16.1 STUDY INFORMATION

16.1.1 Protocol

CLINICAL STUDY PROTOCOL

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

SHORT TITLE: Ganaxolone Two-year Open-label Extension Study

PROTOCOL NUMBER: 1042-0604
STUDY PHASE: III
STUDY DRUG(S): Ganaxolone (CCD 1042:3α-hydroxy-3β-methyl-5α-pregnan-20-one)
IND NUMBER: 44,020
INDICATION: Epilepsy with drug-resistant partial-onset seizures

SPONSOR: Marinus Pharmaceuticals, Inc.
Three Radnor Corporate Center
100 Matsonford Road, Suite 304
Radnor, PA 19087

SPONSOR CONTACT: [redacted]
Sr. Director, Clinical Operations
Telephone: [redacted]
Email: [redacted]

SPONSOR'S MEDICAL REPRESENTATIVE: [redacted], MD, PhD
Vice President, Clinical Development
Office Phone: [redacted]
Mobile Phone: [redacted]
Email: [redacted]

INITIAL VERSION: January 15, 2015

AMENDMENT 1: February 29, 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: 1042-0604	**Phase of Development**: III
Title of the Protocol: A follow-on, two-year open-label extension study of ganaxolone as add-on therapy in adult subjects with drug-resistant partial-onset seizures	
Primary Objectives: To assess the safety and tolerability of adjunctive ganaxolone during a two-year open-label treatment in adult subjects with drug-resistant partial-onset seizures	
Secondary Objectives: To assess efficacy of adjunctive ganaxolone during a two-year open-label treatment in adult subjects with drug-resistant partial-onset seizures	
Study Design and Methodology: Subjects who successfully completed Study 1042-0603 and meet inclusion/exclusion criteria are eligible to enter Study 1042-0604 and continue open-label adjunctive treatment with ganaxolone capsules in the dose range of 900 - 1800 mg daily.	
Study Population and Main Criteria for Inclusion/Exclusion: Adults with drug-resistant partial onset seizures currently taking 1-3 prescribed AEDs who completed all scheduled clinical study visits in Study 1042-0603, were compliant, derived benefit from open-label ganaxolone and did not experience any serious or medically important adverse event judged probably or definitely due to ganaxolone.	
Number of Subjects: A maximum of approximately 350 subjects may enter this protocol, after satisfactorily completing Study 1042-0603.	
Test Product, Dose and Mode of Administration: Ganaxolone 225 mg capsules administered in BID in the dose range of 900 to 1800 mg/day.	
Duration of Treatment: Up to 104 weeks treatment on the maintenance dose with an additional 2 weeks of dose de-escalation.	
Reference Therapy, Dose and Mode of Administration: None	
Safety Criteria for Evaluation: Adverse Events, vital signs, safety laboratory assessments, ECGs	

2.1 Table 1: Schedule of Events

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

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

TABLE OF CONTENTS

3. LIST OF ACRONYMS, ABBREVIATIONS, AND DEFINITIONS OF TERMS

Term	Definition
3α,5α-P	3α-hydroxy-5α-pregnan-20-one; allopregnanolone
AE	adverse event
AE CRF	adverse event 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
°C	degrees centigrade
CGI-I	Clinician's Global Impression of Improvement
CNS	central nervous system
CPS	complex partial seizures
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
DB	double-blind
DDI	drug-drug interaction
ECG, EKG	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

Term	Definition
mg/d	milligram per day
min	minutes
mL	millilitre
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
n	number of subjects
OL	open-label
OLE	open-label extension
oz	ounces
PCGI-I	Patient/Caregiver Global Impression of Improvement
PK	pharmacokinetics
POS	partial-onset seizure
PTZ	pentylenetetrazol
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

4. ETHICS

4.1 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.

4.2 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.

4.3 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, subject will give their written consent to the study after having been informed about the nature and purpose of the study, conditions for study participation/termination, and potential risks and benefits.

5. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This will be a multi-center study with approximately 58 investigational sites in the USA, the Russian Federation (Russia), Australia, Bulgaria, Germany and Poland with approximately 6 subjects enrolled at each site. Duration of subject participation is 106 weeks.

6. 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 will evaluate the safety, tolerability and efficacy in a second year of open-label treatment with ganaxolone when used as an add-on therapy in adult subjects with drug-resistant partial-onset (focal) seizures.

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 neurologic and psychiatric conditions such as adult and pediatric 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 in Study 1042-0404 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 completed 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 tid) 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 in a second year of open-label treatment with ganaxolone when used as an add-on therapy in adult subjects with drug-resistant partial-onset (focal) seizures.

7. STUDY OBJECTIVES

7.1 Primary

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

7.2 Secondary

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

8. INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan

Study 1042-0604 is an open-label extension of Study 1042-0603, providing a two-year adjunctive ganaxolone treatment (900-1800 mg/d) to adult subjects with epilepsy consisting of partial-onset seizure (POS). Subjects will enter the study at their current dose of ganaxolone from study 1042-0603. The dose of ganaxolone may be adjusted for tolerability and response.

8.2 Discussion of Study Design

This open-label protocol is designed to provide ganaxolone to adult subjects with epilepsy consisting of uncontrolled POS who are deriving significant benefit from current ganaxolone adjunctive therapy. Subjects who have completed all scheduled clinical study visits in the previous protocol 1042-0603 and have shown a minimum 35% improvement in mean seizure frequency per 28-days vs. baseline over the three 28-day periods preceding study entry, and acceptable tolerability, are eligible to participate. Safety and tolerability will be assessed by diary record and at clinic visits approximately every four months. During the study if the patient fails to continue to meet the minimum improvement criteria (mean 28-day seizure frequency over the past three 28-day periods before the study visit showing 35% improvement over baseline) at any study visit the investigator should consider discontinuing the patient from the study. Efficacy will primarily be assessed based on daily seizure calendar entries. Baseline for evaluation of seizure frequency will be each subject's baseline from Study 1042-0603, though other calculations may also be performed.

Adjunctive therapies (1-3 background AED medications, with or without implanted VNS) should be stable for the one month prior to study entry but may be adjusted as clinically warranted at other times during the study. The dose of ganaxolone may be adjusted as minimum 3 day intervals as warranted for tolerability and efficacy, up to a maximum of 1800 mg/d.

8.3 Selection of Study Population

8.3.1 Number of Subjects:

This study may treat up to approximately 350 subjects depending upon the number of subjects continuing from the previous Study 1042-0603.

8.3.2 Inclusion Criteria

1. Subjects who have completed all scheduled clinical study visits in the previous protocol 1042-0603 and have shown a minimum 35% improvement in mean 28-day seizure frequency over the last three 28-day periods in study 1042-603 as compared to the baseline of study 1042-0603.

2. Subjects whose daily study drug compliance in Study 1042-0603 was 90% or greater, and for whom the investigator feels that the subject was compliant with the full dose as prescribed.

3. Able to give informed consent in writing, or have a legally authorized representative able to do so, after being properly informed of the nature and risks of the study and prior to engaging in any study-related procedures.

4. Currently being treated and maintained with a stable regimen of 1, 2, or 3 AEDs at a consistent dose for one month prior to study entry. See Section 8.4.8 for restrictions on certain AEDs.

5. Implanted VNS (Vagus Nerve Stimulator) is permitted and will not count towards the number of concomitant AEDs.

6. 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.

7. Able and willing to take drug with food twice daily. Ganaxolone must be administered with food.

8. Sexually active women of childbearing potential (WCBP) must be using a medically acceptable method of birth control and have a negative pregnancy test at Visit 1 and at 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. Birth control should be continued for a minimum of 3 days after the last dose of study drug.

8.3.3 Exclusion Criteria

1. 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.

2. Experienced a Serious Adverse Event or a moderate or severe medically important adverse event judged probably or definitely related to open-label ganaxolone in the previous study, 1042-0603.

3. Have Alanine transferase (ALT; SGPT) or Aspartate transferase (AST; SGOT) levels >3 times upper limits of normal (ULN), or total bilirubin >1.5 times ULN during Study 1042-0603. (Since Study 1042-0603 Visit 10 safety laboratory results will not be available at the time of inclusion in Study 1042-0604, these results will be assessed against Section 8.3.4.Criteral for withdrawal #11.)

4. Have a history of malignancy within the past 2 years, with the exception of basal cell carcinoma.

5. 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.

6. Have active suicidal plan/intent, or have had active suicidal thoughts in the past 6 months. 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).

7. Have a history of drug or alcohol abuse within the past 5 years. As with other AEDs, the use of alcohol is not advised.

8. Are currently following or planning to follow a ketogenic diet.

9. Current use of vigabatrin or ezogabine (retigabine; Potiga; Trobalt) is not permitted.

10. Females who are pregnant, currently breastfeeding or planning to become pregnant during the study.

11. Inability/unwillingness to withhold grapefruit and grapefruit juice from diet during the entire clinical trial.

Subjects meeting all inclusion and exclusion criteria will be allowed to enroll into this

study at the Investigator's discretion.

8.3.4 Removal of Subjects from Therapy or Assessments

8.3.4.1 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. QTc interval >500 msec or uncorrected QT interval >600 msec; for subjects with bundle branch block, QTc >530 msec based on average QTc value of triplicate ECGs. A subject with an increase in QTc of >60 msec from Visit 1 must also be withdrawn.
    a. If an 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. Should a prohibited CYP 3A 4, 5, 7 inhibitor or inducer be required for short term treatment, the subject may be permitted to remain in the study with permission from the Sponsor's Medical Monitor.
4. Use of benzodiazepines as rescue for innumerable seizure clusters more than three times in a 28-day period must be reviewed with Sponsor's Medical Monitor to assess suitability for continuation.
5. 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;
6. Subject is noncompliant with procedures set forth in the protocol in an ongoing or repeated manner;
7. Subject experiences an adverse event (AE) that warrants withdrawal from the clinical investigation;
8. Patient's mean 28-day seizure rate over the past three 28-day periods before the study visit shows less than 35% improvement in comparison to the patient's baseline in the 1042-603 study;
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 in medical history.
    c. Status epilepticus at any time during the clinical investigation.
    d. Any Suicidal Behavior as classified by the Columbia Suicide Severity Rating 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.

11. Any subject who has the following liver enzyme findings should be immediately contacted and instructed to stop the study drug or start immediate 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 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 $\leq$ 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.

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.

8.3.4.2 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, will be asked to complete the procedures for Visit 7 (Study Completion/Early Term) which include: concomitant AED review, vital signs, physical and neurological exams, laboratory assessments, ECG, pregnancy test, C-SSRS, collection of adverse events, CGI-I, PCGI-I 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.

8.3.4.3 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 dose de-escalation.

8.4 TREATMENTS

8.4.1 Identity of Investigational Product(s)

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 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.

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 25°C (59°F to 77°F).

8.4.2 Treatment Groups

Starting at Visit 1, all subjects will take ganaxolone beginning with the dose currently being taken in the 1042-0603 study, between 900 - 1800 mg/d.

8.4.3 Subject Numbering

Subjects will retain the 6-digit subject number assigned by each site's study staff for preceding protocol 1042-0603. The subject's number and initials (first/middle/last, in regions where permitted) are required to be entered on all clinical investigation documentation (i.e., CRFs, labeling of clinical materials and samples containers, drug accountability logs, etc.).

8.4.4 Selection of Doses in the Study

In meeting efficacy and tolerability criteria to participate in the study, it is expected that the subject will continue with the dose of ganaxolone (between 900-1800 mg/d) last prescribed in Study 1042-0603. Changes at V1 can be addressed with the Sponsor's Medical Monitor. During the study, the dose of ganaxolone may be adjusted at the Investigator's discretion based on tolerability and efficacy between 900 and 1800 mg/d, typically on the MTD of ganaxolone that provides adequate seizure control. 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 treatment period. 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 2). The subject will return for final post-taper safety assessment visit.

Details of the de-escalation regimen are provided in the table below.

Table 2. Dosing Schedule for De-Escalation Period

De-Escalation, Study Completion or Early Termination (ET)			
Visit	**Taper Day**	**Dose (mg)/day**	**225 mg cap/day**
Visit 7 (Study Comple-tion/Early Term)	Last full dose	1800	8
	1	1350	6
	2	1350	6
	3	1350	6
	4	1350	6
	5	900	4
	6	900	4
	7	900	4
	8	900	4
	9	450	2
	10	450	2
	11	450	2
	12	450	2
	13	0	0
	14	0	0

8.4.5 Dose Administration

Ganaxolone will be administered BID, 12 hours apart with food, i.e. 8:00 AM with breakfast and 8:00 PM after the evening meal. 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 8.4.6 Missing a Dose). It is important that ganaxolone be dosed with food.

The dose of ganaxolone may be adjusted based upon tolerability or efficacy. Subjects experiencing intolerable AEs at any dose level may have the dose reduced per Investigator direction to attempt to alleviate the event. See section 8.4.4 for dosage adjustments and de-escalation procedures.

8.4.6 Missing a Dose

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 doses at 7:00 AM and 7:00 PM and forgets to take a 7:00 PM dose at

dinnertime, that dose may be taken up to 9:00 PM at night (2 hrs after the evening meal, more than 8 hours until the next 7:00 AM dose). Alternatively, that dose could be taken until 11:00 PM 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.

8.4.7 Blinding

This study is not blinded so all subjects will receive active drug. All bottles will be labeled with a unique 6-digit number to help track study drug accountability, lot number, expiry date, and ganaxolone 225 mg capsules.

8.4.8 Excluded, Prior and Concomitant Medications

Subjects participating in the study are to be taking 1-3 AEDs in addition to the investigational medication. AEDs may be adjusted during the course of the study, but subjects must continue on at least on AED. 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.

Ezogabine (retigabine; Potiga; Trobalt): Current use of ezogabine (retigabine) is not permitted.

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 Visit 1 and has not experienced any serious psychiatric and behavioral reactions and is expected to remain on a constant dose throughout the study.

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

Benzodiazepines: If a subject is taking a benzodiazepine chronically for epilepsy and/or non-epilepsy conditions, it will be counted as 1 of the 3 AEDs.

Vagal Nerve Stimulator: Subjects receiving treatment with a VNS may be included. VNS will not be counted as one of the 3 concomitant AEDs.

8.4.9 Excluded Concomitant Medications

A list of medications that are **inducers or inhibitors of CYP 3A4/5/7** and are not permitted during the study are in Appendix 2. Consult with your in-country Medical

Monitor if you have any questions. Note that **phenytoin, carbamazepine** and **phenobarbital** are permitted as background AEDs though they are moderate CYP 3A4 inducers. Treatment with the 5-α-reductase inhibitor **finasteride** is not permitted 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 case report form (CRF).

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. If a subject requires use of rescue benzodiazepines 3 times or more during a 28-day period, the Sponsor's Medical Monitor should be consulted regarding the subject's continued participation.

Use of dietary supplements or herbal preparations are permitted if subject has been using them consistently for more than 6 months prior to Visit 1, and does not plan changing the regimen for the duration of the study. Changes may be made during the study at the discretion of the Principal Investigator. Use of St. John's Wort is not permitted (see Appendix 2 for prohibited medications).

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.

8.4.10 Treatment Compliance

A record of all investigational products dispensed and returned 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), the date investigational product containers are returned from the subject, and the quantity returned. Investigational product and associated accountability forms that are maintained at the clinical site will be present for review by Clinical Investigation 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. If the subject is suspected to be non-compliant with study medication or seizure calendar recording, he/she may be discontinued from the study.

8.5 Efficacy and Safety Variables

8.5.1 Efficacy Measurements, Safety Assessments and Schedule of Study Procedures

8.5.1.1 Efficacy Measurements

Efficacy will be assessed using the daily seizure calendar, the Clinician's Global Impression of Improvement, and the Patient/Caregiver Global Impression of Improvement.

8.5.1.2 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
- AE monitoring: frequency, severity, duration, causality, outcome

Safety laboratories, 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 CRF.

See Schedule of Events for timing of Safety Assessments.

8.5.1.3 Schedule of Study Procedures

8.5.1.3.1 Visit 1 (same as Study1042-0603 Visit 10/Open Label Month 12)

1042-0603 Visit 10/Last Visit procedures: physical and neurological examination, 12-lead ECG, vital signs, blood and urine samples for safety laboratory tests and urine pregnancy test for WCBP, trough concomitant AED levels, subject diaries, C-SSRS, CGI-I, PCGI-I , AEs reviewed, medication compliance checked and study medication returned;

Additional 1042-0604 procedures: informed consent reviewed and signed; inclusion/exclusion and demographics/medical history reviewed; and 1042-0604 seizure calendars and study medication dispensed. Any Adverse Event that occurred in study 1042-0603 which is not resolved at the time of enrollment into 1042-0604 or is deemed significant by the Principal Investigator is to be captured in the subject's 1042-0604 medical history. If the frequency, severity or duration of this event changes in any way then it is to be captured as an Adverse Event in 1042-0604.

8.5.1.3.2 Visit 2 (Week 17)

Concomitant AEDs reviewed, brief physical and neurological exams, vital signs, safety laboratory tests, urine pregnancy test, C-SSRS, review safety and record AEs, subject calendar review, study medication return and compliance check and dispense study medication.

8.5.1.3.3 Visit 3 (Week 34)

Concomitant AEDs reviewed, brief physical and neurological exams, vital signs, safety laboratory tests, urine pregnancy test, C-SSRS, review safety and record AEs, subject calendar review, study medication return and compliance check and dispense study medication.

8.5.1.3.4 Visit 4 (Week 52)

Concomitant AEDs reviewed, physical and neurological exams, vital signs, local ECG, safety laboratory tests, urine pregnancy test, C-SSRS, review safety and record AEs, subject calendar review, CGI-I, PCGI-I, study medication return and compliance check and dispense study medication.

8.5.1.3.5 Visit 5 (Week 69)

Concomitant AEDs reviewed, brief physical and neurological exams, vital signs, safety laboratory tests, urine pregnancy test, C-SSRS, review safety and record AEs, subject calendar review, study medication return and compliance check and dispense study medication.

8.5.1.3.6 Visit 6 (Week 86)

Concomitant AEDs reviewed, brief physical and neurological exams, vital signs, safety laboratory tests, urine pregnancy test, C-SSRS, review safety and record AEs, subject calendar review, study medication return and compliance check and dispense study medication.

8.5.1.3.7 Visit 7/Early Term Visit (Week 104; start of dose de-escalation period)

Concomitant AEDs reviewed, physical and neurological exams, vital signs, local ECG, safety laboratory tests, urine pregnancy test, C-SSRS, review safety and record AEs, subject calendar review, CGI-I, PCGI-I, study medication return and compliance check and dispense study medication.; dose de-escalation instructions given.

8.5.1.3.8 Visit 8 Safety Follow-up (Week 106; follow-up for end of dose de-escalation period)

Concomitant AEDs reviewed, brief physical and neurological exams, vital signs, safety laboratory tests, urine pregnancy test, C-SSRS, review safety and record AEs, subject calendar review and study medication return and compliance check.

8.5.1.3.9 Unscheduled Visit

Activities to be determined by the nature of the visit, are at the Investigator's discretion. In most cases basic safety procedures (vital signs, review of adverse events) should be completed.

8.6 Data Quality Assurance

Steps to be taken to assure the accuracy and reliability of safety 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 by a Sponsor representative. Case report forms will be reviewed for accuracy and completeness by a Sponsor representative during on-site monitoring visits and after their return to the Sponsor, and any discrepancies will be resolved with the Investigator or designees, as appropriate. The data will be entered into the clinical trial database and verified for accuracy.

8.7 Statistical Methods Planned and Determination of Sample Size

8.7.1 Statistical and Analytical Plans

8.7.1.1 Randomization

This is an open-label extension study and no randomization will occur.

8.7.1.2 Analysis Populations

All subjects who sign informed consent and take one dose of study medication in this study will be included in the ITT Safety Population. Subjects who return at least 25 days of seizure calendar data will be included in the Full Analysis Population.

8.7.1.3 Analysis of Efficacy Variables

The primary outcome measure is the percentage change in seizure (POS with or without secondary generalization) frequency per 28-days relative to baseline in study 1042-0603. Results will be expressed in mean and median change.

Secondary efficacy outcome measures include proportion of subjects experiencing a ≥ 50% reduction at the end of the study compared with Study 1042-0603 baseline

(proportion of Responders), seizure free intervals and seizure free days. The CGI-I and PCGI-I are also secondary efficacy assessments.

8.7.1.4 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, by dose 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. Important changes in laboratory, ECG values and vital signs will be flagged in data listings. Listings of most abnormal changes will be provided.

8.7.2 Determination of Sample Size

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

9. INVESTIGATOR REQUIREMENTS

9.1 Study Initiation

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

1. Completed FDA Form 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 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. 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.
7. A signed Clinical Research (Protocol) Agreement.
8. Certified translations of IRB/EC approval letters, pertinent correspondence, and approved ICF (when applicable).
9. Financial disclosure form for Principal Investigator and all sub-investigators.

9.2 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 Visit 1 through the end of the study (e.g., clinical data, all special test results).
2. Information properly recorded in the CRFs by appropriate study personnel and 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).

9.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include the following:

- 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.
- Subject enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.

9.4 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 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.

9.5 Adverse Events

The AE definitions and reporting procedures provided in this protocol comply with current CFR 21 Part 312. The Medical Monitor assigned by the Sponsor must promptly review all information relevant to the safety of an investigational new product received from any source. The Investigator will carefully monitor each subject throughout the study for possible AEs. All AEs will be documented on CRFs designed specifically for this purpose, and will be followed until either completely resolved or until a stable chronic outcome is determined by the Investigator. It is also important to report all AEs that result in permanent discontinuation of the investigational drug, whether serious or non-serious.

9.5.1 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.

9.5.2 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 CRF 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, **but is 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 CRF, a specific disease or syndrome rather than individual associated signs and symptoms should be recorded on the AE CRF. 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 CRF (clinically significant laboratory abnormalities are those that are identified as such by the Investigator and/or those that require intervention).

9.5.3 Reporting of Adverse Events

9.5.3.1 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) 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 or a medical emergency occurs you may contact your local medical monitor or local team leader. If they are not available contact the Global Study Leader or Study Team Physician noted below.

Role in the study	Name	Address & telephone number
Global Study Leader	[redacted]	O: [redacted] M: [redacted]
Study Team Physician	[redacted], MD, PhD	O: [redacted] M: [redacted]
Chief Medical Officer	[redacted], MD	O: [redacted] M: [redacted]

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-study604-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-study604-Bulgaria@gctrials.com

SAE reporting for German & Polish Sites:

Telephone number (Mon.-Fri.; 9am-6pm CET): +49 2173-10947-17

Prisma FAX Number: (24 hours; 7 days/week): +49 2173-10947-20

Prisma email: safety@prisma-cro.com

SAE reporting for Australian Sites:

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

9.5.3.2 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:

For US Sites & Australian Sites outside of business hours:

[redacted], MD, PhD
Marinus Pharmaceuticals
Office Telephone: [redacted]
Mobile phone: [redacted]
Email: [redacted]

For Bulgarian sites:

[redacted], M.D.
Global Clinical Trials (BCT Global)
Telephone: [redacted]
Email: [redacted]

For Russian sites:

[redacted], M.D.
Global Clinical Trials (RCT Global)
Telephone: [redacted]
Email: [redacted]

For German and Polish Sites:

[redacted], M.D.
Prisma – CRO GmbH

Telephone: [redacted]
Email: [redacted]

For Australian Sites (during business hours):
Prof. [redacted], M.D.
The Royal Melbourne Hospital
Telephone: [redacted]
Email: [redacted]

9.5.3.3 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 CRF 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.

9.6 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, CRFs, 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.).

9.7 Case Report Forms (CRFs)

CRFs will be used to store subject information. The CRFs will be provided by the Sponsor and should be handled in accordance with the instructions provided. CRFs must be completed as soon as possible after any subject evaluation or communication. CRFs should be completed by examining personnel or the study coordinator and must be reviewed, and signed and dated by the Investigator. CRFs must be accessible to study monitors and other regulatory auditors.

9.8 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.

9.9 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.

9.10 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 CRFs, 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.

For German and Polish sites all records and documents pertaining to the conduct of this study must be retained for 15 years after the completion of the study unless a longer period is required by applicable laws or regulations.

9.11 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/EC. Each Investigator will be responsible for enrolling only those subjects who have met protocol eligibility criteria.

10. 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.

11. 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.

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.

12. APPENDICES

12.1 Appendix 1: 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		
CO_2		
Total Protein		
Serum Albumin		

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

12.2 Appendix 2: 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 aprepitant atazanavir boceprevir ciprofloxacin clarithromycin conivaptan (not sold in Germany, Poland) diltiazem erythromycin fluconazole fluvoxamine fosamprenavir grapefruit juice imatinib indinavir itraconazole ketoconazole mibefradil (not sold in US, Russia, Poland, Germany) nefazodone (not sold in US, Russia, Poland, Germany) nelfinavir (not sold in Germany, Poland) posaconazole ritonavir saquinavir telaprevir telithromycin troleandomycin (not sold in US, Russia, Poland, Germany) verapamil voriconazole	avasimibe (not sold in Germany, Poland) bosentan efavirenz etravirine modafinil nafcillin (not sold in Germany, Poland) rifabutin (not sold in Germany, Poland) rifampin St. John's wort troglitazone (not sold in US, Russia, Poland, Germany)

*Carbamazepine, phenytoin and phenobarbital are 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

12.3 Appendix 3: Dosing Instructions for Subjects

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

GANAXOLONE IN ADULT PARTIAL ONSET SEIZURE STUDY SECOND YEAR EXTENSION
SUBJECT DOSING INSTRUCTIONS

Name: _____

Next Appointment: _____

These are your dosing instructions for the next _____weeks/ months (please circle one) from ____/____/____(start date) to ____/____/____(end date). Depending on your dose, you may be gradually increasing (titration), maintaining the same amount (maintenance) or gradually decreasing the amount of study drug (de-escalation) during this time. The chart below lists the day or week, dose, and how many capsules you should take for each dose. **Please take each dose just before or up to 2 hours after a meal or snack with 8 ounces (240 ml) of water. Grapefruit and grapefruit juice are not allowed at any time during your participation in this clinical trial.** 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 dose should not be taken. Please keep track of the days you missed a dose and contact the study coordinator if you miss 4 doses in a row or more. Please save all empty, partially used and unused bottles of the study drug and return the bottles at your next visit.

Example 1:

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

Day / Week _____ Date___/___/___	Dose (mg)	Number of capsules to take at EACH DOSE x TWICE/DAY
Day 1; 1/23/15	450	1
Day 2; 1/24/15	450	1
Day 3; 1/25/15	450	1
Day 4; 1/30/15	900	2

Example 2:

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

Day / Week _____ Date___/___/___	Dose (mg)	Number of capsules to take at EACH DOSE x TWICE/DAY
Week 3-6; 1/30/15 to 2/4/15	1800 mg	4

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

Day / Week _____ Date___/___/___	Dose (mg)	Number of capsules to take at EACH DOSE x TWICE/DAY

If you experience any side effects from the study medication that interfere with your daily activities or have any questions, please contact your study doctor at the telephone number below to see if a dose adjustment is necessary.

Study Doctor: _____

Telephone Number: _____

12.4 Appendix 4: Subject Seizure Calendar

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

MARINUS
PHARMACEUTICALS, INC.

Subject Seizure Calendar

Protocol 1042-0604

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. 14Jan2015 USA

Investigator Seizure Code:

Investigators, please use the following codes A-E 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

12.5 Appendix 5: Clinical Global Impression – Improvement (Patient/Caregiver)

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

Participant ID:	Visit #:	Visit Date:
Check if the assessment was not completed:		

Clinical Global Impression – Improvement (CGI-I) Subject

Circle the appropriate response that adequately describes how your symptoms have improved or worsened relative to baseline before the study drug was introduced.

1= very much improved

2= much improved

3= minimally improved

4= no change

5= minimally worse

6= much worse

7= very much worse

12.6 Appendix 6: Columbia Suicide Severity Rating Scale (C-SSRS) Since Last Visit

Translations in Bulgarian, German, Polish and Russian 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 for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

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.	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** ☐ ☐
Completed 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* _____

12.7 Appendix 7: Protocol History

Amendment 1 Summary of Changes from January 15, 2015

Page	Section, Title, Paragraph, Line	Original Text	Revised Text
1	Study Title	A follow-on, second year open-label extension study of ganaxolone as add-on therapy in adult patients with drug-resistant partial-onset seizures	A follow-on, two-year open-label extension study of ganaxolone as add-on therapy in adult patients with drug-resistant partial-onset seizures
1	Short Title	Ganaxolone Second Year Extension Study	Ganaxolone Two-year Open-label Extension Study
Reason for Change: Updated to increase the study duration from one to two years			
1	Sponsor Contact	[redacted], Ph.D. Sr. Director, Clinical Development Telephone: [redacted] Email: [redacted]	[redacted] Sr. Director, Clinical Operations Telephone: [redacted] Email: [redacted]
1	Sponsor's Medical Representative	[redacted], M.D., MBA Chief Medical Officer Office Phone: [redacted] Mobile phone: [redacted] Email: [redacted]	[redacted], MD, PhD Vice President, Clinical Development Office Phone: [redacted] Mobile Phone: [redacted] Email: [redacted]
Reason for Change: Administrative change - contact information			
3	Synopsis-Title of the Protocol	A follow-on, second year open-label extension study of ganaxolone as add-on therapy in adult subjects with drug-resistant partial-onset seizures	A follow-on, two-year open-label extension study of ganaxolone as add-on therapy in adult subjects with drug-resistant partial-onset seizures
3	Synopsis-Primary Objectives	To assess the safety and tolerability of adjunctive ganaxolone during a second year of open-label treatment in adult subjects with drug-resistant partial-onset seizures	To assess the safety and tolerability of adjunctive ganaxolone during a two-year open-label treatment in adult subjects with drug-resistant partial-onset seizures
3	Synopsis-Secondary Objectives	To assess efficacy of adjunctive ganaxolone during a second year of open-label treatment in adult subjects with drug-resistant partial-onset seizures	To assess efficacy of adjunctive ganaxolone during a two-year open-label treatment in adult subjects with drug-resistant partial-onset seizures
3	Synopsis-Duration of Treatment	Up to 52 weeks treatment on the maintenance dose with an additional 2 weeks of dose de-escalation.	Up to 104 weeks treatment on the maintenance dose with an additional 2 weeks of dose de-escalation.
Reason for Change: Updated to increase the study duration from one to two years			

4	2.1 Table 1: Schedule of Events	Week 52/Early Term –V4 Week 54 – V5 ECG (12 lead, 2-3 hours after dosing)	The Schedule of Events was revised to incorporate the changes to the protocol. Week 52 – V4 Week 69 – V5 Added: Week 86 – V6 Added: Week 104 (Study completion/ET – V7 Added: Week 106 (Post-Taper Safety Follow-Up) – V8 ECG (12 lead) Added: Footnotes 1, 3 and 5
Reason for Change: Clarification of the visit labels/schedule for the additional year			
10	5. Investigators and Study Administrative Structure	Duration of subject participation is 54 weeks.	Duration of subject participation is 106 weeks.
Reason for Change: Updated to increase the study duration from one to two years			
14	7.1 Primary Objectives	To assess the safety and tolerability of adjunctive ganaxolone during a second year of open-label treatment in adult subjects with drug-resistant partial on-set seizures.	To assess the safety and tolerability of adjunctive ganaxolone during two-year open-label treatment in adult subjects with drug-resistant partial on-set seizures.
14	7.2 Secondary Objectives	To assess the efficacy of adjunctive ganaxolone during a second year of open-label treatment in adult subjects with drug-resistant partial on-set seizures.	To assess the efficacy of adjunctive ganaxolone during two-year open-label treatment in adult subjects with drug-resistant partial on-set seizures.
Reason for Change: Updated to increase the study duration from one to two years			
15	8.1 Overall Study Design and Plan, Line 1	Study 1042-0604 is an open-label extension of Study 1042-0603, providing a second year of adjunctive ganaxolone treatment (900-1800 mg/d) to adult subjects with epilepsy consisting of partial-onset seizure (POS).	Study 1042-0604 is an open-label extension of Study 1042-0603, providing a two-year adjunctive ganaxolone treatment (900-1800 mg/d) to adult subjects with epilepsy consisting of partial-onset seizure (POS).
Reason for Change: Updated to increase the study duration from one to two years			
16	8.2 Discussion of Study Design, Paragraph 1, Line 8		Added: During the study if the patient fails to continue to meet the minimum improvement criteria (mean 28-day seizure frequency over the past three 28 day periods before the study visit showing 35% improvement over baseline) at any study visit the investigator should consider discontinuing the patient from the study.

Reason for Change: Clarification of criteria for discontinuation. This criteria is intended to ensure that the patients are periodically assessed for benefits and risks of ganaxolone, and that the patients who no longer derive significant benefit from ganaxolone are considered for exclusion.			
16	8.3.2 Inclusion Criteria	1. Subjects who have completed all scheduled clinical study visits in the previous protocol 1042-0603 and have shown a minimum 35% improvement in mean seizure frequency per 28 days vs. baseline over the three 28 day periods preceding study entry.	1. Subjects who have completed all scheduled clinical study visits in the previous protocol 1042-0603 and have shown a minimum 35% improvement in mean 28-day seizure frequency over the last three 28 day periods in study 1042-603 as compared to the baseline of study 1042-603.
16	8.3.2 Inclusion Criteria	4. Currently being treated and maintained with a stable regimen of 1, 2, or 3 AEDs at a consistent dose for one month prior to study entry. a.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. b.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 reac	4. Currently being treated and maintained with a stable regimen of 1, 2, or 3 AEDs at a consistent dose for one month prior to study entry. See Section 8.4.8 for restriction on certain AEDs. Deleted: a. & b.
Reason for Change: This section was redundant with section 8.4.8 of the protocol. The criteria for using concomitant AEDs, including Felbamate and Perampanel, is explained in section 8.4.8.			
17	8.3.3 Exclusion Criteria	3. 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 during Study 1042-0603.	Added: (Since Study 1042-0603 Visit 10 safety laboratory results will not be available at the time of inclusion in Study 1042-0604, these results will be assessed against Section 8.3.4.1 Criteria for withdrawal #11.)
Reason for Change: Clarification for assessing subject eligibility post Visit 1.			
18	8.3.4.1 Investigator-initiated withdrawal of a subject	8.3.4.1 Investigator-initiated withdrawal of a subject	8.3.4.1 Criteria for withdrawal
18	8.3.4.1 Investigator-initiated	1. Post-treatment QTc interval >500 msec or uncorrected QT interval >600 msec; for subjects with bundle	1. QTc interval >500 msec or uncorrected QT interval >600 msec; for subjects with bundle branch block, QTc >530 msec

	withdrawal of a subject	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 Visit 1 must also be withdrawn. a. If the initial 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.	based on average QTc value of triplicate ECGs. A subject with an increase in QTc of >60 msec from Visit 1 must also be withdrawn. a. If an 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.
18	8.3.4.1 Investigator-initiated withdrawal of a subject		Added: 8. Patient's mean 28-day seizure rate over the past three 28-day periods before the study visit shows less than 35% improvement in comparison to the patient's baseline in the 1042-603 study.
18	8.3.4.1 Investigator-initiated withdrawal of a subject	9. 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 in medical history. c. Status epilepticus at any time during the clinical investigation. d. An "actual suicide attempt" as classified by the Columbia-Suicide Severity Rating Scale (C-SSRS).	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 in medical history. 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 questions 4 and 5 in the Suicidal Ideation section of the C-SSRS. These patients should be referred to psychiatric evaluation immediately.
18	8.3.4.1 Investigator-initiated withdrawal of a subject		Added: 11. Any subject who has the following liver enzyme findings should be immediately contacted and instructed to stop the study or start immediate down titration of the study drug: a. ALT or AST >8xULN b. ALT or AST >5xULN for more than 2 weeks c. ALT or AST >3xULN with the

			appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia Patients with ALT or AST .3xULN but <8xULN 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 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**: Subjects with <35% improvement in seizure frequency as compared to baseline**: This criteria is intended to ensure that patients are periodically assessed for benefits and risks of ganaxolone, and that the patients who no longer derive significant benefit from ganaxolone are considered for exclusion. **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)			
20	8.3.4.2 Early Termination Procedures, Line 3	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 4 (52 weeks/pre-taper/ET) which include: concomitant AED review, vital signs, physical and neurological exams, laboratory assessments, ECG, pregnancy test, C-SSRS, collection of adverse events, CGI-I, PCGI-I and seizure calendar review.	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 will be asked to complete the procedures for Visit 7 (Study Completion/Early Term) which include: concomitant AED review, vital signs, physical and neurological exams, laboratory assessments, ECG, pregnancy test, C-SSRS, collection of adverse events, CGI-I, PCGI-I and seizure calendar review.
Reason for Change: Clarification of the visit label/schedule			
20	8.3.4.3 Consequences of Early Termination, Line 5	Every effort will be made to ensure implementation of the de-escalation.	Every effort will be made to ensure implementation of the dose de-escalation.

21	8.4.4 Selection of Doses in the Study, Paragraph 2	De-escalation Period: The study drug will be decreased in increments of 450mg/d in 3-day intervals over 12 days for 1800 mg. Decreases from doses less than 1800 mg will be adjusted accordingly (See Table 1). The subject will return for final post-taper safety assessment visit.	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 2). The subject will return for final post-taper safety assessment visit.
Reason for Change: Text in section 8.4.4. has been corrected to reflect the dose de-escalation schedule presented in Table 2. According to Table 2, which presents the correct de-escalation schedule, ganaxolone dose is decreased every 4 days.			
22	Table 2. Dosing Schedule for De-Escalation Period	De-Escalation, Study Completion or Early Termination **Visit** Visit 4/ Taper Visit/	De-Escalation, Study Completion or Early Termination (ET) **Visit** Visit 7 (Study Completion/ Early Term)
Reason for Change: Clarification of the visit label/schedule			
23	8.4.8 Excluded, Prior and Concomitant Medications, Paragraph 1	Subjects participating in the study are to 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:	Subjects participating in the study are to be taking 1-3 AEDs in addition to the investigational medication. AEDs may be adjusted during the course of the study, but subjects must continue on at least one AED. Marketed medications indicated for the treatment of partial seizures are acceptable with the exceptions noted below:
Reason for Change: Provides clarification that the investigators may adjust the concomitant medications during this trial.			
23	8.4.9 Excluded Concomitant Medications, Paragraph 1, Line 3	Note that **phenytoin** and **carbamazepine** are permitted as background AEDs though they are moderate CYP 3A4 inducers.	Note that **phenytoin, carbamazepine** and **phenobarbital** are permitted as background AEDs though they are moderate CYP 3A4 inducers.
23	8.4.9 Excluded Concomitant Medications, Paragraph 4	Use of dietary supplements or herbal preparations are permitted if subject has been using them consistently for more than 6 months prior to Visit 1, and does not plan changing the regimen for the duration of the study. Use of St. John's Wort is not permitted (see Appendix 2).	Use of dietary supplements or herbal preparations are permitted if subject has been using them consistently for more than 6 months prior to Visit 1, and does not plan changing the regimen for the duration of the study. Any changes during the study should be approved by the medical monitor. Use of St. John's Wort is not permitted (see Appendix 2)
Reason for Change: Clarification of permitted medication and process. Phenobarbital is an AED and CYP3A4 inducer akin to phenytoin and carbamazepine, and may be permitted as a concomitant AED.			

26	8.5.1.3.1 Visit 1 (same as Study 1042-0603 Visit 10/Open Label Month 12), Paragraph 2	**Additional** 1042-0604 procedures: informed consent reviewed and signed; inclusion/exclusion and demographics/medical history reviewed; and 1042-0604 seizure calendars and study medication dispensed.	Added: Any Adverse Event that occurred in study 1042-0603 which is not resolved at the time of enrollment into 1042-0604 or is deemed significant by the Principal Investigator is to be captured in the subject's 1042-0604 medical history. If the frequency, severity or duration of this event changes in any way then it is to be captured as an Adverse Event in 1042-0604.
27	8.5.1.3.4 Visit 4, Line 1 and 4	Visit 4/Early Term (Week 52; start of dose de-escalation period) Concomitant AEDs reviewed, physical and neurological exams, vital signs, ECG, safety laboratory tests, urine pregnancy test, C-SSRS, review safety and record AEs, subject calendar review, CGI-I, PCGI-I, study medication return and compliance check and dispense study medication.; dose de-escalation instructions given.	Visit 4 (Week 52) Added: local ECG Deleted: …dose de-escalation instructions given.
27	8.5.1.3.5 Visit 5	Visit 5 (Week 54; follow-up for end of dose de-escalation period) Concomitant AEDs reviewed, brief physical and neurological exams, vital signs, safety laboratory tests, urine pregnancy test, C-SSRS, review safety and record AEs, subject calendar review and study medication return and compliance check.	Visit 5 (Week 69) Concomitant AEDs reviewed, brief physical and neurological exams, vital signs, safety laboratory tests, urine pregnancy test, C-SSRS, review safety and record AEs, subject calendar review and study medication return and compliance check and dispense study medication.
27	8.5.1.3.6 Visit 6	Unscheduled Visit Activities to be determined by the nature of the visit, are at the Investigator's discretion. In most cases basic safety procedures (vital signs, review of adverse events) should be completed.	Visit 6 (Week 86) Concomitant AEDs reviewed, brief physical and neurological exams, vital signs, safety laboratory tests, urine pregnancy test, C-SSRS, review safety and record AEs, subject calendar review, study medication review and compliance check and dispense study medication.
27	8.5.1.3.7		Section Added: Visit 7/Early Term Visit (Week 104; start of dose-escalation period) Concomitant AEDs reviewed, physical and neurological exams, vital signs, local ECG, safety laboratory tests, urine pregnancy tests, C-SSRS, review safety and record AEs, subject calendar review, CGI-I, PCGI-I, study medication return

			and compliance check and dispense study medication; dose de-escalation instructions given.
27	8.5.1.3.8		Section Added: Visit 8 Safety Follow-up (Week 106; follow-up for end of dose de-escalation period) Concomitant AEDs reviewed, brief physical and neurological exams, vital signs, safety laboratory tests, urine pregnancy test, C-SSRS, review safety and record AEs, subject calendar review and study medication return and compliance check.
28	8.5.1.3.9 Unscheduled Visit	8.5.1.3.6 Unscheduled Visit	8.5.1.3.9 Unscheduled Visit
Reason for Change: Clarification of Visit labels/schedule and study assessments			
30	9.1 Study Initiation	1. Completed original USA FDA 1572…	1. Completed FDA Form 1572…
Reason for Change: Clarification that a completed form is required			
34	9.5.3.1 SAE Reporting, Paragraph 1	If a fatal or imminently life-threatening SAE occurs during a US holiday, sites are encouraged to call [redacted] M.D. ([redacted]) or [redacted] M.D. [redacted] in addition to faxing the SAE report.	If a fatal or imminently life-threatening SAE or a medical emergency occurs you may contact your local medical monitor or local team leader. If they are not available contact the Global Study Leader or Study Team Physician noted below: **Global Study Leader**: [redacted] O: [redacted] M: [redacted] [redacted] **Study Team Physician:** [redacted] MD, PhD O: [redacted] M: [redacted] [redacted] **Chief Medical Officer:** [redacted] MD O: [redacted] M: [redacted] [redacted]
34	9.5.3.1 SAE Reporting, Last Paragraph	If a fatal or imminently life-threatening SAE occurs with relationship suspected to study drug, necessitating immediate telephone contact, call [redacted] M.D. [redacted]	Deleted

		[redacted], M.D. ([redacted]) in addition to faxing the SAE report.	
Reason for Change: Administrative change – Contact information			
36	9.5.3.2 Medical Inquiries	**For US & Australian Sites:** [redacted], M.D. Marinus Pharmaceuticals Office Telephone: [redacted] Mobile phone: [redacted] Email: [redacted]	**For US & Australian Sites outside of business hours:** [redacted], MD, PhD Marinus Pharmaceuticals Office Telephone: [redacted] Mobile phone: [redacted] Email: [redacted] Added: **For Australian Sites (during business hours)** Prof. [redacted], M.D. The Royal Melbourne Hospital Telephone: [redacted] Email: [redacted]
Reason for Change: Administrative change – Contact information			
43	12.2 Appendix 2, Line 1 below table	*Carbamazepine and phenytoin are both moderate CYP 3A4 inducers but are permitted as background AEDs during the study.	*Carbamazepine, phenytoin and phenobarbital are moderate CYP 3A4 inducers but are permitted as background AEDs during the study.
58	12.7 Appendix 7: Protocol History		Added