authorized representative (if permitted in your country/region) must be presented with the ICF, given an opportunity to ask questions, and must sign the ICF before the subject may participate in any study-related procedures or activities. The consent process should be documented in the subject's medical record. A signed copy of the ICF must be provided to the subject or the subject's legally authorized representative. When applicable, it will be provided in a certified translation of the local language.

Signed consent forms must remain in each subject's study file and must be available for verification by study monitors at any time.

10.5 Adverse Events

The AE definitions and reporting procedures provided in this protocol comply with current CFR 21 Part 312. The Investigator will carefully monitor each subject throughout the study for possible adverse events. All necessary information about an AE (onset, duration, severity, seriousness, causality to study drug, action taken, and outcome) should be documented on adverse event eCRFs (AE eCRFs) and the AEs should be followed until either completely resolved or until a stable chronic outcome is determined by the Investigator

10.5.1 Definitions

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. Any worsening of a preexisting condition (i.e., any clinically significant adverse change in frequency and/or intensity) which is temporally associated with the use of the investigational product, is also an adverse event.

A serious adverse event (SAE) is any untoward medical occurrence that at any dose (including overdose) that meets one or more of the following criteria:

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

  This serious criterion applies if the subject, in the view of the Investigator, is at substantial risk of dying from the AE as it occurs. It does not apply if an AE hypothetically might have caused death if it were more severe.
- Requires or prolongs inpatient hospitalization

  This serious criterion applies if the reported AE necessitates an inpatient admission

(in the US) or a minimum 24-hour inpatient hospitalization (outside US) or, if in the opinion of the Investigator, prolongs an existing hospitalization. A hospitalization for an elective procedure, a routinely scheduled treatment or a social admission is not an SAE.

- Results in permanent or significant disability/incapacity

  This serious criterion applies if the "disability" caused by the reported AE results in a substantial disruption of the subject's ability to carry out normal life functions.

- Results in a congenital anomaly/birth defect

  This serious criterion applies if a subject exposed to the investigational product gives birth to a child with congenital anomaly or birth defect.

Important medical events that do not meet any of the criteria above may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

10.5.2 Evaluating and Recording of Adverse Events

At each visit all adverse events that are observed, elicited by the Investigator, or reported by the subject, will be recorded in the appropriate section of the AE eCRF and evaluated by the Investigator.

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 on the AE eCRF. 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).

10.5.3 Reporting of Adverse Events

10.5.3.1 Serious Adverse Events

Any SAEs, including death due to any cause, which occurs to any subject who has signed Informed Consent (personally or by legally authorized representative [if permitted in your country/region]) 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.

SAEs can be reported by faxing a completed SAE Fax Cover Sheet and serious adverse event CRF (SAE CRF) or by direct telephone communication to the SAE telephone reporting numbers below. A completed SAE Fax Cover Sheet and SAE CRF should follow all telephone reports within 24 hours.

SAE REPORTING

If a fatal or imminently life-threatening SAE occurs, sites are encouraged to call their local Medical Monitor noted in Section 10.5.3.2 or [redacted], M.D., PhD (+1 484-801-4678) in addition to faxing the SAE report.

SAE reporting for US Sites:

Telephone number (Mon.-Fri.; 9am-4pm EST): 1-800-265-1542

Fax Number (24 hours; 7 days/week): 1-877-464-7787

SAE reporting for Russian Sites:

Telephone number (Mon-Fri.; 10am-7pm MSK): +7 (812) 703-00-08

GCT FAX Number: (24 hours; 7 days/week): +7 (812) 703-00-09

GCT Email: SAE-study603-Russia@gctrials.com

SAE reporting for Bulgarian Sites:

Telephone number (Mon.-Fri.; 9am-6pm SOF): +359 2 983 53 58

GCT FAX Number: (24 hours; 7 days/week): +359 2 998 30 05

GCT Email: SAE-study603-Bulgaria@gctrials.com

SAE reporting for Australian Sites:

Fax SAE reports to INC Global Fax Number (24 hours; 7 days/week; 365 days; can be used during holiday period): 8-10-8002-8631012

10.5.3.2 Medical Inquiries

For medical inquiries related to inclusion/exclusion criteria, concomitant medications and other medical inquires not related to SAEs, please call or email the following:

Global Medical Monitor and Monitor for US Sites:

[redacted] INC Research

Telephone: [redacted]

Alternate Telephone: [redacted]

Email: [redacted]

Medical Monitor for Bulgarian Sites:

[redacted] M.D.

Global Clinical Trials (BCT Global)

Telephone: [redacted]

Email: [redacted]

[redacted], M.D.

R

[redacted]

Email: [redacted]

Medical Monitor for Russian Sites:

[redacted] M.D.

R

[redacted]

Email: [redacted]

Email: [redacted]

Medical Monitor for German and Polish Sites:

[redacted], M.D.

Prisma – CRO GmbH

Telephone: [redacted]

Email: [redacted]

Medical Monitor for Australian Sites (during business hours only; during off-duty hours contact Sponsor MM):

Prof. [redacted] M.D.

The Royal Melbourne Hospital

Telephone: [redacted]

Email: [redacted]

10.5.3.3 Pregnancy

Although not considered an AE, it is the responsibility of the Investigator or their designees to report and record any pregnancy in a subject (whether spontaneously reported or identified via testing) that occurs during the study or within 14 days of completing the study. Pregnancy will be documented in the AE eCRF for purposes of reporting. All subjects who become pregnant should be discontinued from the study and must be followed to the completion or termination of the pregnancy. Efforts will be made to follow the newborn for at least 8 weeks post-delivery. The decision whether to taper the study medication is up to the discretion of the Investigator, taking into account the dose, duration of treatment, and other relevant factors. If the pregnancy continues to term, the outcome (health of infant) must also be reported to the Sponsor or their designee.

10.6 Study Monitoring and Audit Requirements

Site visits will be conducted by the Sponsor or their representative to inspect all study related documentation and records including study data, subject's medical records, eCRFs, etc.

The Principal Investigator will permit the Sponsor, their authorized representative including quality assurance groups, the USA FDA, EC/IRB, and the respective national and local authorities to inspect facilities and records relevant to this study. The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

10.7 Electronic Case Report Forms

An eCRF will be used to store and transmit subject information. The file structure and format for the eCRF will be provided by the Sponsor or their representative and should be handled in accordance with the instructions provided. The eCRF must be reviewed and electronically signed, and dated by the Investigator.

Access to the eCRF will be strictly password protected and limited to personnel directly participating in the study. Data should be entered into the eCRF completely by examining personnel or the study coordinator. The eCRF must be completed as soon as possible after any subject evaluation or communication. If data is to be changed due to erroneous input or other reason, an electronic audit trail will track these changes. The eCRFs and computers that store them must be accessible to study monitors and other regulatory auditors.

10.8 Study Drug Accountability

All study drug required for completion of this study will be provided by the Sponsor or their designee. The recipient will acknowledge receipt of the drug indicating shipment content and condition. Damaged supplies will be replaced.

Accurate records of all study drug dispensed from and returned to the study site should be maintained.

All partially used, empty, expired and/or assigned, unused bottles of study drug will be reconciled by the Clinical Monitor and returned for disposal as directed by the Sponsor.

10.9 Confidentiality of Data

Subject medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

With the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection by representatives of the USA FDA, national and local health authorities, the Sponsor or their designee, and the IRB/EC.

10.10 Retention of Records

USA FDA regulations (21 CFR 312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including eCRFs, consent forms, laboratory test results, and medical inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the investigation is discontinued and the USA FDA and the applicable national and local health authorities are notified. The Sponsor or their designee will notify the Principal Investigator of these events.

10.11 Protocol Adherence

Each Investigator must adhere to the protocol as detailed in this document and agrees that any changes to the protocol must be approved by the Sponsor or their designee prior to seeking approval from the IRB. Each Investigator will be responsible for enrolling only those subjects who have met protocol eligibility criteria.

11. PUBLICATION PLAN

The study will be listed in the ClinicalTrials.gov registry. Study results will be made public and disseminated to individual research sites in a timely manner, and no later than one year after study completion.

12. REFERENCES

Bialer, M., et al. (2010) Progress report on new antiepileptic drugs: A summary of the Tenth Eilat Conference (EILAT X). Epilepsy Res 92:89-124.

Carter RB, Wood PL, Wieland S, Hawkinson JE, Belelli D, Lambert JJ, White HS, Wolf HH, Mirsadeghi S, Tahir SH, Bolger MB, Lan NC, Gee KW (1997) Characterization of the anticonvulsant properties of ganaxolone (CCD 1042; 3alpha-hydroxy-3beta-methyl-5alpha-pregnan-20-one), a selective, high-affinity, steroid modulator of the gamma-aminobutyric acid(A) receptor. J Pharmacol Exp Ther 280:1284-1295.

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

French JA, Kanner AM, Bautista J, Abou-Khalil B, Browne T, Harden CL, Theodore WH, Bazil C, Stern J, Schachter SC, Bergen D, Hirtz D, Montouris GD, Nespeca M, Gidal B, Marks WJ, Jr., Turk WR, Fischer JH, Bourgeois B, Wilner A, Faught RE, Jr., Sachdeo RC, Beydoun A, Glauser TA (2004) Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 62:1261-1273.

Kaminski RM, Livingood MR, Rogawski MA (2004) Allopregnanolone analogs that positively modulate GABA receptors protect against partial seizures induced by 6-Hz electrical stimulation in mice. Epilepsia 45:864-867.

Reddy DS, Castaneda DC, O'Malley BW, Rogawski MA (2004) Anticonvulsant activity of progesterone and neurosteroids in progesterone receptor knockout mice. J Pharmacol Exp Ther 310:230-239.

APPENDICES

12.1 Appendix 1: Schedule of Events

Cohort 1 Period 1: Double-blind Phase (Weeks -8 thru 9)						
Period/Phase	**Determination of Baseline and Eligibility**			**Titration+ Maintenance**		
WEEK	-8	-4	0	1	5	9
VISIT	**Historical baseline**	**Screening visit V1**	**Randomization visit V2**	**Up-titration V3**	**Evaluation visit V4**	**Final DB Evaluation visit V5**
Screening and Diagnosis						
Informed consent		X				
Demographics & Medical		X				
Seizure Identification & Diagnostic Review Form Approval		X				
Inclusion/Exclusion criteria		X	X			
Concomitant AEDs[1] Review		X	X	X	X	X
Randomization			X			
Safety Assessments						
Physical examination		X		X		X
Physical follow-up exam			X		X	
Vital signs		X	X	X	X	X
Neurological examination		X		X		X
Neurological follow-up exam			X		X	
ECG		X[4]		X[2]		X[2]
Safety Labs		X[8]	X	X	X	X[8]
Urine Drug Screen		X[3]				
Pregnancy test (WCBP)		X[6]	X[7]	X[7]	X[7]	X[7]
Columbia Suicide Scale		X	X	X	X	X
Review safety and record AEs			X	X	X	X
Efficacy Assessments						
Retrospective Seizure Diary[5] (weeks -8 to -4)	X					
Retrospective Seizure Diary Collection and Review		X				
Subject Calendar Review (prospective)		X	X	X	X	X
Clinician's Global Impression of Improvement					X	X
Patient/Caregiver Global Impression of Improvement					X	X

Continued on next page

Cohort 1 Period 1: Double-blind Phase (Weeks -8 thru 9)						
Period/Phase	**Determination of Baseline and Eligibility**			**Titration+ Maintenance**		
WEEK	-8	-4	0	1	5	9
VISIT	**Historical baseline**	**Screening visit V1**	**Randomization visit V2**	**Up-titration V3**	**Evaluation visit V4**	**Final DB Evaluation visit V5**
PK Assessments						
Concomitant AED blood sample		X	X	X	X	X
Study drug blood samples					X	X
Study Medication						
Dispense study medication			X	X	X	X
Study medication compliance check				X	X	X

[1] Concomitant AEDs or their dose must be stable for 1 month prior to historical baseline and cannot be changed at any time prior to Visit 5, but may be adjusted during the Open-Label Phase of the study; if the subject is using VNS, the settings cannot be changed during the course of the study
[2] 12-lead ECG at study drug T_{max}, which is 2 to 3 hours after dosing.
[3] Drug Screen mandatory at Screening Visit and at Investigator's discretion at subsequent visits
[4] ECG can be repeated at baseline, if medically necessary
[5] Retrospective Seizure Diary contains seizure information provided by the patient for Week -8 through Week-4 at time of screening, and reviewed following ICF. Combinations of 4-week retrospective seizure diary contiguous with 4-week prospective seizure calendar (week -4 through week 0) will be used to determine qualifications for study entry.
[6] Qualitative serum pregnancy test
[7] Urine pregnancy test
[8] Thyroxine and TSH will only be conducted at Screening Visit and Visit 5
AEs = adverse events; AED = antiepileptic drug; ECG = electrocardiogram; Tmax = time to maximum concentration; WCBP = women

Continued on next page

Cohort 1 Period 2: Open-label Phase (Weeks 10-63)								
Period/Phase	**Open-label Phase**							**De-escalation period**
WEEK	10	14	22	32	42	52	61	63
VISIT	**Visit 6 (DB conversion, Wk 1)**	**Visit 7**	**Visit 8**	**Telephone Follow-up**	**Visit 9**	**Telephone Follow-up**	**Visit 10 (Pre-taper/ ET)**	**Post-Taper Safety Follow up**
Screening and Diagnosis								
Informed consent								
Demographics & Medical HX								
Inclusion/Exclusion criteria								
Concomitant AEDs[1]	X	X	X		X		X	X
Randomization								
Safety Assessments								
Physical examination		X					X	
Physical follow-up exam	X		X		X			X
Vital signs	X	X	X		X		X	X
Neurological examination		X					X	
Neurological brief exam	X		X		X			X
ECG		X					X	
Safety Labs	X	X	X		X		X	
Urine pregnancy test (WCBP)	X	X	X		X		X	X
Columbia Suicide Scale	X	X	X		X		X	X
Review safety and record AEs	X	X	X		X		X	X
Telephone Follow Up				X[2]		X[2]		
Efficacy Assessments								
Subject Calendar Review (prospective)	X	X	X		X		X	X
Clinician's Global Impression of Improvement			X		X		X	
Patient/Caregiver Global Impression of Improvement			X		X		X	

Cohort 1 Period 2: Open-label Phase (Weeks 10-63)								
Period/Phase	**Open-label Phase**							**De-escalation period**
WEEK	10	14	22	32	42	52	61	63
VISIT	**Visit 6 (DB conversion, Wk 1)**	**Visit 7**	**Visit 8**	**Telephone Follow-up**	**Visit 9**	**Telephone Follow-up**	**Visit 10 (Pre-taper/ ET)**	**Post-Taper Safety Follow up**
PK Assessments								
Concomitant AED blood sample[1]		X	X		X		X	
Study drug blood samples		X	X		X		X	
Study Medication								
Dispense study medication	X	X	X		X		X	
Study med compliance check	X	X	X		X		X	X

[1] Concomitant AEDs or their dose must be stable for 1 month prior to screening and cannot be changed at any time prior to Visit 5, but may be adjusted during the Open-Label Phase of the study; if the subject is using VNS, the settings cannot be changed during the course of the study.
[2] Review safety and record AEs. Review and record changes to concomitant AEDs & medications

Cohort 2 Period 1: Double-blind Phase (Weeks -8 thru 14)							
Period/Phase	**Determination of Baseline* and Eligibility**		**Titration+ Maintenance**				
WEEK	-8	0	2	5	8	11	14
VISIT	**Screening V1**	**Randomiza-tion V2**	**Up-titration V3**	**Telephone Follow up**	**Evaluation V4**	**Telephone Follow up**	**Final DB Evaluation V5**
Screening and Diagnosis							
Informed consent	X						
Demographics & Medical HX	X						
Seizure Identification & Diagnostic Review Form Approval	X						
Inclusion/Exclusion criteria	X	X					
Concomitant AEDs[1] Review	X	X	X		X		X
Randomization		X					
Safety Assessments							
Physical examination	X		X				X
Physical follow-up exam		X			X		
Vital signs	X	X	X		X		X
Neurological examination	X		X				X
Neurological follow-up exam		X			X		
ECG	X[4]		X[2]				X[2]
Safety Labs	X[8]	X	X		X		X[8]
Urine Drug Screen	X[3]						
Pregnancy test (WCBP)	X[6]	X[7]	X[7]		X[7]		X[7]
Columbia Suicide Scale	X	X	X		X		X
Review safety and record AEs		X	X		X		X
Telephone Follow Up				X[9]		X[9]	

* Subjects who entered into Cohort 2 under Protocol Amendment 2 and prior attended the Screening Visit at Week -4.

Cohort 2 Period 1: Double-blind Phase (Weeks -8 thru 14)							
Period/Phase	**Determination of Baseline and Eligibility**		**Titration+ Maintenance**				
WEEK	-8	0	2	5	8	11	14
VISIT	**Screening V1**	**Randomization V2**	**Up-titration V3**	**Telephone Follow up**	**Evaluation V4**	**Telephone Follow up**	**Final DB Evaluation V5**
Efficacy Assessments							
Subject Calendar Review (prospective)[5]	X	X	X		X		X
Clinician's Global Impression of Improvement					X		X
Patient/Caregiver Global Impression of Improvement					X		X
PK Assessments							
Concomitant AED blood sample	X	X	X		X		X
Study drug blood samples					X		X
Study Medication							
Dispense study medication		X	X		X		X
Study medication compliance check			X		X		X

[1] Concomitant AEDs or their dose must be stable for 1 month prior to Screening and cannot be changed at any time prior to Visit 5, but may be adjusted during the Open-Label Phase of the study; if the subject is using VNS, the settings cannot be changed during the course of the study
[2] 12-lead ECG at study drug T_{max}, which is 2 to 3 hours after dosing.
[3] Drug Screen mandatory at Screening Visit and at Investigator's discretion at subsequent visits
[4] ECG can be repeated at baseline, if medically necessary
[5] Prospective 8 week seizure calendar will be used to determine qualifications for study entry.
[6] Qualitative serum pregnancy test
[7] Urine pregnancy test
[8] Thyroxine and TSH will only be conducted at Screening Visit and Visit 5
[9] Review safety and record AEs. Review and record changes to concomitant AEDs & medications
AEs = adverse events; AED = antiepileptic drug; ECG = electrocardiogram; Tmax = time to maximum concentration; WCBP = women

Cohort 2 Period 2: Open-label Phase (Weeks 16-68)								
Period/Phase	**Open-label Phase**							**De-escalation period**
WEEK	16	20	28	36	44	56	66	68
VISIT	**Visit 6 (DB conversion, Wk 2)**	**Visit 7**	**Visit 8**	**Telephone Follow-up**	**Visit 9**	**Telephone Follow-up**	**Visit 10 (Pre-Taper/ ET)**	**Post-Taper Safety Follow up**
Screening and Diagnosis								
Informed consent								
Demographics & Medical HX								
Inclusion/Exclusion criteria								
Concomitant AEDs[1]	X	X	X		X		X	X
Randomization								
Safety Assessments								
Physical examination		X					X	
Physical follow-up exam	X		X		X			X
Vital signs	X	X	X		X		X	X
Neurological examination		X					X	
Neurological brief exam	X		X		X			X
ECG		X					X	
Safety Labs	X	X	X		X		X	
Urine pregnancy test (WCBP)	X	X	X		X		X	X
Columbia Suicide Scale	X	X	X		X		X	X
Review safety and record AEs	X	X	X		X		X	X
Telephone Follow Up				X[2]		X[2]		
Efficacy Assessments								
Subject Calendar Review (prospective)	X	X	X		X		X	X
Clinician's Global Impression of Improvement			X		X		X	
Patient/Caregiver Global Impression of Improvement			X		X		X	

Cohort 2 Period 2: Open-label Phase (Weeks 16-68)								
Period/Phase	**Open-label Phase**							**De-escalation period**
WEEK	16	20	28	36	44	56	66	68
VISIT	**Visit 6 (DB conversion, Wk 2)**	**Visit 7**	**Visit 8**	**Telephone Follow-up**	**Visit 9**	**Telephone Follow-up**	**Visit 10 (Pre-Taper/ ET)**	**Post-Taper Safety Follow up**
PK Assessments								
Concomitant AED blood sample[1]		X	X		X		X	
Study drug blood samples		X	X		X		X	
Study Medication								
Dispense study medication	X	X	X		X		X	
Study med compliance check	X	X	X		X		X	X

[1] Concomitant AEDs or their dose must be stable for 1 month prior to screening and cannot be changed at any time prior to Visit 5, but may be adjusted during the Open-Label Phase of the study; if the subject is using VNS, the settings cannot be changed during the course of the study.
[2] Review safety and record AEs. Review and record changes to concomitant AEDs & medications

12.2 Appendix 2: Clinical Laboratory Tests

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		Drug screen*
CO_2		
Total Protein		
Serum Albumin		
Thyroxine		
Thyroid Stimulating Hormone		
Qualitative serum β-human chorionic growth hormone (β-HCG) pregnancy		

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

* At Screening and as needed at the Investigator's discretion; includes phencyclidine, opiates, THC, methamphetamines/amphetamine, cocaine and oxycodone.

12.3 Appendix 3: Strong and Moderate Cytochrome P450 CYP 3A4, 5, 7 Inducers and Inhibitors Prohibited During Study 1042-0603

Prohibited Strong and Moderate CYP 3A4 Inhibitors	Prohibited Strong and Moderate CYP 3A4 Inducers*
amprenavir	avasimibe
aprepitant	bosentan
atazanavir	efavirenz
boceprevir	etravirine
ciprofloxacin	modafinil
clarithromycin	nafcillin
conivaptan	rifabutin
diltiazem	rifampin
erythromycin	St. John's wort
fluconazole	troglitazone (not sold in US, Russia)
fluvoxamine	
fosamprenavir	
grapefruit juice	
imatinib	
indinavir	
itraconazole	
ketoconazole	
mibefradil (not sold in US, Russia)	
nefazodone (not sold in US, Russia)	
nelfinavir	
posaconazole	
ritonavir	
saquinavir	
telaprevir	
telithromycin	
troleandomycin (not sold in US, Russia)	
verapamil	
voriconazole	

*Carbamazepine and phenytoin are both moderate CYP 3A4 inducers but are permitted as background AEDs during the study.

Note: This list is not exhaustive so please consult with your in-country Medical Monitor.

Data from http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm and http://medicine.iupui.edu/clinpharm/ddis/ClinicalTable.aspx; accessed 12June13

12.4 Appendix 4: Titration Dosing Instructions for Subjects

Translations in Bulgarian, German and Polish are available upon request.

J Vqlmt r Mg Vql Vbdt slbVkr) Dnb Cnrhmf Dnrsqt bshnmr u0-.
Mqnsnbnk0. 31,. 5. 2 07It kw02

D8J 8UL IL J CGI 8BSIRN8ORGI L J PCR PCGKS OC PRS BW
PS 8HCAR BL PGI D GI PROS ARGL J P

E Wk c8TTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTT

E cvr : nnmgl rk cl r8 TTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTT

Pf cqc Wpc wms pbmqgl e gl qrps argml q dmp rf c l cvr TTTTTTTTu cci q. k ml rf q njc Wqc agpajc ml c(dpmk TTTT. TTTTT. TTTTT qrWpr bWc(rm TTTT. TTTTT. TTTTT cl b bWc(- ; cncl bgl e ml u f gaf nf Wqc wms Wpc gl rf c qrsbw) wms k Ww_c epWbs Wjjwgl apcWqgl e rgrpWgml () k Wgl rWgl gl e rf c qWk c Wk ms l r k Wgl rcl Wl ac(mpepWbs Wjjwbcapc Wqgl e rf c Wk ms l r mdqrsbwbpse bc,cqaWjWgml (bspgl e rf gq rgk c- Pf c af Wpr _cjmu jgqrq rf c bWwmpu cci) bmqc) Wl b f mu k Wl w aWnqsjcq wms qf ms jb rWi c dmpc Waf bmqc- **NjcZpc rZi c cZaf bmpc hs pr _cdmoc mos n rm0 f ms op ZdrcoZ k cZj mopl Zai t gf 4 ms l acp 02/ k j(mdt Zrco- DoZncdbs gr Zl b eoZncdbs gr hs gac Zoc l mr Zjjmt cb Zr Zl wrgk c bs ogl e wms onZorgagnZrgml gl rf gp ajgl gaZj rogZj)** AWaf bmqc qf ms jb _c qcnWpWrcb _w Wk gl gk sk md5 f ms pq Wl b Wk Wgk sk md01 f ms pq- : k gqqcb bmqc mdqrsbwk cbgaWgml k Ww_c rWi cl s n rm5 f ms pq _cdmpc rf c l cvr qafcbsjcb bmqc9 mrf cpu gqc) rf c bmqc qf ms jb l mr _c rWi cl - I jcWqc iccn rpWai mdrf c bWwq wms k gqqcb Wbmqc Wl b aml rWar rf c qrsbw ammpbgl Wmp gd wms k gqq 3 bmqcq gl Wpmu mp k mpc- I jcWqc qWc Wjjck nrw) nWprgWjjws qcb Wl b s l s qcb _mrrjcq md rf c qrsbwbps e Wl b pcrspl rf c _mrrjcq Wr wms pl cvr tggr-

Example 1:

Dose Titration / Dose Maintenance / Dose De-Escalation (Please circle phase)

BZw. T cci ________ BZrcYYY. YYY. YYY	Bmpc k e(	J sk _comdaZnps jcprmrZi c Zr C8AE BL PC u RT GAC. B8W
; Ww09 8. 12. 02	3//	0
; Ww198. 13. 02	3//	0
; Ww298. 14. 02	5//	1
; Ww398. 2/. 02	5// k e	1

Example 2:

Dose Titration / Dose Maintenance / Dose De-Escalation (Please circle phase)

BZw. T cci ________ BZrcYYY. YYY. YYY	Bmpc k e(	J sk _comdaZnps jcprmrZi c Zr C8AE BL PC u RT GAC. B8W
S cci 1,49 8. 2/. 02 rm0/. 15. 02	01// k e	2

I Wec 0 md1

Dose Titration / Dose Maintenance / Dose De-Escalation (Please circle phase)

BZw. T cci _________ BZrcYYY. YYY. YYY	Bmpc k e(	J sk _comdaZnpsjcprmrZi c Zr C8 AE BL PC u RT GAC. B8 W

; spgl e rf c dgpqr 8 u cci q mdrf c qrs bw) wms u gjj l mr i l mu gdwms Wpc rWigl e qrs bwbps e u grf rf c Wargtc gl epcbgcl r, eWl Wmjml c mprf c qrs bwbps e u grf ms r rf c gl epcbgcl r , njWac_m- Nmk c ncmnjc k Wwpcnmpr dccjgl e bgxxw) rgpcb) mp qjccnwWdrcprWigl e eWl Wmjml c- Pf cqc qgbc cddcarq s qs Wjjwem Wu Ww Wdrcp 1,2 bWwq- Dlwms cvncpgcl ac Wl wqgbc cddcarq dpmk rf c qrs bwk cbgaWrgml rf Wr gl rcpdcpc u grf wms p bWgjw Warg grgcq mp f Wtc Wl wos cqrgml q) njc Wqc aml rWar wms p qrs bwbmarmp Wr rf c rcjcnf ml c l s k _cp_cjmu rmqcc gdWbmqc Wbhs qrk cl r gq l cacqqWpw-

Nrs bw; marmp8TTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTT

Pcjcnf ml c Esk _cp8 TTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTT

12.5 Appendix 5: Subject Seizure Calendar

Translations in Bulgarian, German and Polish are available upon request.

MARINUS
PHARMACEUTICALS, INC.

Subject Seizure Calendar

Protocol 1042-0603

Subject ID: ____ ____ ____ ____ ____ ____ Subject Initials: ____ ____ ____

Dates: _____ to _____

Please fill out on the morning of the next visit.		
	Date of Last Dose	**Time of Last Dose**
Study Drug		
AED 1:		
AED 2:		
AED 3:		

****This booklet contains important information. If found please return. ****

Dr. Name: _____Phone #:_____

Street Address: _____City_____ State: _____ Zip: _____

v. 24Jul2013 USA

Investigator Seizure Code:

Investigators, please use the following codes A-F to denote the type of partial onset seizure. If the subject only has 1 type of seizure, then only 1 letter will be used and the others left blank. If the subject has more than 1 subtype of seizure (ie two different complex partial seizures), use only 1 letter.

A: Simple partial seizure without motor/observable component

B: Simple partial seizure WITH motor/observable component

C: Complex partial seizure (alteration of awareness or dyscognitive features)

D. Partial seizure consisting of or ending in a secondarily generalized tonic clonic convulsion

E: Other type 1

Please provide the subject with the following example:
On March 2, she experiences 1 seizure described as a strange electrical smell followed by a weird taste (SPS w/o motor) and 1 seizure described as loss of awareness, staring, and then the left side becoming stiff (CPS). She noted that she took all her study medication and non-study AEDs. On March 3, she did not experience any seizures and took all of study medication but skipped 1 non-study AED.

02/MAR
☐ **No Seizures Today**
A: 1 **C: 1**
Study Drug Taken? **X** Y ☐N Non-Study AEDs Taken? **X** Y ☐N

03/MAR
X No Seizures Today
Study Drug Taken? **X** Y ☐N Non-Study AEDs Taken? ☐ Y **X** N

Subject ID: _ _ _ _ _ _ _ Subject Initials: _ _ _ Month: _ _ _ Year: _ _ _ _

Subject Instructions:

1. Take this diary home and use it every day to keep track of your seizures.
2. The research staff will review your seizures with you and each seizure type will be assigned a special code.
3. If you have a seizure, record the number of seizures and the type of seizure (using the assigned code) on the diary.
4. If you do not have any seizures on that day, mark the 'no seizure' box.
5. Bring the seizure diary with you to every appointment.

Seizure Code: Description given by patient/caregiver (Seizure Type)

A:

B:

C:

D:

E:

Subject ID: __ __ __ __ __ __ Subject Initials: __ __ __ Month: __ __ __ Year: __ __ __ __

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
__ __/ __ __ __	__ __/ __ __ __	__ __/ __ __ __	__ __/ __ __ __	__ __/ __ __ __	__ __/ __ __ __	__ __/ __ __ __
☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures
Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N	Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N	Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N	Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N	Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N	Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N	Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N
__ __/ __ __ __	__ __/ __ __ __	__ __/ __ __ __	__ __/ __ __ __	__ __/ __ __ __	__ __/ __ __ __	__ __/ __ __ __
☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures
Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N	Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N	Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N	Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N	Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N	Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N	Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N
__ __/ __ __ __	__ __/ __ __ __	__ __/ __ __ __	__ __/ __ __ __	__ __/ __ __ __	__ __/ __ __ __	__ __/ __ __ __
☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures
Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N	Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N	Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N	Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N	Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N	Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N	Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N
__ __/ __ __ __	__ __/ __ __ __	__ __/ __ __ __	__ __/ __ __ __	__ __/ __ __ __	__ __/ __ __ __	__ __/ __ __ __
☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures
Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N	Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N	Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N	Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N	Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N	Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N	Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N
__ __/ __ __ __	__ __/ __ __ __	__ __/ __ __ __	__ __/ __ __ __	__ __/ __ __ __	__ __/ __ __ __	__ __/ __ __ __
☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures	☐ No Seizures
Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N	Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N	Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N	Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N	Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N	Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N	Study Drug Taken? ☐Y ☐N Non-Study AEDs Taken? ☐Y ☐N

Date:	**Description of illness, injury, side effect, or missed doses**	**Any action taken including medication**

12.6 Appendix 6: Clinical Global Impression- Improvement (Patient/Caregiver)

Translations in Bulgarian, German, and Polish are available upon request.

MVqshbhoVms DC8	Phrhs 8	PhrhsCVsd8
=gdbi hesgd Vrrdrrl dms v Vr rms bnl okdsdc8		

-jemebSj CjnaSjCl opcrrenm–Cl opnucl cms -CQ)C(Itaicbs

=hqbkd sgd VooqnoqhVsd qdronmrd sgVs Vc dpt Vsdkwc drbqhadr gnv wnt qrwl osnl r gVud
Hl oqnudc nq v nqrdmdc qdkVshud sn aVrdkhmd adenqd sgd adf hmmhmf nesgd rst c w#adenqd
sgd c nt akd, akhmc onqshmmnesgd rst c w(-

0: udqwl t bg Hl oqnudc

1: l t bg Hl oqnudc

2: l hmHl Vkwvl oqnudc

3: rn bg Vmf d

4: l hmHl Vkwvv nqrd

5: l t bg v nqrd

6: udqwl t bg v nqrd

Mqnsnbnk0. 31,. 5. 2 u-15Itl02

12.7 Appendix 7: Columbia Suicide Severity Rating Scale (C-SSRS) Baseline/Screen

Baseline version (1/14/09)
To be used at Screen and Baseline Visits

Translations in Bulgarian, German and Polish are available upon request.

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Lifetime: Time He/She Felt Most Suicidal

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?

If yes, describe:

Yes ☐ No ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan.
Have you actually had any thoughts of killing yourself?

If yes, describe:

Yes ☐ No ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go throug h with it."*
Have you been thinking about how you might do this?

If yes, describe:

Yes ☐ No ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?

If yes, describe:

Yes ☐ No ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill you rself? Do you intend to carry out this plan?

If yes, describe:

Yes ☐ No ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.

Most Severe Ideation: ____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

Appendix 7 Continued: Columbia Suicide Severity Rating Scale (C-SSRS)-Since Last Visit

Since Last Visit version (1/14/09)
To be used at visits post Baseline/Randomization
Translations in Bulgarian, German and Polish are available upon request.

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e g , *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period This is different than a specific plan with time, place or method details worked out (e g , thought of method to kill self but not a specific plan) Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself Intent does not have to be 100% If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt ***There does not have to be any injury or harm***, just the potential for injury or harm If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e g , gunshot to head, jumping from window of a high floor/story) Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** **No** ☐ ☐ Total # of Attempts _____ **Yes** **No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting Once they ingest any pills, this becomes an attempt rather than an interrupted attempt Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger Once they pull the trigger, even if the gun fails to fire, it is an attempt Jumping: Person is poised to jump, is grabbed and taken down from ledge Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt This can include anything beyond a verbalization or thought, such as assembling a specific method (e g , buying pills, purchasing a gun) or preparing for one's death by suicide (e g , giving things away, writing a suicide note) ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** **No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** **No** ☐ ☐
Suicide:	**Yes** **No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0 No physical damage or very minor physical damage (e g , surface scratches) 1 Minor physical damage (e g , lethargic speech; first-degree burns; mild bleeding; sprains) 2 Moderate physical damage; medical attention needed (e g , conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel) 3 Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e g , comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures) 4 Severe physical damage; *medical* hospitalization with intensive care required (e g , comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area) 5 Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over) 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

12.8 Appendix 8: Protocol History

Amendment 4 Summary of Changes from version September 23, 2014 to April 08, 2016

Page	Section, Title, Paragraph, Line	Original Text	Revised Text
1	Sponsor	Marinus Pharmaceuticals, Inc. 142 Temple Street, Suite 205 New Haven, CT 06510	Marinus Pharmaceuticals, Inc. 170 N. Radnor Chester Road Suite 250 Radnor, PA 19087
1	Sponsor Contact	[redacted] Ph.D. [redacted] Clinical Development Telephone: [redacted]	[redacted] [redacted] Clinical Operations Telephone: [redacted] Email: [redacted]
1	Sponsor's Medical Representative	[redacted] Ph.D. Clinical Development & Regulatory Officer Telephone: [redacted] [redacted], M.D., Ph.D. Marinus Medical Advisor [redacted]	[redacted] MD, Ph.D. [redacted] Clinical Development Office Phone: +1 484-801-4678 Mobile Phone: [redacted] Email: [redacted]
	Amendment		Added: Amendment 4: April 08, 2016
Reason for Change: Administrative change – address and contact information			
3	Synopsis-Design and Methodology, Line 9	Cohort 2 (N=292)…	Cohort 2 (approximately N=359)…
4	Synopsis-Number of Subjects	Approximately 400 subjects will be screened to randomize approximately 50 subjects into Cohort 1 and 292 subjects into Cohort 2 at 1:1 ganaxolone or placebo.	Approximately 525 subjects will be screened to randomize approximately 46 subjects into Cohort 1 and 359 subjects into Cohort 2 at 1:1 ganaxolone or placebo.
4	Synopsis-Criteria for Evaluation	**Criteria for Evaluation**: **Primary Efficacy**: Primary efficacy will be percent change in seizure (POS with or without secondary generalization) frequency per 28 days in the Cohort 2 double blind 12-week maintenance period relative to the baseline. **Secondary Efficacy**: Secondary efficacy assessments include	**Criteria for Efficacy Evaluation**: 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. The primary endpoint analysis will consist of rank analysis of covariance (ANCOVA) conducted on the percent change data, with treatment and pooled countries as

		evaluation of seizure frequency, response rate and seizure-free rate by dose in double-blind phase, and in open-label phase. See Section 9.5.2.	factors and the rank baseline seizure frequency per 28 days as a covariate. The primary efficacy endpoint for European registration is 50% responder rate during the maintenance treatment phase of the double-blind phase for Cohort 2. A 50% responder is an individual who experiences at least a 50% decrease in seizure frequency compared to baseline. Key secondary end-points: The three 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. k) Percent change in the 28-day seizure frequency from baseline to the DB phase during the maintenance treatment period for Cohort 2 l) Change from baseline in 28-day seizure frequency during the DB phase for Cohort 2 (titration + maintenance and maintenance only). m) 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 n) 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% o) 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 p) 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 q) 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 r) 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) s) Patient Global Impression of Change – Improvement (PGI-I; Patient/Caregiver) at each assessment visit t) Clinical Global Impression of Change – Improvement (CGI-I; Investigator) at each assessment visit Exploratory endpoint [redacted] The primary and secondary efficacy outcome measures will be assessed for each of the time periods listed below in Cohort 1 DB phase ([a-e] below) and Cohort 1+Cohort 2 OL if below: g) Ganaxolone Titration + Maintenance 1200 mg/day + Maintenance 1800 mg/day vs Placebo (Cohort 1: Weeks 1-9).

			h) Ganaxolone Maintenance 1200 mg/day + Maintenance 1800 mg/day vs Placebo (Cohort 1: Weeks 2-9). i) Ganaxolone Titration + Maintenance 1200 mg/d vs placebo (Cohort 1: Weeks 1-5). j) Ganaxolone Maintenance 1800 mg/d vs placebo (Cohort 1: Weeks 6-9). k) Ganaxolone Maintenance 1200 mg/d vs placebo (Cohort 1: Weeks 2-5) l) OL (Cohort 1: Weeks 10-61; Cohort 2: Weeks 16-66)
6	Synopsis – Safety		Added: Columbia Suicide Severity Scale (C-SSRS)
6	Synopsis-Statistical Methods	The primary endpoint analysis will consist of analysis of covariance (ANCOVA) conducted on the log-transformed percent change data, with treatment and pooled countries as factors and the logged baseline seizure frequency per 28 days as a covariate. All secondary efficacy variables will be summarized using descriptive statistics. The responder rates and seizure-free rates between ganaxolone and placebo will be compared using a Cochran-Mantel-Haenszel analysis. Mean monthly seizure frequency for each week after dosing will be analyzed in a manner similar to the primary endpoint analysis. Change and percent change of mean monthly seizure frequencies will be analyzed by Kruskal-Wallis test. Adverse events (AEs) will be tabulated by Overall, system organ class (SOC), and Preferred Term using the MedDRA v.16.0 coding system. Incidence and percentage of adverse events will be for each phase of the study, and in Phase 1, by dose level and overall.	The primary endpoint analysis will consist of rank analysis of covariance (ANCOVA) conducted on the percent change data, with treatment and pooled countries as factors and the rank baseline seizure frequency per 28 days as a covariate. Added: The responder rates and seizure-free rates between ganaxolone and placebo will be compared using a logistic regression analysis. To take into account the ordinal nature of the response to Clinical Global Impression of Change and Patient Global Impression of Change scales (CGI-I, PGI-I), the Row Mean Score Difference, and the p-value based on Cochran-Mantel-Haenszel test adjusting for pooled center (either US or ROW), will be used to test if there is a treatment effect. Adverse events (AEs) will be tabulated by Overall, system organ class (SOC), and Preferred Term using the MedDRA v.16.1 coding system. Frequency 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 double-blind phase, by dose level and overall.

Reason for Change: The sample size calculations for this study were based on results from one previous study. After analysis of blinded data, including the rate of discontinuations from this study, it was determined that additional patients may be needed to ensure an appropriate sample size.			
19	9.1 Overall Study Design and Plan, Paragraph 1, Line 1, 5 & 8	This is a 2-cohort study with each cohort comprised of 2 treatment phases in each cohort. Cohort 1 (N=approximately 50)… Cohort 2 (N=292) will enroll into a 76-week study comprising an 8-week baseline phase and two treatment phases: a 14-week double-blind treatment phase followed by a 52-week open label treatment phase.	This is a 2-cohort study with each cohort comprised of 2 treatment phases. Cohort 1 (N=approximately 46)… Cohort 2 (N=359) will enroll into a 76-week study comprising an 8-week baseline phase and two treatment phases: a 14-week double-blind treatment phase followed by a 52-week open label treatment phase.
19	9.1 Overall Study Design and Plan, Paragraph 8, Line 2	The complete list of tasks per visit is described in Section 9.5.1.5…	The complete list of tasks per visit is described in Section 9.5.5…
Reason for Change: Clarification of the CSP section location for Schedule of Study Procedures			
21	Figure 1. Cohort 1 Trial Design	WK 46 – Visit 9	WK 42 – Visit 9
22	9.3.1 Number of Subjects	Approximately 400 subjects will be screened to randomize approximately 50 subjects into Cohort 1 and approximately 292 subjects into Cohort 2 at a 1:1 ratio of ganaxolone to placebo, assuming a screen-failure rate of 15%. It is estimated that approximately 263 subjects will complete the 14-week Double-Blind Phase of Cohort 2, which assumes approximately 10% discontinuation rate.	Approximately 525 subjects will be screened to randomize approximately 46 subjects into Cohort 1 and approximately 356 subjects into Cohort 2 at a 1:1 ratio of ganaxolone to placebo, assuming a screen-failure rate of 15%. It is estimated that approximately 320 subjects will complete the 14-week Double-Blind Phase of Cohort 2, which assumes approximately 10% discontinuation rate.
Reason for Change: Clarification of the revised visit week and number of subjects to be screened and randomized in each Cohort			
22	9.3.2 Inclusion Criteria #1, Line 2		Added: …, if permitted in your country/region,
22	9.3.2 Inclusion Criteria #4		Added: For Poland, a CT or MRI of the brain to rule out progressive structural lesions should be performed within 2 years prior to screening visit.
22	9.3.2 Inclusion Criteria #6		Added: (AEDs may be adjusted during the open-label phase of the study).

25	9.3.3 Exclusion Criteria #11	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.	11. Current use of vigabatrin is not permitted, as well as prior use of vigabatrin without stable visual fields tested prior to screening. If used during the last 12 months two visual fields tests are required.
25	9.3.3 Exclusion Criteria #25		… (See Section 9.4.1: Excluded, Prior, and Concomitant Medications).
Reason for Change: Clarification that local regulations may apply; addition of country-specific criteria and clarification of AED dosing adjustments			
28	9.3.4.1 Investigator-initiated Withdrawal of Subject	Investigator-initiated Withdrawal of Subject	Criteria for Withdrawal
28	9.3.4.1 Investigator-initiated Withdrawal of Subject, #10	d. An "actual suicide attempt" as classified by the Columbia-Suicide Severity Rating Scale (C-SSRS).	d. Any Suicidal Behavior as classified by the Columbia Suicide Severity Scale (C-SSRS) or a 'yes" answer to questions 4 and 5 in the Suicidal Ideation section of the C-SSRS. These patients should be referred to psychiatric evaluation immediately.
28	9.3.4.1 Investigator-initiated Withdrawal of Subject		Added: 11. Any subject who has the following liver enzyme findings should be immediately contacted and instructed to stop the study drug or start down titration of the study drug a.ALT or AST > 8 x ULN b.ALT or AST > 5 x ULN for more than 2 weeks c.ALT or AST > 3 x ULN and total bilirubin > 2 x ULN d.ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia Patients with ALT or AST > 3 x ULN but <8 x ULN and no clinical signs or symptoms indicating liver dysfunction can, at the discretion of the investigator, continue the intake of study drug with close monitoring. All patients who fall into either category (patients who must discontinue the study drug [a, b, c, and d] and who may continue the study drug with close monitoring) must be brought back to the study center without any delay, the next day if possible, but no later than 72 hours after the study results have been received, for evaluation of the underlying cause and confirmatory laboratory testing.

			More frequent monitoring of the liver tests should be initiated.
Reason for Change: C-SSRS: More specific guidance how to utilize the C-SSRS instrument in assessing risk for suicide is provided. Specifically, patients with any suicidal behavior and/or suicidal ideation with intent or plan (ideation questions 4 and 5 in the C-SSRS) should be discontinued from the study and referred to psychiatric evaluation. **Managing elevated LFTs**: These stopping rules are intended to guide the investigator how to manage patients with elevated liver enzymes during the study. These stopping rules are in line with FDA's recommendation on managing patients with elevated liver enzymes during clinical trials (Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation)			
31	9.4.2 Identity of Investigational Products		Added: All study medication will be labeled according to regional regulatory requirements. At minimum labels will contain the study number; a blinded bottle number; contents including quantity; dose and form; route of administration; storage conditions, instructions for study drug administration; caution that this compound is an investigative drug intended for clinical trial use only; warning to keep out of reach of children; and the identity of manufacturer and Sponsor. For those regions that require it, a blinded lot number and an expiry date will also be listed.
Reason for Change: Provided Investigational Product labeling content			
33	9.4.5 Study Dosing and Dosage Adjustments, Open-Label Phase		Subjects will start with 450 mg/d in divided doses BID for 3 days, 900 mg/d in divided doses BID for 3 days, 1350 mg/d in divided doses BID for 4 days, and 1800 mg/d in divided doses BID for 4 days until their Visit 6 (Table 2). At Visit 6, all subjects in both cohorts will be evaluated for tolerability and the investigator will make the determination to maintain the subject on 1800 mg/d or adjust their dose. Added: If the patient experiences any tolerability issues during the transition to OL, such as sedation or dizziness, changes to the titration schedule (e.g., conducting the titration over 3 weeks vs. 2 weeks) may be approved after discussion with the medical monitor.
33	9.4.5 Study Dosing and Dosage Adjustments, De-Escalation Period	De-escalation Period: The study drug will be decreased in increments of 450mg/d in 3-day intervals over 12 days for 1800 mg.	De-escalation Period: The study drug will be decreased in increments of 450mg/d in 4-day intervals over 12 days for 1800 mg.

33	9.4.5 Table 2 Dosing Schedule for Cohort 2 Double-blind Phase, Open-Label Phase, and De-Escalation Period	(Visit 3) – Study Day 15-42 (Visit 4) – Study Day 43-98	(Visit 3) – Study Day 15-56 (Visit 4) – Study Day 57-98
Reason for Change: Clarification of the Visit period			
40	9.4.9 Un-blinding, Line 4	The Medical Monitor must be contacted to initiate unblinding in the IWRS system. Subjects who are unblinded will be terminated from the study.	The Medical Monitor or the Sponsor must be contacted to initiate unblinding in the IWRS system. Subjects who are unblinded during the double-blind phase will be terminated from the study.
40	9.4.9 Un-blinding	**Medical Monitor for US Sites:** [redacted], M.D. INC Research Sr. Medical Director Telephone: [redacted] **Medical Monitor for Russian, Bulgarian and Australian Sites:** [redacted] M.D. Global Clinical Trials (RCT Global) Telephone: [redacted] **Back up:** [redacted] M.D. Global Clinical Trials (BCT Global) Telephone: [redacted] **Sponsor Contact** [redacted] Ph. D. Marinus Pharmaceuticals, Inc. Telephone: [redacted]	**Global Medical Monitor and Monitor for US Sites:** [redacted] D.O. INC Research Telephone: [redacted] Alternate Telephone: [redacted] Email [redacted] **Medical Monitor for Bulgarian Sites:** [redacted], M.D. Global Clinical Trials (BCT Global) Telephone: [redacted] Email: [redacted] **Back up**: [redacted] M.D. Global Clinical Trials (RCT Global) Telephone: [redacted] Email: [redacted] **Medica [redacted] tes**: Global Clinical Trials (RCT Global) Telephone: [redacted] Email: [redacted] Back up: [redacted] M.D. Global Clinical Trials (BCT Global) Telephone: [redacted] Email: [redacted] **Medical Monitor for German and Polish Sites:** [redacted], M.D. Prisma-CRO GmbH Telephone: [redacted]

			Email: [redacted] **Medical Monitor for Australian Sites** (during business hours only; during off-duty hours contact Sponsor MM): Prof. [redacted], M.D. The Royal Melbourne Hospital Telephone: [redacted] Email: [redacted]
40	9.4.9 Un-blinding, Paragraphs 3 & 4	Investigators at Australian, Bulgarian, German, Polish and Russian sites should contact the US Medical Monitor if their "in-country" Medical Monitor and backup cannot be reached. If neither the Medical Monitor nor the Sponsor Contact can be reached in an emergency, the site should contact: **Sponsor Medical Advisor** [redacted] M.D., Ph.D. Marinus Pharmaceuticals, Inc. Telephone: [redacted]	Investigators at Australian, Bulgarian, German, Polish and Russian sites should contact the Global Medical Monitor if their "in-country" Medical Monitor and backup cannot be reached. If neither the Local nor Global Medical Monitor can be reached in an emergency, the site should contact: **Sponsor Medical Contact** [redacted] M.D., Ph.D. Marinus Pharmaceuticals, Inc. Phone: +1 484-801-4678 Mobile Phone: [redacted] Email: [redacted]
Reason for Change: Administrative change – contact information			
42	9.4.10 Background AED medication, Paragraphs 4, 5 & 6	**Vigabatrin**: …as well as prior use of vigabatrin without stable visual fields tested twice over the 12 months after the last dose of vigabatrin. **Perampanel (Fycompa)**: …and is expected to remain on a constant dose throughout the study. **Felbamate:** …and is expected to remain constant throughout the study. **Benzodiazepines**: …and the dose cannot be changed during the study.	**Vigabatrin**: …as well as prior use of vigabatrin without stable visual fields tested prior to screening. If used in the last 12 months two visual fields tests are required. **Perampanel (Fycompa):** …and is expected to remain on a constant dose through the double-blind phase of the study. **Felbamate**: …and is expected to remain constant through the double-blind phase of the study. **Benzodiazepines**: …and the dose cannot be changed during the double-blind phase of the study.
Reason for Change: Clarification of when changes to AED dosing is not permitted			
45	9.5.2 Efficacy Assessments, Paragraph 1, Line 5, 6 &10	…conducted at Weeks 32 (5-month OL) and 52 (10-month OL) in Cohort 1. Cohort 2 subjects entered under this version (Amendment 3) of the protocol…	…conducted at Weeks 32 and 52 in Cohort 1. Cohort 2 subjects entered under Amendment 3 of the protocol…, and enter the information in the eCRF.
45	9.5.2 Efficacy Assessments		Added: Please refer to Section 9.7 and the Statistical Analysis Plan (SAP) for further details regarding the statistical methods and derivation of key secondary and secondary

	Paragraph 2, Line 3	Results will be expressed and mean and median.	end-points. Clinical Global Impression of Change – Improvement (CGI-I; Investigator) and Patient Global Impression of Change – Improvement (PGI-I; Patient or Caregiver) will be assessed at Weeks 5 and 9 for Cohort 1 during the double-blind phase and at Weeks 22, 42 and 61 during the open-label phase. PGI-I and CGI-I will be assessed at Weeks 8 and 14 during the double-blind phase and Weeks 28, 44 and 66 during the open-label phase for Cohort 2. Additional analyses may be considered as appropriate. Deleted
45	9.5.2 Efficacy Assessments, Paragraph 3	Secondary efficacy outcome measures include those listed below. All outcome variables will be assessed for these time periods for Cohort 1 & 2: ganaxolone vs placebo Titration + Maintenance (Cohort 1:Weeks 1-9, Cohort 2: Weeks 1-14), ganaxolone vs placebo Maintenance only (Cohort 1: Weeks 2-9, Cohort 2: Weeks 3-14), 1200 mg/d vs placebo (Cohort 1: Weeks 2-5), and 1800 mg/d vs placebo (Cohort 1: Weeks 6-9) for the ITT and Completer populations; open-label (Cohort 1: Weeks 10-61, Cohort 2: 16-66), double-blind plus open-label (Cohort 1: Weeks 1-61, Cohort 2: Weeks 1-66).	Deleted
45	Table - Secondary Efficacy Parameters		Deleted
Reason for Change: These changes are intended to simplify this section be removing duplication of text elsewhere in the protocol and in the Statistical Analysis Plan.			
46	9.5.3 Safety Assessments		Added: Columbia Suicide Severity Scale (C-SSRS)
46	9.5.3 Safety Assessments	Secondary safety outcome measures include those listed below. All outcome variables will be presented for these time periods for Cohorts 1 & 2: ganaxolone vs placebo Titration + Maintenance (Cohort 1: Weeks 1-9, Cohort 2: Weeks 1-14), 1200	Adverse events will be presented for these time periods for Cohorts 1 & 2: ganaxolone vs placebo Titration + Maintenance (Cohort 1: Weeks 1-9, Cohort 2: Weeks 1-14), 1200 mg/d vs placebo (Cohort 1: Weeks 2-5), and 1800 mg/d vs placebo (Cohort 2: Weeks 6-9) for the safety population; open-label

		mg/d vs placebo (Cohort 1: Weeks 2-5), and 1800 mg/d vs placebo (Cohort 2: Weeks 6-9) for the ITT population; open-label (Cohort 1: Weeks 10-61, Cohort 2: 15-66, and total open-label), double-blind plus open-label (Cohort 1: Weeks 1-61, Cohort 2: 1-66).	(Cohort 1: Weeks 10-61, Cohort 2: 15-66,). Added: In addition, tolerability of ganaxolone during the up-titration phases of the study will be compared between the two cohorts. AEs with onset during the titration phase 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 phase will be compared to AEs with onset during the maintenance phase. AEs that emerge during the de-escalation period will be tabulated to investigate whether discontinuation of ganaxolone is associated with withdrawal symptoms. Secondary safety outcome measures include those listed below.
46	9.5.3 Secondary Safety Parameters for Cohorts 1 & 2 - Table	**Secondary Safety Parameters for Cohorts 1 & 2** Type and incidence of AES **Combine Cohorts 1 & 2** **DB Phase** "X" populated for 7 parameters listed in table	The frequency and proportion of subjects with AEs **Combine Cohorts 1 & 2** **DB Phase** "X" deleted
50	9.5.5.9 Visit 7	Visit 7 (Open-Label Month 1; Cohort 1: Week 14; Cohort 2: Week 20)	Visit 7 (Cohort 1: Week 14; Cohort 2: Week 20)
50	9.5.5.10 Visit 8	Visit 8 (Open-Label Month 3; Cohort 1: Week 22; Cohort 2: Week 28)	Visit 8 (Cohort 1: Week 22; Cohort 2: Week 28)
51	9.5.5.11 Telephone Follow Up	Telephone Follow Up (Month 5; Cohort 1: Week 32; Cohort 2: Week 36)	Telephone Follow Up (Cohort 1: Week 32; Cohort 2: Week 36)
51	9.5.5.12 Visit 9	Visit 9 (Cohort 1: Open Label Month 8, Week 42; Cohort 2: Open Label Month 7, Week 44)	Visit 9 (Cohort 1: Week 42; Cohort 2: Week 44)

51	9.5.5.13 Telephone Follow Up	Telephone Follow Up (Cohort 1: Month 10, Week 52; Cohort 2: Month 10, Week 56)	Telephone Follow Up (Cohort 1: Week 52; Cohort 2: Week 56)
51	9.5.5.14 Visit 10	Visit 10 (Open Label Month 12; Cohort 1: Week 61; Cohort 2: Week 66)/ Pre-Taper/ET Visit	Visit 10 Pre-Taper/ET Visit (Cohort 1: Week 61; Cohort 2: Week 66)
Reason for Change: Clarification of the revised Visit labels/schedule			
52	9.7.2 Analysis Population – Modified Intent to Treat Population (mITT)		Added: <u>The modified intent to treat (mITT) population (Full Anaysis Population in the earlier version of the 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.</u>
52	9.7.2 Analysis Population – Per Protocol Population (PP)	The per protocol (PP) population includes all FAP subjects who received at least 12 weeks of treatment without major protocol violations. The PP population is for supportive efficacy analysis. Major protocol violations will be defined prior to database lock.	The per protocol (PP) population includes all FAP subjects without major protocol violations <u>during the double-blind phase</u>. The PP population is for supportive efficacy analysis. Major protocol violations will be defined prior to database lock.
53	9.7.3 Missing Data	Before performing any statistical analyses, a complete review of all data, both quantitative and qualitative, will be conducted in order to account for all missing values. A missing value code(s) will be documented and incorporated into the database. Similarly, when data are recorded on official eCRFs and not subsequently used in any formal statistical analysis the reasons for such actions will be documented.	Deleted

		All quantitative data will be assessed for the presence of spurious or outlying results, both from a descriptive examination of the frequency distribution for each variable, as well as, examination of logical multivariate distributions and, if necessary, the use of appropriate univariate and multivariate outlier screening tests. The removal or correction of any data value will be documented.	
53	9.7.4 Baseline and Demographic Characteristics, Line 2	…overall for the FAP population.	…overall for the mITT population.
53	9.7.5 Analysis of Primary Efficacy Variable, Paragraphs 1 (Line 3), 2 & 3	…period relative to baseline in the FAP analysis. The hypothesis for percent change in seizure frequency per 28 days is: H0: $\mu1 - \mu2 = 0$ Ha: $\mu1 - \mu2 \neq 0$ where $\mu1$ and $\mu2$ are the mean percent change in seizure frequency. An analysis of covariance (ANCOVA) will be conducted on the log-transformed percent change data, with treatment and country as factors and the logged baseline seizure frequency per 28 days as a covariate. Rank-transformation based ANCOVA to explore the median difference of percentage change is also conducted to assess the robustness of the analysis method. Both the baseline seizure frequencies per 28 days and the percentage change per 28 days will be rank-transformed before applying the ANCOVA model. Point estimates and associated 95% confidence interval and p-values will be reported.	…period relative to baseline in the mITT population. The hypothesis for percent change in seizure frequency per 28 days is: H0: $\mu1 - \mu2 = 0$ Ha: $\mu1 - \mu2 \neq 0$ where $\mu1$ and $\mu2$ are the <u>median</u> percent change in seizure frequency. A <u>rank</u> analysis of covariance (ANCOVA) will be conducted on <u>ranked</u> percent change data, with treatment and country as factors and the ranked baseline seizure frequency per 28 days as a covariate. <u>The p-value based</u> on <u>the rank ANCOVA will be presented</u>. <u>Hodges-Lehmann estimator and its 95% confidence interval (CI) will also be calculated.</u> Added: <u>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</u>

			2000 iterations. This analysis provides a robustness assessment of the results. Added: 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 analyzed independently of the US registration end-point. The key-secondary end-point analysis (below) is not predicated on the results of this end-point.
54	9.7.6 Analysis of Secondary Endpoints	Secondary efficacy outcome measures include those listed below. All outcome variables will be assessed for these time periods in both Cohort 1 and 2: ganaxolone vs placebo Titration + Maintenance (Cohort 1: Weeks 1-9, Cohort 2: Weeks 1-14), ganaxolone vs placebo Maintenance only (Cohort 1: Weeks 2-9, Cohort 2: Weeks 3-14), 1200 mg/d vs placebo (Cohort 1: Weeks 2-5), and 1800 mg/d vs placebo (Cohort 1: Weeks 6-9) for the FAP and Completer populations; open-label (Cohort 1: Weeks 10-61; Cohort 2: Weeks 15-66), double-blind plus open-label (Cohort 1: Weeks 1-61; Cohort 2: Weeks 1-66).	The three key secondary endpoints (below) 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] The primary and secondary efficacy outcome measures will be assessed for each of the time periods listed below in Cohort 1 DB phase ([a-e] below) and Cohort 1+Cohort 2 OL if below: a) Ganaxolone Titration + Maintenance 1200 mg/day + Maintenance 1800 mg/day vs Placebo (Cohort 1: Weeks 1-9).

			b) Ganaxolone Maintenance 1200 mg/day + Maintenance 1800 mg/day vs Placebo (Cohort 1: Weeks 2-9). c) Ganaxolone Titration + Maintenance 1200 mg/d vs placebo (Cohort 1: Weeks 1-5). d) Ganaxolone Maintenance 1800 mg/d vs placebo (Cohort 1: Weeks 6-9). e) Ganaxolone maintenance 1200 mg/d vs placebo (Cohort 1: Weeks 2-5). f) OL (Cohort 1: Weeks 10-61; Cohort 2: Weeks 16-66). The responder rates and seizure-free rates between ganaxolone and placebo will be compared using a logistic regression analysis. To take into account the ordinal nature of the response to Clinical Global Impression of Change and Patient Global Impression of Change scales (CGI-I, PGI-I), the Row Mean Score Difference, and the p-value based on Cochran-Mantel-Haenszel test adjusting for pooled center (either US or ROW), will be used to test if there is a treatment effect. Additional assessments may be conducted as considered appropriate. All secondary efficacy variables will also be summarized using descriptive statistics. The exploratory end-point of [redacted] will be summarized descriptively only without formal statistical analysis.
54	9.7.6 Analysis of Primary Efficacy Variable – Table Secondary Efficacy for Cohort 1 and 2		Deleted
54	9.7.6 Analysis of Primary Efficacy Variable, Paragraph 1 after Table	All secondary efficacy variables will be summarized using descriptive statistics. The responder rates and seizure-free rates between ganaxolone and placebo will be compared using a Cochran-Mantel-Haenszel analysis. Mean monthly seizure frequency for each week after dosing will be analyzed using similar methodology as the primary efficacy variable. Change and	Deleted

		percent change of mean monthly seizure frequencies will be analyzed by Kruskal-Wallis test.	
57	9.7.7 Analysis of Safety Variables	Adverse events (AEs) will be tabulated by Overall, system organ class (SOC), and Preferred Term using the MedDRA v.16.0 coding system. Incidence and percentage of adverse events will be for each phase of the study, and in Phase 1, by dose level and overall. Additional tables, with AEs subset by severity and by relationship to drug as assessed by the investigator will be presented. Subset listings will be produced for adverse events that cause withdrawal and for SAEs. Laboratory data, vital signs and ECGs will be summarized using descriptive statistics by treatment including changes from baseline. Critically significant changes in laboratory and ECG values and vital signs will be flagged in data listings. Listings of most abnormal changes will be provided.	Adverse events (AEs) will be tabulated by Overall, system organ class (SOC), and Preferred Term using the MedDRA v.16.1 coding system. Frequency 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 double-blind phase, by dose level and overall. Additional tables, with AEs subset by severity and by relationship to drug as assessed by the investigator will be presented. Subset listings will be produced for adverse events that cause withdrawal and for SAEs. Actual values and changes from baseline for laboratory data, vital signs and ECGs will be summarized using descriptive statistics by visit, by treatment and overall for each cohort and phase separately in safety population. Shifts from baseline in low/normal/high classification will be summarized for each laboratory and vital sign parameter. Critically significant changes in laboratory and ECG values and vital signs will be flagged in data listings. 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 and urine drug screen test results will be listed.
57	9.7.9 Determination of Sample Size	Marinus 1042-0600 study results using a medium dose (1500mg/day oral suspension) showed that mean difference of percentage change in seizure frequency was -19.58%, with standard deviation of 54.019% and thus giving an effect size of 0.3625. Assuming an effect size of 0.38 could be achieved in Cohort 2 comparing placebo to high dose ganaxolone (1800 mg/day capsule), a sample size of 146 in each group produces a two-sided 95% confidence interval around	Marinus 1042-0600 study results using a medium dose (1500mg/day oral suspension) showed that mean difference of percentage change in seizure frequency was -19.58%, with standard deviation of 54.019% and thus giving an effect size of 0.3625. Assuming an effect size of 0.30 could be achieved in Cohort 2 comparing placebo to high dose ganaxolone (1800 mg/day capsule) in a 1:1 ratio, a sample size of 178 in each group provides approximately 80% power when the estimated difference is -15% and standard deviations are approximately 50% in each

		the treatment mean difference when the estimated standard deviations are approximately 50% in each group.	group when Wilcoxon rank sum test is used with the two-sided α of 0.05.
Reason for Change: These modifications reflect the changes made to the Study 1042-0603 Study Statistical Analysis Plan, including detailed listing of primary and secondary end-points and statistical methodology.			
60	10.4 Informed Consent, Paragraph 2, Line 1		Added: …,if permitted in your country/region
Reason for Change: Clarification that local regulations may apply			
64	10.5.3.1 Serious Adverse Events, Paragraph 1, Line 2		Added: [if permitted in your country/region]
64	10.5.3.1 Serious Adverse Events – SAE Reporting	If a fatal or imminently life-threatening SAE occurs during a US holiday, sites are encouraged to call [redacted] M.D. ([redacted]) or [redacted] Ph.D. [redacted] in addition to faxing the SAE report.	If a fatal or imminently life-threatening SAE occurs, sites are encouraged to call their local Medical Monitor noted in Section 10.5.3.2 or [redacted] M.D., Ph.D. (+1 484-801-4678) in additional to faxing the SAE report.
64	10.5.3.1 Serious Adverse Events – SAE Reporting -	If a fatal or imminently life-threatening SAE occurs with relationship suspected to study drug, necessitating immediate telephone contact, call [redacted] M.D. [redacted] or [redacted] Ph.D. [redacted]) in addition to faxing the SAE report.	Deleted
66	10.5.3.2 Medical Inquiries	Medical Monitor for US Sites: [redacted] M.D. INC Research Sr. Medical Director Telephone: [redacted] Medical Monitor for Russian, Bulgarian and Australian Sites: [redacted] M.D. Global Clinical Trials (RCT Global) Telephone: [redacted] Back up: [redacted] M.D. Global Clinical Trials (BCT Global) Telephone: [redacted] Sponsor Contact [redacted] Ph. D. Marinus Pharmaceuticals, Inc. Telephone: [redacted]	**Global Medical Monitor and Monitor for US Sites:** [redacted] D.O. INC Research Telephone: [redacted] Alternate Telephone: [redacted] Email: [redacted] **Medical Monitor for Bulgarian Sites:** [redacted] M.D. Global Clinical Trials (BCT Global) Telephone: [redacted] Email: [redacted] **Back up:** [redacted] M.D. Global Clinical Trials (RCT Global) Telephone: [redacted] Email: [redacted] **Medical Monitor for Russian Sites:** Global Clinical Trials (RCT Global) Telephone: [redacted]

			Email: [redacted] **Back up:** [redacted] M.D. Global Clinical Trials (BCT Global) Telephone: [redacted] Email: [redacted] **Medical Monitor for German and Polish Sites:** [redacted], M.D. Prisma-CRO GmbH Telephone: [redacted] Email: [redacted] **Medical Monitor for Australian Sites:** (during business hours only; during off-duty hours contact Sponsor MM) Prof. [redacted] M.D. The Royal Melbourne Hospital Telephone: [redacted] Email: [redacted]
Reason for Change: Clarification that local regulations may apply; Administrative change – contact information			
72	12.1 Appendix 1: Schedule of Events – Cohort 1 Period 1: Double-blind Phase (Weeks -8 thru 9) - footnote	[1] Concomitant AEDs or their dose must be stable for 1 month prior to historical baseline and cannot be changed at any time during the course of the study; if the subject is using VNS, the settings cannot be changed during the course of the study	[1]Concomitant AEDs or their dose must be stable for 1 month prior to historical baseline and cannot be changed at any time prior to Visit 5, but may be adjusted during the Open-Label Phase of the study; if the subject is using VNS, the settings cannot be changed during the course of the study
74	12.1 Appendix 1: Schedule of Events – Cohort 2 Period 2: Open-label Phase (Weeks 10-63) – VISIT labels	Visit 7 (1 month) Visit 8 (3 month) Telephone Follow-up (5 month) Visit 9 (8 month) Telephone Follow-up (10 month) Visit 10 (12 month Pre-taper/ET)	Visit 7 Visit 8 Telephone Follow-up Visit 9 Telephone Follow-up Visit 10 (Pre-taper/ET)
74	12.1 Appendix 1: Schedule of Events – Cohort 2 Period 2: Open-label Phase (Weeks 10-63) – footnote	[1] Concomitant AEDs or their dose must be stable for 1 month prior to historical baseline and cannot be changed at any time during the course of the study; if the subject is using VNS, the settings cannot be changed during the course of the study	[1]Concomitant AEDs or their dose must be stable for 1 month prior to historical baseline and cannot be changed at any time prior to Visit 5, but may be adjusted during the Open-Label Phase of the study; if the subject is using VNS, the settings cannot be changed during the course of the study
77	12.1 Appendix 1: Schedule of Events – Cohort 2 Period 1:	[1] Concomitant AEDs or their dose must be stable for 1 month prior to historical baseline and cannot be changed at any time during the	[1]Concomitant AEDs or their dose must be stable for 1 month prior to historical baseline and cannot be changed at any time prior to Visit 5, but may be adjusted during the Open-

	Double-blind Phase (Weeks -8-14) – footnote	course of the study; if the subject is using VNS, the settings cannot be changed during the course of the study	Label Phase of the study; if the subject is using VNS, the settings cannot be changed during the course of the study
78	12.1 Appendix 1: Schedule of Events – Cohort 2 Period 2: Open-label Phase (Weeks 16-68) – VISIT labels	Visit 7 (1 month) Visit 8 (3 month) Telephone Follow-up (5 month) Visit 9 (8 month) Telephone Follow-up (10 month) Visit 10 (12 month Pre-taper/ET)	Visit 7 Visit 8 Telephone Follow-up Visit 9 Telephone Follow-up Visit 10 (Pre-taper/ET)
79	12.1 Appendix 1: Schedule of Events – Cohort 2 Period 2: Open-label Phase (Weeks 16-68) – footnote	[1] Concomitant AEDs or their dose must be stable for 1 month prior to historical baseline and cannot be changed at any time during the course of the study; if the subject is using VNS, the settings cannot be changed during the course of the study	[1]Concomitant AEDs or their dose must be stable for 1 month prior to historical baseline and cannot be changed at any time prior to Visit 5, but may be adjusted during the Open-Label Phase of the study; if the subject is using VNS, the settings cannot be changed during the course of the study
Reason for Change: Clarification when AED dosing can and cannot be adjusted; clarification of Visit numbers/labels			
113	12.8 Appendix 8 Protocol History	Amendment 3 Summary of Changes from version March 10, 2014 to September 23, 2014	Amendment 4 Summary of Changes from version September 23, 2014 to April 08, 2016