MARINUS
PHARMACEUTICALS, INC.

CLINICAL STUDY PROTOCOL

STUDY TITLE: A Multicenter, 26 week Open-Label Proof-of-Concept Trial of Ganaxolone in Children with PCDH19 Female Pediatric Epilepsy And Other Rare Genetic Epilepsies Followed by 52 Week Open Label Treatment

PROTOCOL NUMBER: 1042-0900

STUDY PHASE: 2a

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

IND NUMBER: 44,020

INDICATION: PCDH19 Female Pediatric Epilepsy

SPONSOR: Marinus Pharmaceuticals, Inc.
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VERSION/DATE: version 6.0: 08 April 2016

1. SIGNATURE PAGE

Sponsor Approval

Signature: _____ **Date:** _____

Name (print): [redacted] MD
Chief Medical Officer

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: 1042-0900	**Phase of Development:** 2a
Title of Protocol: A 26 week Multicenter, Open-Label Proof-of-Concept Trial of Ganaxolone in Children with PCDH19 Female Pediatric Epilepsy And Other Rare Genetic Epilepsies Followed by a 52 Week Open Label Treatment	
Primary Objectives: To evaluate the efficacy of open-label ganaxolone as adjunctive therapy for uncontrolled seizures in children with genetic epilepsies. These include, but are not limited to children with protocadherin19 (PCDH19) mutation, cyclin-dependent kinase like 5 (CDKL5) Disorder, Dravet Syndrome and other epileptic syndromes such as idiopathic or genetic types of Lennox-Gastaut syndrome (LGS), Continuous Spike Wave in Sleep (CSWS) and other potential genetic or clinical conditions with or without corresponding genetic condition (referred to as genetic epilepsies) in an open-label proof-of-concept study.	
Secondary Objectives: To evaluate the safety and tolerability of open-label ganaxolone as adjunctive therapy for uncontrolled seizures in children with genetic epilepsies.	
Study Design and Methodology: After establishing baseline seizure frequency, qualifying subjects will enter the study and be treated with ganaxolone oral suspension or ganaxolone capsules at doses up to 63 mg/kg but not more than 1800 mg/day for up to six months.	
Study Population and Main Criteria for Inclusion/Exclusion: Subjects between 2 and 18 years of age with a confirmed PCDH19 mutation, or a confirmed CDKL5 mutation or Dravet syndrome with a confirmed SCN1A mutation or LGS, or CSWS or potential other genetic or clinical conditions with or without corresponding genetic condition and consent of a parent or guardian may be eligible to enter the study. Seizure criteria as follows: a. Have uncontrolled cluster seizures (3 or more seizures over the course of 12 hours) every 6 weeks or less during baseline, or bouts of status epilepticus on intermittent basis, or b. Have uncontrolled non-clustered seizures (focal dyscognitive, focal convulsive, atypical absences, hemiclonic seizures, spasms, or tonic-spasm seizures) with a frequency ≥4 seizures per 28-day period during baseline, or c. Have ≥4 generalized convulsive (tonic-clonic, tonic, clonic, atonic seizures) per 28-day baseline period during baseline, or	

d. Have subclinical CSWS syndrome with or without clinical events on electroencephalogram (EEG). Subjects should be on a stable regimen of AED medication, and generally in good health without active central nervous system (CNS) infection or progressive disease or clinically unstable psychiatric disorder likely to require new treatment during the study Subjects who have completed all scheduled clinical study visits and have shown a minimum 35% improvement in mean seizure frequency per 28 days vs. baseline may be enrolled in the 52 week open label extension.
Number of Subjects: Approximately ten (10) subjects with PCDH19, 10 subjects with CDKL5 Disorder, 10 subjects with Dravet Syndrome, and up to 10 subjects with LGS, CSWS, encephalopathic epilepsy or other genetic epilepsies will be enrolled.
Test Product, Dose and Mode of Administration: Ganaxolone oral suspension 50 mg/mL dosed TID, or ganaxolone 200 mg or 225 mg capsules administered in BID. Oral suspension or capsules to be administered up to a total of 63 mg/kg/day but not more than 1800 mg/day.
Duration of Treatment: After establishing baseline seizure type and frequency for a minimum of 4 weeks and up to 12 weeks, subjects entering the study will be treated with ganaxolone for 26 weeks, in the main portion of the study, and up to an additional 52 weeks if clinical response is established plus additional time to down-titrate (1 to 4 weeks).
Reference Therapy, Dose and Mode of Administration: Not applicable

Criteria for Evaluation: **Primary Efficacy:** Primary efficacy will be percent change in seizure frequency (focal dyscognitive or focal convulsive) per 28 days relative to the baseline. **Secondary Efficacy:** Secondary efficacy assessments include evaluation of inter-cluster interval, time to reach baseline number of seizures, seizure-free interval, 50% responder proportion, proportion with 50% increase in inter-cluster interval, CGI-I.
Safety: Neurological and physical examinations, clinical laboratory tests, electrocardiogram (ECG), vital signs, EEG and spontaneously reported adverse events (AEs).
Serum Levels: Blood samples will be drawn at baseline, 2 weeks, 8 weeks, 26 weeks and at each visit in the open labeled extension and at unscheduled visits as needed for evaluation of blood chemistry and hematology, and to measure levels of ganaxolone, concomitant AED medications, allopregnanolone, and related endogenous CNS-active steroids.
Statistical Methods: The primary and secondary efficacy variables will be summarized and using descriptive statistics for the populations of all subjects and completers. Individual subject data will also be presented.

Adverse events (AEs) will be tabulated by Overall, system organ class (SOC), and Preferred Term using the MedDRA coding system. Incidence and percentage of adverse events will be presented 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 including changes from baseline.

3. TABLE OF CONTENTS

4. LIST OF ACRONYMS, ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Definition
3α,5α-P	3α-hydroxy-5α-pregnan-20-one; allopregnanolone
ACTH	adrenocorticotropic hormone
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)
BID	bis in die; two times per day
CBD	cannabadiol
CDKL5	cyclin-dependent kinase like 5
CFR	Code of Federal Regulations
°C	degrees centigrade
CGII-C	Clinical Global Impression of Improvement -Clinician
CGII-P	Clinical Global Impression of Improvement – Patient/Caregiver
CNS	central nervous system
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CSWS	Continuous Spike Wave in Sleep
DDI	drug-drug interaction
EC	Ethics Committee
EEG	electroencephalogram
ESES	Epileptic Status Epilepticus in Sleep
ET	early termination
°F	degrees Fahrenheit
FDA	Food and Drug Administration
FLE	Female-limited epilepsy
FPE	Female pediatric epilepsy
$GABA_A$	γ-aminobutyric $acid_A$
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Conference on Harmonisation
IND	investigational new drug
IRB	Institutional Review Board
ITT	intent-to-treat
Kg	kilogram
LGS	Lennox-Gastaut Syndrome
m	meter
MedDRA	Medical Dictionary for Regulatory Activities
MEG	magnetoencephalography
mg	milligram
mg/day	milligram per day
min	minutes
mL	millilitre
MRI	magnetic resonance imaging
MTD	maximum tolerated dose

Term	Definition
n	number of subjects
oz	ounces
PCDH19	protocadherin19
PK	pharmacokinetics
SAE	serious adverse event
SAE CRF	serious adverse event case report form
SOC	system organ class
TID	three times daily
T_{max}	time to maximum concentration
ULN	upper limits of normal
USA	United States of America
VAS	Visual Analogue Scale

5. ETHICS

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

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

5.2 Ethical Conduct of Study

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

5.3 Subject Information and Consent

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

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This will be a multi-center study with approximately 8 participating centers in the USA, and Italy with ~1-3 subjects per condition enrolled at each site.

Study enrollment is planned for 6 months from the time of first subject visit. After signing informed consent, subjects may be asked to chart seizures in order to establish baseline frequency for up to 12 weeks. Eligible subjects will be treated with open-label ganaxolone for up to 26 weeks, 52 weeks of additional open-label treatment and at the end of the study or at discontinuation they will be down-titrated for up to 4 weeks.

7. INTRODUCTION

Patients with rare epilepsy conditions such as PCDH19 Female Pediatric Epilepsy, CDKL5 Disorder, and Dravet Syndrome as well as many other refractory genetic epilepsy conditions that may share common seizure types and often their seizures become treatment resistant. These may overlap idiopathic Lennox-Gastaut syndrome (LGS) patients or other genetically based conditions with intractable epilepsy clinically resembling LGS. This population has been, at times, treated with and responsive to classes of corticosteroids like prednisone or adrenocorticotropic hormone (ACTH). Another epileptic diagnostic condition Continuous Sleep Wave in Sleep (CSWS) or Epileptic Status Epilepticus in Sleep (ESES) may also respond to steroid medications and be refractive to standard antiepileptic agents. The mechanism by which any of these mutations contributes to the development of epilepsy is not well understood. No one anticonvulsant has been found to be uniformly effective, and often multiple anticonvulsants are needed. Even then, patients still become treatment resistant. Therefore the need for novel treatments to address seizure control is critical for patients living with these conditions.

This study will test ganaxolone as an experimental drug with a new and distinct mechanism of action. Ganaxolone is the 3β-methylated synthetic analog of allopregnenolone, an endogenous allosteric modulator of $GABA_A$ receptors in the CNS. Ganaxolone has potency and efficacy comparable to allopregnanolone[11] in activating synaptic and extrasynaptic $GABA_A$ receptors at a site distinct from the benzodiazepine site. Ganaxolone has protective activity in diverse rodent seizure models. [12, 13, 15] and has been shown in clinical trials to be effective as adjunctive treatment for partial-onset seizures.

Clinical studies have demonstrated ganaxolone has anticonvulsant efficacy with an acceptable safety and tolerability profile in the dose range of 900-1800 mg in adults and children, the present study is planned to investigate whether ganaxolone provides efficacy for children with uncontrolled seizures and PCDH19 Female-Pediatric Epilepsy, and other genetic epilepsies.

BACKGROUND ON PCDH19

Protocadherin (PCDH)19- female-pediatric epilepsy (FPE), also known as PCDH19 female-limited epilepsy (FLE) or epilepsy in females with mental retardation (EFMR), is a serious epileptic syndrome characterized by early-onset cluster seizures, cognitive and sensory impairment of varying degrees, and behavioral disturbances in some individuals.[1] This disorder is associated with a mutation of the PCDH19 gene, the gene that encodes for protocadherin19 on the X chromosome.[2,3] The mechanism by which this mutation contributes to the development of epilepsy and intellectual impairment is not fully understood, however protocadherin19 is a transmembrane protein of calcium-dependent cell-cell adhesion molecules that is strongly expressed in neural tissue (e.g., hippocampus, cerebral cortex, thalamus, amygdale), and which appears to be related to synaptic transmission and formation of synaptic connections during brain development.[3] Research suggests impairment of GABAergic signaling both at the agonist and receptor levels is present in girls with PCDH19 mutations and pediatric-onset epilepsy.[4]

The hallmark characteristics of PCDH19-FPE are clusters of seizures which start in infancy or early childhood often associated with fever or immunization.[5-7] Patients with PCDH19-FPE may experience individual seizures in addition to clusters and multiple seizure types. In some patients, seizures improve as patients reach puberty, possibly due to increased endogenous levels of progesterone and allopregnanolone.[8-10]

Background on CDKL5 Disorder

CDKL5 disorder or CDKL5 stands for cyclin dependent kinase like 5, and is located on the X chromosome. The CDKL5 gene was previously called STK9. CDKL5 is a rare X linked genetic disorder that results in early onset, difficult to control seizures, and severe neuro-developmental impairment. [19]

Most of the children affected by CDKL5 present with irritability in the perinatal period, early epilepsy, hand stereotypies, severely impaired psychomotor development and severe hypotonia. In contrast to classical Rett syndrome they also may have absence of a classic regression period, poor eye contact, generally normal head circumference and other growth parameters and relative absence of autonomic dysfunction. [19]

Other symptoms of a CDKL5 disorder often include: Low muscle tone, hand wringing movements or mouthing of the hands, marked developmental delay, limited or absent speech, lack of eye contact or poor eye contact, gastroesophageal reflux, constipation, small, cold feet, breathing irregularities such as hyperventilation, grinding of the teeth, episodes of laughing or crying for no reason, low/Poor muscle tone, very limited hand skills, some autistic-like tendencies, scoliosis, Cortical Visual Impairment (CVI), aka "cortical blindness", apraxia, eating/drinking challenges, sleep difficulties and characteristics such as a sideways glance, and habit of crossing leg. [20]

BACKGROUND ON DRAVET SYNDROME

Dravet syndrome is a rare genetic epileptic encephalopathy described in 1978. It begins in the first year of life in an otherwise healthy infant. Prior to 1989, this syndrome was known as epilepsy with polymorphic seizures, polymorphic epilepsy in infancy (PMEI) or severe myoclonic epilepsy in infancy (SMEI). The disease begins in infancy but is lifelong. [17,18]

About 80% of people with this syndrome have a gene mutation (SCN1A is the most frequent) that causes problems in the way that ion channels in the brain work. Approximately 95% of patients with Dravet syndrome have de novo heterozygous mutations, which explains the unaffected status of many siblings and parents. [17,18]

The first seizure is often associated with a fever and may be a tonic clonic seizure or a seizure involving clonic movements on one side of the body. The seizures are refractory in most cases. Most children develop some level of developmental disability and have other conditions that are associated with the syndrome. Infants have normal development at the time the seizures begin, magnetic resonance imaging (MRI) and electroencephalogram (EEG) tests are also normal in infancy. [17,18]

Myoclonic seizures appear between 1 and 5 years in 85% of children with Dravet syndrome. Seizures early in life are often prolonged (lasting more than 2 minutes) or repetitive and can result in status epilepticus. Children with Dravet syndrome can develop

many different seizure types: myoclonic seizures, tonic clonic seizures, absence or atypical absence seizures, atonic seizures, partial seizures, non-convulsive status epilepticus. [17,18]

Seizures occur without a fever. However, these children are very sensitive to infections and frequently have seizures when they are ill or have a fever. Seizures can also be triggered by slight changes in body temperature that are not caused by infection for example a warm or hot bath water or hot weather. Many children have photosensitive seizures. Emotional stress or excitement can also trigger seizures in some children. [17,18]

Children usually develop normally in the early years. After age 2, they may lose developmental milestones or do not progress as quickly as they get older and have more seizures. There seems to be a correlation between frequency of seizures, how often status epilepticus occurs, and the degree of developmental delay in children. Around 6 years of age, cognitive problems in some children may stabilize or may start improving. However, most children with Dravet syndrome have some degree of developmental disability that persists. [17,18]

Other problems that may be seen include: low motor tone – can lead to painful foot problems, unsteady walking, some may develop a crouched gait, chronic infections, low humoral immunity, growth and nutrition problems, problems with the autonomic nervous system and behavioral or developmental problems such as autism spectrum disorder. [17,18]

BACKGROUND ON LGS AND CSWS

Lennox-Gastaut syndrome is a severe form of epilepsy. Seizures usually begin before 4 years of age. Seizure types, which vary among patients, include tonic, atonic, atypical absence, and myoclonic. There may be periods of frequent seizures mixed with brief, relatively seizure-free periods. Most children with LGS experience some degree of impaired intellectual functioning or information processing, along with developmental delays, and behavioral disturbances. Lennox-Gastaut syndrome can be caused by brain malformations, perinatal asphyxia, severe head injury, central nervous system infection and inherited degenerative or metabolic conditions. In 30-35 percent of cases, no cause can be

found. Many cases of LGS have had genetic mutations associated with the diagnosis clinically. These can include known encephalopathic epilepsy genes in Rett Syndrome, CNTNAP1, XP22.33, SCN2A, GABR3, Shank2, Shank3, and other genetic conditions associated with LGS-type clinical epilepsy. Non –degenerative genetic types of LGS or idiopathic refractive cases may respond to the neurosteroid mechanism of ganaxolone.

Continuous spike way in sleep starts with seizures between 2 to 12 years; peaks at 4 to 5 years with EEG continuous spikes and waves during slow-wave sleep, usually 1 to 2 years from seizure onset. Males (62%) show preponderance and up to 1/3 of the patients have abnormal mental state. The clinical manifestations include three stages of evolution:

- First stage before CSWS: infrequent nocturnal motor focal seizures, often hemiclonic status epilepticus, absences, atonic, complex focal seizures, and generalized tonic-clonic seizures occur.
- Second stage with CSWS: seizures more frequent and complicated with typical or more frequent atypical absences, myoclonic absences, absence status epilepticus, rarely atonic or clonic seizures, and focal simple or partial complex dyscognitive seizures, usually nocturnally during CSWS condition on EEG and some secondary or primary generalized tonic-clonic seizures. Tonic seizures do not occur. Eminent psychomotor decline and behavioral abnormalities, and a Wernicke's type or global language regression occurs with localization of perisylvian cortex on EEG and magnetoencephalography (MEG) studies.
- Third stage (after months to usually 2 to 10 years) with remission of CSWS and seizures and general improvement, normalization of CSWS pattern, and residual language or other learning difficulties.
- New genetic overlap to autism genetics and epilepsy genetics have been noted, mainly Grin2A or Grin2B among others. Many may be idiopathic to testing.

BACKGROUND ON GANAXOLONE

More than 1,000 adult and pediatric subjects have received treatment with ganaxolone in clinical trials, ranging in duration from one day to more than two years using doses from 50 to 2000 mg/day. In the Phase 2 program, 697 adults received ganaxolone in 9 completed

trials, 6 of which were in epilepsy. To date, the largest placebo-controlled study (N=147) of ganaxolone in epilepsy was 10-week, double-blind Study 1042-0600 followed by an open-label extension of up to two years duration. Study 1042-0600 showed ganaxolone (500 mg 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% median decrease in placebo (2.0% mean increase for the placebo arm).

Ganaxolone has been studied in 5 studies of pediatric seizure disorders in children aged 4 months through 15 years. Genotyping was not performed in any of these trials. Four open-label studies tested ganaxolone oral suspension at doses up to 36 mg/kg/day in subjects with history or current infantile spasms plus other seizure types including focal and generalized tonic-clonic, resistant to available medications. Across the four studies, approximately two thirds of subjects experienced some improvements in seizures and one third of subjects in these open-label investigations experienced improvements of 50% or greater from baseline seizure frequency. A double-blind, placebo controlled partial crossover trial of ganaxolone in infants (N=57) with infantile spasms did not show a statistically significant reduction in spasms between treatment groups over the 8-10 day treatment period, though only 18 subjects were exposed to placebo. Fifty-four subjects entered the long term open-label extension study, where 25% were recorded as seizure-free on the video EEG at study endpoint.

Most of the adverse events reported in the clinical development program were mild or moderate in severity, dose-related, resolved upon treatment discontinuation, and expected based on ganaxolone pharmacology. The most common adverse events across clinical trials are dizziness, fatigue and somnolence. The adverse event profile of ganaxolone in pediatric studies is similar to that seen in adults, without evidence of unique, clinically meaningful adverse events specific to the pediatric population. Adult and pediatric subjects in open label extension studies to the epilepsy trials have been dosed with ganaxolone for > 2 years (a few children as long as 4 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.

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 (References 13-16 and Marinus, data on file).

Preclinical safety pharmacology and toxicology testing with ganaxolone has not revealed any end organ toxicity nor potential for ganaxolone to cause cellular mutations or carcinogenicity in studies to date. In reproductive toxicology testing, ganaxolone did not cause any malformations of the embryo or fetus in rats or mice and did not significantly affect the development of offspring. Ganaxolone is primarily metabolized by the CYP3A family of liver enzymes, but interactions based on hepatic metabolism are limited to those caused by induction or inhibition of CYP3A4/5 by other drugs such as ketoconazole.

As studies have demonstrated ganaxolone has anticonvulsant efficacy with an acceptable safety and tolerability profile in the dose range of 900-1800 mg in adults and children, the present study is planned to investigate whether ganaxolone provides anticonvulsant efficacy for female children with uncontrolled seizures and PCDH19 mutation.

8. STUDY OBJECTIVES

8.1 Primary Objective

To evaluate the efficacy of open-label ganaxolone as adjunctive therapy for uncontrolled seizures in children with PCDH19 Female Pediatric Epilepsy, CDKL5 Disorder, Dravet Syndrome, and other epileptic syndromes such as LGS, CSWS and other potential genetic or clinical conditions with or without corresponding genetic condition (referred to as genetic epilepsies) in an open-label proof-of-concept study.

8.2 Secondary Objectives

To evaluate the safety and tolerability of open-label ganaxolone as adjunctive therapy for uncontrolled seizures in children with genetic epilepsies.

9. INVESTIGATION PLAN

9.1 Overall Study Design and Plan

The purpose of this proof-of-concept study is to evaluate ganaxolone as adjunctive therapy for uncontrolled seizures in female children with PCDH19 mutations, CDKL5 mutation and SCN1A mutation (Dravet syndrome) and other epileptic syndromes such as LGS, CSWS and other potential genetic or clinical conditions with or without corresponding genetic condition (referred to as genetic epilepsies) in an open-label proof-of-concept study. After establishing baseline seizure frequency, qualifying subjects will enter the study and be treated with open-label ganaxolone oral suspension or ganaxolone capsules at doses up to a maximum of 1800 mg/day for up to six months. Maximum study participation will be 94 weeks: a screening period to establish baseline seizure frequency, 26 weeks treatment, and a 52 week extension for patients who benefit from ganaxolone treatment and up to 4 weeks down-titration.

9.2 Discussion of Study Design

This proof-of-concept study was designed to evaluate ganaxolone in a small number of pediatric subjects with open-label treatment. The open-label design eliminates exposure to placebo, and the flexible dose selection allows optimization of the dose for these pediatric subjects. Administration of the test article as adjunctive therapy to background antiepileptic drugs (AEDs) provides standard-of-care therapy in addition to any benefit that study medication might provide.

9.3 Selection of study population

9.3.1 Number of Subjects

Approximately 10 subjects with PCDH19, 10 subjects with CDKL5 Disorder, 10 subjects with Dravet Syndrome, and up to 10 subjects with LGS, CSWS, encephalopathic epilepsy or other genetic epilepsy cases will participate.

9.3.2 Inclusion Criteria

1. Have parent or legal guardian available and willing to give written informed consent, after being properly informed of the nature and risks of the study and prior to engaging in any study-related procedures.

2. Outpatients between 2 and 18 years of age at time of consent.

3. In the opinion of the investigator have confirmed PCDH19 genetic mutation, confirmed CDKL5 genetic mutation or Dravet Syndrome confirmed by a SCN1A mutation, or genetic epilepsy testing confirming a LGS or CSWS condition associated with this genetic phenotype. Refractive cases of LGS or CSWS that remain idiopathic or have prior history of steroid or ACTH response can also be entered if documentation confirms specific genetic defects are not found and prior steroid response clinically occurred.

4. Seizure criteria:

    a. Have uncontrolled cluster seizures (3 or more seizures over the course of 12 hours) every 6 weeks or less during baseline, or bouts of status epilepticus on intermittent basis, or

    b. Have uncontrolled non-clustered seizures (focal dyscognitive, focal convulsive, atypical absences, hemiclonic seizures, spasms, or tonic-spasm seizures) with a frequency ≥4 seizures per 28-day period during baseline, or

    c. Have ≥4 generalized convulsive (tonic-clonic, tonic, clonic, atonic seizures) per 28-day baseline period during baseline, or

    d. Have subclinical CSWS syndrome with or without clinical events on EEG

5. Subjects should be on a stable regimen of AED medication, and generally in good health.

6. Parent or guardian is able and willing to maintain an accurate and complete daily written seizure calendar for the duration of the study.

7. Able and willing to take study medication with food, two or three times daily. Ganaxolone must be administered with food.

8. Sexually active women of child bearing potential (WCBP) must be using a medically acceptable method of birth control and have a negative urine sample at the baseline visit. A woman of childbearing potential is defined as a female who is biologically capable of becoming pregnant. A medically acceptable method of birth control includes intrauterine devices in place for at least 3 months, surgical sterilization, or adequate barrier methods (e.g., diaphragm and foam). An oral contraceptive alone is not considered adequate for the purpose of this study. Use of oral contraceptives in combination with another method (e.g., a spermicidal cream) is acceptable. In subjects who are not sexually active, abstinence is an acceptable form of birth control and urine will be tested per protocol.

9. Subject must be approved to participate by Sponsor and Principal Investigator

after review of medical history and baseline seizure calendars.

10. For entry into the 52 week open label extension, subjects must have completed all scheduled clinical study visits and have shown a minimum 35% improvement in mean seizure frequency per 28 days vs. baseline over the 28 day periods preceding study entry.

9.3.3 Exclusion Criteria

1. Have had previous exposure to ganaxolone.

2. Known sensitivity or allergy to any component in the study drug, progesterone, or other related steroid compounds.

3. For PCDH19 FPE subjects, have a combination of PCDH19 and SCN1A genetic mutation.

4. Exposure to any investigational drug or device $\leq$ 90 days prior to screening, or plans to participate in another drug or device trial at any time during the study.

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. Concurrent use of vigabatrin, tiagabine, ezogabine or finasteride is not permitted, nor use of moderate or severe inducers or inhibitors of CYP3A4/5/7. Individuals with prior use of vigabatrin must have had stable visual fields tested twice over the 12 months after the last dose of vigabatrin. A list of CYP3A4/5/7 inhibitors and inducers is included in the Appendix. For Dravet Syndrome subjects the following are also excluded: phenytoin, fosphenytoin, carbamazepine, oxcarbazepine, lamotrigine, rufinamide and stiripentol (Italy specific).

    - Patients on cannabadiol (CBD) products that have shown < 75% improvement must be withdrawn from CBD and be off product >28 days prior to Visit 2.
    - Patients on CBD products that have shown $\geq$ 75% improvement and have completed or discontinued from the blinded clinical study, are on maintenance CBD for > 6 months or taking epidolex with stable laboratory values and no SAEs will, on a case by case basis, be considered for enrollment. The decision to taper or leave the patient on the drug before adding ganaxolone will be made, if it is believed to be unethical to take the patient off drug and

promote status epilepticus or loss of gained > 75% improvement of seizure control. The patient will need to meet criteria for current entry seizure frequency for ganaxolone study.

7. 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.

8. Have active suicidal plan/intent, or have had active suicidal thoughts in the past 6 months or a suicide attempt in the past 3 years.

9. Have Alanine transferase (ALT; SGPT) or Aspartate transferase (AST; SGOT) levels > 3 times upper limits of normal (ULN), or total bilirubin >1.5 time ULN at the baseline visit.

10. Are planning to follow a ketogenic diet. If on ketogenic diet for more than 6 months with stable laboratory values and seizure control then enrollment will be made on a case by case basis.

11. Is sexually active or pregnant.

12. Unwilling to forgo grapefruit and grapefruit juice from diet during the entire clinical trial.

9.3.4 Removal of Subjects from the Study

9.3.4.1 Investigator-initiated withdrawal of a subject

All subjects have 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 if the subject's condition changes such that the Investigator feels it is not in her best interest to continue, or if she develops a concomitant illness that necessitates treatment which might affect the outcome of the investigation, or if the subject is non-compliant.

Discontinuation decisions will be made at each participating site by the Investigator. If feasible, the process of discontinuation should be discussed with the Study Principal Investigator and the Sponsor.

9.3.4.2 Early Termination Procedures

Subjects who are terminated from the study will be asked to return to the study center for a final safety assessment, initiate a down-titration, and to return unused study medication and to deliver remaining seizure calendars.

9.3.4.3 Consequences of Early Termination

The protocol suggests dose de-escalation of study medication over one to four 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 down-titration.

9.4 Treatments

9.4.1 Treatments administered

Study medication will be provided as either oral suspension or capsules. Ganaxolone oral suspension should be administered through an oral dosing syringe three times daily (TID) by a parent or guardian, following the morning, midday, and evening meal or snack. Each dose should be separated by a minimum of 4 hours and a maximum of 8 hours. A missed dose of ganaxolone suspension may be taken up to 4 hours before the next scheduled dose, otherwise, the missed dose should not be given.

Ganaxolone capsules will be administered two times daily (BID), following the morning and evening meal or snack. A missed dose of ganaxolone capsules may be taken up to 8 hours before the next scheduled dose, otherwise, the missed dose should not be given.

9.4.2 Identity of Investigational Products

Ganaxolone (3α-hydroxy-3β-methyl-5α-pregnan-20-one) suspension contains ganaxolone (50 mg ganaxolone/mL), hydroxypropyl methylcellulose, polyvinyl alcohol, sodium lauryl sulfate, simethicone, methyl paraben, propyl paraben, sodium benzoate, citric acid, and sodium citrate at pH 3.8 – 4.2 and is sweetened with sucralose and flavored with artificial cherry. The suspension has a milky appearance and is packaged in HDPE bottles with a child resistant closure. Ganaxolone will be supplied at a concentration of 50 mg/mL (ganaxolone equivalent) in 120 mL bottles, containing 110 mL ganaxolone.

Ganaxolone capsules will be provided in size 00 white/opaque gelatin capsules packaged in HDPE bottles with a foil induction seal and child resistant closure. Each capsule contains either 200 mg or 225mg 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 (oral suspension and capsules) should be stored at room temperature 15°C to 25°C (59°F to 86°F).

9.4.3 Subject Numbering

Each subject will be assigned a unique 6-digit subject number by the study staff. The subject number will consist of a 3-digit clinical investigational site number assigned by the Sponsor, followed by a three-digit subject number (e.g., 001) assigned by the study staff.

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

9.4.4 Study Dosing and Dosage Adjustments

<u>For subjects >30 kg</u>

After Sponsor and Principal Investigator have reviewed subject's history, baseline seizure data and inclusion/exclusion criteria and determined a subject to be eligible for the study, ganaxolone treatment will be initiated at a dose of 900 mg/day in divided doses. The dose will be increased by approximately 20 to 50% (e.g., an increase from 900 mg/day to 1200 mg/day is a 33% increase) at intervals of not less than 3 days and not more than 2 weeks provided current dose is reasonably tolerated, until desired efficacy is achieved or a maximally tolerated dose (MTD) level is reached. Subsequent dose adjustments should

be made in increments of approximately 20 to 50% with a minimum of three days between dose changes, unless required for safety. Any and each dose escalation above 1500 mg/day requires a clinic visit scheduled 4-6 days after the dose increase to assess safety and tolerability. The maximum allowable dose is 1800 mg/day.

For subjects ≤30 kg

For children weighing 30 kg (66 lbs) or less, dosing should start at 18 mg/kg/day and be increased in ~20-50% increments at intervals of not less than 3 days and not more than 2 weeks provided current dose is reasonably tolerated, until desired efficacy is achieved or a maximally tolerated dose (MTD) level is reached. Subsequent dose adjustments should be made in increments of ~20-50% with a minimum of three days between dose changes, unless required for safety. Any and each dose escalation above 54 mg/kg/day requires a clinic visit scheduled 4-6 days after the dose increase to assess safety and tolerability. The maximum allowable dose is 63 mg/kg/day. (see Appendix 4 for suggested dose escalation schedule.)

DOWN TITRATION

At the conclusion of the study, or upon discontinuation if the subject is terminated from the study prior to Week 26, a period of down-titration from 1 to 4 weeks should be initiated. The down-titration duration will be determined by the site investigator with input from the Sponsor based on subject's age, weight, dose and duration on study medication.

9.4.5 Dose Administration

Study medication will be provided as either oral suspension or capsules. **Ganaxolone should be taken with a meal or snack**, whether oral suspension or capsules. Ganaxolone capsules should be administered with a glass of water or other liquid. Note that grapefruit and grapefruit juice are prohibited during the study.

Ganaxolone oral suspension will be administered through an oral dosing syringe administered or supervised by parents/guardians three times daily (TID), following the morning, noon, and evening meal or snack. Each dose should be separated by a minimum of 4 hours and a maximum of 8 hours. A missed dose of study medication may be taken

up to 4 hours before the next scheduled dose, otherwise, the missed dose should not be given.

Ganaxolone capsules will be administered two times daily (BID), following the morning and evening meal or snack. Each dose should be separated by a minimum of 8 hours and a maximum of 12 hours. A missed dose of medication may be taken up to 8 hours before the next dose, otherwise it should not be given. The capsules should be swallowed whole and not opened, crushed, or chewed.

Subjects and their parent or legal guardian will be informed about possible side effects from the study medication and cautioned to avoid quick postural changes, at least until they know how the study drug affects them. Subjects will be advised that the medication might affect mental alertness. They will also be cautioned that non-adherence to the dosing instructions (e.g. increasing the dose, taking the study medication doses too close together) could produce side effects.

9.4.6 Missing a Dose

Ganaxolone oral suspension: A missed dose of study medication may be taken up to 4 hours before the next scheduled dose, otherwise, the missed dose should not be given.

Ganaxolone capsules: A missed dose of medication may be taken up to 8 hours before the next dose, otherwise it should not be given.

Subjects and their parent or legal guardian should be instructed that if s/he misses two days in a row or more, the site should be contacted to determine whether any adjustment in study medication is needed.

9.4.7 Background AED medication:

Marketed medications indicated for the treatment of seizures are acceptable with the exception of **vigabatrin**, **tiagabine**, and **ezogabine**. **Felbamate** has restricted use. Chronic and rescue **benzodiazepine** use should be discussed with the Principal Investigator and Sponsor. Note:

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

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.

9.4.8 Concomitant Medications

A list of medications that are **inducers or inhibitors of CYP 3A4/5** and are not permitted during the study are included in the Appendix. Note that phenytoin and carbamazepine are permitted as background AEDs though they are moderate CYP 3A4 inducers. Finasteride is not permitted as it inhibits synthesis of endogenous allopregnanolone.

Generally, concomitant medications including non-prescription medication can be used if medically necessary 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. Concomitant medications prescribed by a physician other than the Investigator should be communicated to the Investigator promptly. 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 Sponsor and the study Principal Investigator 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 the case report form (CRF).

9.4.9 Treatment Compliance

Subjects who are not compliant with study visits, study medications and seizure calendars may be removed from the study at the discretion of the Investigator or Sponsor.

9.5 Efficacy and Safety Variables

9.5.1 Calculation of Baseline

Baseline will be calculated from a maximum of 12 weeks' of seizure calendar data with a minimum of 4 weeks of data required, which should include contiguous retrospective ratings provided after signing informed consent. Acceptable retrospective daily seizure

data include a diary record of the frequency and type of seizures by day. Source data may include a seizure diary or calendar, recorded data from smart phones or other devices. Seizure clusters are to be identified, and the number of seizures in the daily cluster should be counted or given as best estimate.

9.5.2 Efficacy Assessments

Parent or legal guardian will record the type and number of seizures daily in the Subject Seizure Calendars that will be used for the primary analysis of efficacy.

The primary outcome measure is the percentage change in seizure (focal dyscognitive or focal convulsive) frequency per 28 days relative to baseline.

Secondary efficacy outcome measures include evaluation of inter-cluster interval; time to reach baseline number of seizures (per 28 days); seizure-free intervals; proportion of subjects with 50% improvement in number of seizures compared with baseline: and proportion of subjects whose inter-cluster interval increases by 50% or more. Additional measures may be added. Data will be analyzed for the ITT and Per Protocol populations if they differ.

The Clinical Global Impression of Improvement: Clinician (CGII-C) and Clinical Global Impression of Improvement: Patient/Caregiver (CGII-P) are secondary efficacy assessments.

9.5.3 Safety Assessments

Planned safety assessments include:

Neurological and physical examinations
Clinical laboratory tests
12-lead ECG
EEG
Vital signs including temperature, blood pressure, pulse rate, and weight
AE monitoring: frequency, severity, duration, causality, outcome
Columbia-Suicide Severity Rating Scale (CSSRS)

Clinical labs, vitals, EEG 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 Appendix 1 Schedule of Study Events for timing of Safety Assessments.

Additional assessments may be conducted as considered appropriate.

9.5.4 Other Assessments

Blood samples will be drawn at baseline, 2 weeks, 8 weeks, 26 weeks, all visits in the 52 week extension and at unscheduled visits as needed for evaluation of blood chemistry and hematology, and/or to measure levels of ganaxolone, concomitant AED medications, allopregnanolone, and related endogenous CNS-active steroids. (See Appendix 2 Schedule of Events).

EEG will be collected at baseline and at visit 4, 5, 6 and 7 and at all visits in the 52 week extension.

The Visual Analogue Scale (VAS-Targeted Behavior) will be collected at baseline and at Visits 5, 7, 9 and 10.

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

9.5.5 Schedule of Study Procedures

9.5.5.1 Visit 1 (Screening)

- Obtain written informed consent (signed informed consent form)
- Collect demographics, medical history, background AEDs and other concomitant medications
- Review inclusion/exclusion criteria
- Collect and review retrospective seizure calendars if available
- Instruct and provide study Subject Seizure Calendar
- Perform physical and neurological examinations (Physical and neurological exam records performed at the same center within 60 days of screening visits may be used in place of screening exam)
- 12-lead ECG
- Measure vital signs

9.5.5.2 Visit 2 (Baseline; Week 0)

- Review medical history, background AEDs and other concomitant medications
- Review inclusion/exclusion criteria
- Collect and review seizure calendars
- VAS
- Administer Columbia Suicide Scale assessed for children 7 years and older
- Perform physical and neurological examinations
- Measure vital signs
- Draw blood sample for, hematology, chemistry, trough concomitant AED levels, and allopregnanolone, and related endogenous CNS-active steroids; obtain urine sample from subjects who are toilet trained for urinalysis and pregnancy test for WCBP.
- Dispense study medication and dosing instructions
- Instruct and provide study Subject Seizure Calendar
- EEG

- Screening and Baseline visits may be one visit if the seizure calendar data are sufficient.

9.5.5.3 Visit 3 (end of Week 2 +/- 3 days)

- Review background AEDs and other concomitant medications
- Collect and review seizure calendars; provide new calendars
- Administer Columbia Suicide Scale assessed for children 7 years and older
- Perform follow-up physical and neurological examinations
- Assess for adverse events
- Measure vital signs
- Collect bottles from prior visit study medication
- Adjust dose if necessary
- Dispense study medication

9.5.5.4 Visit 4 (end of Week 4 +/- 3 days)

- Review background AEDs and other concomitant medications
- Collect and review seizure calendars; provide new calendars
- Complete CGII-Clinician Ratings
- Instruct and collect CGII-Patient/Caregiver Ratings
- Administer Columbia Suicide Scale assessed for children 7 years and older
- Perform follow-up physical and neurological examinations
- Assess for adverse events
- Measure vital signs
- 12-lead ECG
- EEG
- Collect bottles from prior visit study medication
- Adjust dose if necessary
- Dispense study medication
- Urine Pregnancy Test for WCBP

9.5.5.5 Visit 5 (end of Week 8 +/-3 days)

- Review background AEDs and other concomitant medications
- Collect and review seizure calendars; provide new calendars
- Complete CGII-Clinician Ratings
- Collect CGII-Patient/Caregiver Ratings
- VAS
- Administer Columbia Suicide Scale assessed for children 7 years and older
- Perform follow-up physical and neurological examinations
- Assess for adverse events
- Measure vital signs
- EEG
- Draw blood sample for hematology, chemistry, trough study drug, concomitant AED levels, and allopregnanolone, related endogenous CNS-active steroids; obtain urine sample from subjects who are toilet trained for urinalysis and pregnancy test for WCBP.
- Collect bottles from prior visit study medication
- Adjust dose if necessary & Dispense study medication

9.5.5.6 Visit 6 (end of Week 17 +/-7 days)

- Review background AEDs and other concomitant medications
- Collect and review seizure calendars; provide new calendars
- Complete CGII-Clinician rating
- Collect CGII-Patient/Caregiver rating
- Administer Columbia Suicide Scale assessed for children 7 years and older
- Perform follow-up physical and neurological examinations
- Assess for adverse events
- Measure vital signs

- EEG
- Collect bottles from prior visit study medication
- Adjust dose if necessary
- Dispense study medication
- Urine Pregnancy Test for WCBP

9.5.5.7 Visit 7 (end of Week 26 +/-7 days; final investigative visit)

- Review background AEDs and other concomitant medications
- Collect and review seizure calendars; provide new calendars
- Complete CGII-Clinician rating
- Collect CGII-Patient/Caregiver rating
- VAS
- Perform physical and neurological examinations
- Assess for adverse events
- Measure vital signs
- EEG
- Draw blood sample for study drug, hematology, chemistry, and allopregnanolone, related endogenous CNS-active steroids; obtain urine sample from subjects who are toilet trained for urinalysis and pregnancy test for WCBP.
- Administer Columbia Suicide Scale assessed for children 7 years and older
- Collect bottles from prior visit study medication
- Instruct on down-titration
- Dispense study medication
- Confirm eligibility for 52 week extension

9.5.5.8 Visit 8 (end of Week 44 +/-14 days)

- Review background AEDs and other concomitant medications
- Collect and review seizure calendars; provide new calendars
- Complete CGII-Clinician rating

- Collect CGII-Patient/Caregiver rating
- Perform physical and neurological examinations
- Assess for adverse events
- Measure vital signs
- Draw blood sample for trough study drug, hematology, chemistry, and allopregnanolone, related endogenous CNS-active steroids; obtain urine sample from subjects who are toilet trained for urinalysis and pregnancy test for WCBP.
- EEG
- Administer Columbia Suicide Scale assessed for children 7 years and older
- Collect bottles from prior visit study medication
- Dispense study medication

9.5.5.9 Visit 9 (end of Week 62 +/-14 days)

- Review background AEDs and other concomitant medications
- Collect and review seizure calendars; provide new calendars
- Complete CGII-Clinician rating
- Collect CGII-Patient/Caregiver rating
- VAS
- Perform physical and neurological examinations
- Assess for adverse events
- Measure vital signs
- Draw blood sample for trough study drug, hematology, chemistry, and allopregnanolone, related endogenous CNS-active steroids; obtain urine sample from subjects who are toilet trained for urinalysis and pregnancy test for WCBP.
- EEG
- Administer Columbia Suicide Scale assessed for children 7 years and older
- Collect bottles from prior visit study medication
- Dispense study medication

9.5.5.10 Visit 10 (end of Week 78 +/- 14 days; final investigative visit)

- Review background AEDs and other concomitant medications
- Collect and review seizure calendars; provide new calendars
- Complete CGII-Clinician rating
- Collect CGII-Patient/Caregiver rating
- VAS
- Perform physical and neurological examinations
- Assess for adverse events
- Measure vital signs
- Draw blood sample for trough study drug, hematology, chemistry, and allopregnanolone, related endogenous CNS-active steroids; obtain urine sample from subjects who are toilet trained for urinalysis and pregnancy test for WCBP.
- EEG
- Administer Columbia Suicide Scale assessed for children 7 years and older
- Collect bottles from prior visit study medication
- Instruct on down-titration
- Dispense study medication

9.5.5.11 Visit 11 (end of Week 82 +/-7 days; Post-Drug Follow up visit)

- Review background AEDs and other concomitant medications
- Collect and review seizure calendars
- Assess for adverse events
- Measure vital signs
- EEG
- Administer Columbia Suicide Scale assessed for children 7 years and older
- Collect bottles from prior visit study medication
- Provide information on follow up care

9.5.5.12 Dose Escalation Visit and Unscheduled Visits

- Review background AEDs and other concomitant medications
- Collect and review seizure calendars; provide new calendars
- Administer Columbia Suicide Scale assessed for children 7 years and older
- Perform follow-up physical and neurological examinations
- Assess for adverse events
- Measure vital signs
- Draw blood sample for hematology, chemistry; obtain urine sample from subjects who are toilet trained for urinalysis and pregnancy test for WCBP.
- Collect bottles from prior visit study medication
- Adjust dose if necessary
- Dispense study medication

9.5.6 Appropriateness of Measurements

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

9.6 Data Quality Assurance

Steps to be taken to assure the accuracy and reliability of data include the selection of qualified Investigators and appropriate study centers, review of protocol procedures with the Investigator and associated personnel prior to the study, and periodic monitoring and site audits by the Sponsor or their designee. The data will be entered into the clinical trial database and verified for accuracy.

9.7 Statistical Methods

9.7.1 Analysis Populations

All subjects entered into the study who are administered at least one dose of study drug will be included in the ITT population.

Subjects who receive study drug for at least 6 weeks, at doses between 900 and 1800 mg/day, and are without major protocol violations will be included in a Per Protocol

analysis if the population differs from the ITT population. Subjects in each cohort will be analyzed per cohort using the criteria described above.
Overall efficacy for all subjects will be done as well. Safety will be reported per cohort and for all subjects.

9.7.2 Missing Data

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

9.7.3 Baseline and Demographic Characteristics

Subject demographic data and baseline characteristics will be listed individually and summarized overall for the ITT population per cohort and as a whole for the study. Categorical variables will be summarized by counts and percentages and continuous variables by number of subjects, mean, standard deviation, median, minimum, and maximum.

9.7.4 Analysis of Primary Efficacy Variable

The primary efficacy measure is the percentage change in seizure (focal dyscognitive or focal convulsive) frequency per 28 days relative to baseline in the ITT population. Seizure frequency will be based on the number of seizures per 28 days, calculated as (the number of seizures over the time interval multiplied by 28) and divided by the number of days in the interval. The percent change in seizure frequency will be reported with descriptive statistics. Individual data will also be presented.

9.7.5 Analysis of Secondary Efficacy Variables

All secondary efficacy variables will be summarized using descriptive statistics. Individual data will also be presented.

9.7.6 Analysis of Safety Variables

Adverse events (AEs) will be tabulated by Overall, system organ class (SOC), and Preferred Term using the MedDRA coding system. Incidence and percentage of adverse events will be presented for each cohort and for the study as a whole. Additional tables, with AEs subset by severity and by relationship to drug as assessed by the investigator

will be presented. Subset listings will be produced for adverse events that cause withdrawal and for SAEs.

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

9.7.7 Serum levels of AEDs, Ganaxolone and neurosteroids

Serum levels of concomitant AEDs will be presented in subject listings. Serum levels of ganaxolone will be presented by administered dose by scatterplot per cohort and for the study as a whole. Levels of neurosteroids will be provided in a companion report, in tables and scatterplots as appropriate.

Serum levels of concomitant AEDs will be analyzed at site laboratories. Study drug samples will be analyzed at Quest Pharmaceutical Services (QPS). The Neurosteroid samples will be analyzed at the University of Illinois at Chicago. The addresses are below.

Study Drug PK Samples:
Quest Pharmaceutical Services (QPS)
Delaware Technology Park
3 Innovation Way; Suite 240
Newark, Delaware 19711

Neurosteroid Levels Samples:
The Psychiatric Institute
University of Illinois at Chicago
1601 W. Taylor Street, Office #409
Chicago, IL 60612

9.7.8 Determination of Sample Size

Approximately ten (10) subjects with PCDH19, 10 subjects with CDKL5 Disorder, 10 subjects with Dravet Syndrome, and up to 10 subjects with LGS, CSWS, encephalopathic epilepsy or other genetic epilepsies will be enrolled in this open-label, uncontrolled, proof of concept study.

10. INVESTIGATOR REQUIREMENTS

10.1 Prior to Study Initiation

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

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

10.2 Prior to Study Completion

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

1. All test results from screening through the end of the study (e.g., clinical data, all special test results).
2. Information properly recorded in the 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/IEC approval/notification, if appropriate.
5. Copies of IRB/EC notification of approval for safety updates.

6. A summary of the study prepared by the Principal Investigator (an IRB/EC summary close letter is acceptable).

10.3 Study Discontinuation

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

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

10.4 Informed Consent

It is recommended that the Sponsor 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's legal guardian 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 legal guardian. When applicable, it will be provided in a certified translation of the local language.

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

10.5 Adverse Events

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

10.5.1 Definitions

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

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

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

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

  This serious criterion applies if the reported AE necessitates an inpatient admission (in the US) or a minimum 24-hour inpatient hospitalization (outside US) or, if in the opinion of the Investigator, prolongs an existing hospitalization. A hospitalization for an elective procedure, a routinely scheduled treatment or a social admission is not an SAE.
- Results in permanent or significant disability/incapacity

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

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

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

that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

10.5.2 Evaluating and Recording of Adverse Events

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

When applicable, a syndrome ("flu syndrome") that describes a constellation of AEs should be recorded in the CRF in place of the individual AE terms (fever, sore throat, rhinitis).

10.5.3 Reporting of Adverse Events

10.5.3.1 Serious Adverse Events

Any SAEs, including death due to any cause, which occurs to any subject who has signed Informed Consent (personally or by legal guardian) 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 entered into the database and submitted to the sponsor.

SAE reporting numbers:

Telephone number +1 (484-801-4677) (Medical)

Fax Number (610)-640-4323

10.5.3.2 Pregnancy

If a subject in the study becomes pregnant, the Sponsor should be notified immediately.

10.6 Study Monitoring and Audit Requirements

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

10.7 Electronic Case Report Forms

Paper case report forms (CRFs) will be supplied by the Sponsor. Forms are to be filled out in pen, and any changes or corrections are to be initialed and dated by the individual responsible for the change.

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

10.8 Study Drug Accountability

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

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

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

10.9 Confidentiality of Data

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

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

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

10.10 Retention of Records

USA FDA regulations (21 CFR 312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including 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.

10.11 Protocol Adherence

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

11. PUBLICATION PLAN

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

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13. APPENDICES

13.1 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		

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

13.2 Appendix 2: Schedule of Events – 26 Week Treatment Period

WEEK		0	2	4	8	17	26		
VISIT	**V1 Screening**	**V2 Baseline**	**V3 +/- 3 days**	**V4 +/- 3 days**	**V5 +/- 3 days**	**V6 +/- 7 days**	**V7 Final Visit[4] +/- 7 days**		**Unscheduled Visit or Dose Escalation Visit[6]**
Screening & Diagnosis									
Informed consent	X								
Demographics	X								
Medical History	X	X							
Retrospective Seizure Diary Collection and Review	X								
Inclusion/Exclusion criteria	X	X							
Background AEDs Review	X	X	X	X	X	X	X		X
Concomitant Med Review	X	X	X	X	X	X	X		X
Safety Assessments									
ECG	X			X					
Vital Signs[5]	X	X	X	X	X	X	X		X
Physical Examination[1]	X	X	X	X	X	X	X		X
Neurological Examination[1]	X	X	X	X	X	X	X		X
Safety Labs (Blood[7] and Urine[2])		X			X		X		X
Urine Pregnancy Test (WCBP)		X		X	X	X	X		
Administer C-SSRS		X	X	X	X	X	X		X
EEG		X		X	X	X	X		
Review safety and record AEs			X	X	X	X	X		X
Efficacy Assessments									
Instruct/ Provide Seizure Calendar	X	X	X	X	X	X	X		X
Subject Calendar Review	X	X	X	X	X	X	X		X
Complete CGII-C				X	X	X	X		
Instruct and Collect CGII-P				X	X	X	X		

WEEK		0	2	4	8	17	26		
VISIT	**V1 Screening**	**V2 Baseline**	**V3 +/- 3 days**	**V4 +/- 3 days**	**V5 +/- 3 days**	**V6 +/- 7 days**	**V7 Final Visit[4] +/- 7 days**		**Unscheduled Visit or Dose Escalation Visit[6]**
Other Assessments									
VAS		X			X		X		
PK/PD Assessments									
Concomitant AED medications		X			X		X		
Study Drug Blood Samples					X		X		
Neurosteroid levels		X			X		X		
Study Medication									
Dispense Medication		X	X[3]	X[3]	X[3]	X[3]	X[3]		X[3]
Collect bottles from prior visit study medication			X	X	X	X	X		X
Instruct on Down-titration							X[8]		

		1. Physical and neurological exam records performed at the same center within 60 days of screening visit may be used in place of screening exam. Visits 3, 4, 5 and 6 may be follow-up exams. Tanner Scores will be collected. 2. Obtain urine sample for those who are toilet trained. 3. Adjust dose if necessary. 4. This visit could also be an Early Termination visit. At this visit, investigator confirms if the subject qualifies for the 52 week extension, subjects must have completed all scheduled clinical study visits and have shown a minimum 35% improvement in mean seizure frequency per 28 days vs. baseline. 5. Vital signs including temperature, blood pressure, pulse, height and weight. 6. A dose escalation visit is required 4-6 days after escalation to any dose level above 54 mg/kg/day or above 1500 mg/day. A regularly scheduled visit may serve as a dose escalation visit. An unscheduled visit can occur at any time during the 26 week open-label treatment period or the 52 week extension. Samples for concomitant AEDs and study drug levels may also be drawn if warranted in the opinion of the investigator. 7. Safety labs can be collected at any visit if warranted in the opinion of the investigator. 8. If this is the last study visit, the subject should be instructed on down-titration and scheduled for Visit 11 which is the follow-up visit. AEs = adverse events; AED = antiepileptic drug; ECG = electrocardiogram; C-SSR=Columbia Suicide Severity Rating; EEG= Electroencephalography; VAS=Visual Analogue Scale

Schedule of Events – 52 Week Open-Label Extension

WEEK	44	62	78	
VISIT	**V8** +/- **14 days**	**V9** +/- **14 days**	**V10**[4] +/- **14 days**	**V11** **Follow-up** +/- 7 days
Screening & Diagnosis				
Background AEDs Review	X	X	X	X
Concomitant Med Review	X	X	X	X
Safety Assessments				
Vital Signs[5]	X	X	X	X
Physical Examination	X	X	X	
Neurological Examination	X	X	X	
Safety Labs (Blood[7] and Urine[2])	X	X	X	
Urine Pregnancy Test (WCBP)	X	X	X	
Administer C-SSRS	X	X	X	X
Review safety and record AEs	X	X	X	X
Efficacy Assessments				
Instruct/ Provide Seizure Calendar	X	X	X	
Subject Calendar Review	X	X	X	X
EEG	X	X	X	
Complete CGII-C	X	X	X	
Instruct and Collect CGII-P	X	X	X	
Other Assessments				
VAS		X	X	
PK/PD Assessments				
Concomitant AED medications	X	X	X	
Study Drug Blood Samples	X	X	X	
Neurosteroid levels	X	X	X	
Study Medication				
Dispense Medication	X[3]	X[3]	X[3]	

Collect bottles from prior visit study medication	X	X	X	X
Instruct on Down-titration			X[8]	

		1. Physical and neurological exam records performed at the same center within 60 days of screening visit may be used in place of screening exam. Visits 3, 4, 5 and 6 may be follow-up exams. Tanner Scores will be collected. 2. Obtain urine sample for those who are toilet trained. 3. Adjust dose if necessary. 4. This visit could also be an Early Termination visit. At this visit, investigator confirms if the subject qualifies for the 52 week extension, subjects must have completed all scheduled clinical study visits and have shown a minimum 35% improvement in mean seizure frequency per 28 days vs. baseline. 5. Vital signs including temperature, blood pressure, pulse, height and weight. 6. A dose escalation visit is required 4-6 days after escalation to any dose level above 54 mg/kg/day or above 1500 mg/day. A regularly scheduled visit may serve as a dose escalation visit. An unscheduled visit can occur at any time during the 26 week open-label treatment period or the 52 week extension. Samples for concomitant AEDs and study drug levels may also be drawn if warranted in the opinion of the investigator. 7. Safety labs can be collected at any visit if warranted in the opinion of the investigator. 8. If this is the last study visit, the subject should be instructed on down-titration and scheduled for Visit 11 which is the follow-up visit. AEs = adverse events; AED = antiepileptic drug; ECG = electrocardiogram; C-SSR=Columbia Suicide Severity Rating; EEG= Electroencephalography

13.3 Appendix 3: Strong and Moderate Cytochrome P450 CYP 3A4, 5, 7 Inducers and Inhibitors Prohibited During Study 1042-0900

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

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

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

13.4 Appendix 4: Dose Escalation Suggested Schedules

Suggested Titration Schedule by Weight for Ganaxolone Oral Suspension
Protocol 1042-0900

15 kg (33 lbs)

Titration Step #	mg/kg	Dose (mg)	Dose mg/kg increase	Total mg change	% Dose Change	Total ml Suspension
1	18	270				5.4
2	24	359	6	89	33%	7.2
3	32	478	8	119	33%	9.6
4	42	635	11	158	31%	12.7
5	54	810	12	175	27%	16.2
6	63	945	9	135	16%	18.9

20 kg (44 lbs)

Titration Step #	mg/kg	Dose (mg)	Dose change (mg/kg)	Total mg change	% Dose Change	Total ml Suspension
1	18	360				7.2
2	24	479	6	119	33%	9.6
3	32	637	8	158	33%	12.7
4	42	847	10	210	31%	16.9
5	54	1080	12	233	27%	21.6
6	63	1260	9	180	16%	25.2

25 kg (55 lbs)

Titration Step #	mg/kg	Dose (mg)	Dose change (mg/kg)	Total mg change	% Dose Change	Total ml Suspension
1	18	450				9.0
2	24	599	6	149	33%	12.0
3	32	796	8	198	33%	15.9
4	42	1059	10	263	31%	21.2
5	54	1350	12	291	27%	27.0
6	63	1575	9	225	16%	31.5

30 kg (66 lbs)

Titration Step #	mg/kg	Dose (mg)	Dose change (mg/kg)	Total mg change	% Dose Change	Total ml Suspension
1	18	540				10.8
2	24	718	6	178	33%	14.4
3	32	955	8	237	33%	19.1
4	42	1270	10	315	31%	25.4
5	50	1500	8	230	18%	30.0
6	55	1650	5	150	11%	33.0
7	60	1800	5	150	9%	36.0

Suggested Titration Schedule for Dosing with Ganaxolone Capsules for Subjects ≤30 kgs

	200 mg capsules			225 mg capsules		
Titration Step	Total Daily Dose	No. Caps AM	No. Caps PM	Total Daily Dose	No. Caps AM	No. Caps PM
1	400	1	1	450	1	1
2	600	1	2	675	1	2
3	800	2	2	900	2	2
4	1000	2	3	1125	2	3
5	1200	3	3	1350	3	3
6	1400	3	4	1575	3	4
7	1600	4	4	1800	4	4
8	1800	4	5			

13.5 Appendix 5: Protocol History

Revision #	Date	Revisions
V0:	November 25, 2014	
V1:	December 10, 2014	Minor edits and clarifications.
V2:	January 12, 2015	Minor edits and clarifications. pgs. 25, 26 and 42 For consistency with Section 9.5.4 Other Assessment and the Synopsis, a statement was added regarding the blood collection to measure allopregnanolone, and related neurosteroids in the Visit 2 and Visit 4 Schedule of Study Procedures section and Schedule of Events.
V3:	January 23, 2015	Dosing regimen revised for subjects: p 3, 15, 19-20. A visit at Week 2 and procedures for unscheduled visits have been added: p. 4, 24, 26, 29, and Appendix 2. Collection of blood for Liver Function Test and other laboratory assessments have been added at the Week 26 visit: p. 4, 28, 31 and Appendix 2. Guidance on missed doses for the capsules and suspension has been clarified: p. 18.
V4:	June 8, 2015	Collection of EEG's have been added on Visits 2, 5 and 7. See Synopsis, p.23, 25, 27, 28 and Appendix 2.
V5:	July 15, 2015	See Appendix 5.1 for complete summary of changes. Addition of CDKL5 and Dravet Syndrome Subjects: • Background has been updated. • Seizure criteria has been updated for the CDKL5 and Dravet Syndrome subjects. • Contraindicated medications for Dravet patients have been added. • Male children are also eligible for inclusion. • Age has been increased from 2-10 years to 2-18 years age. o Pregnancy Testing has been added for WCBP. o Tanner Scale score has been added under Physical Exam

		52 week extension for subjects who respond to ganaxolone: • Criteria for inclusion has been added. • 3 additional visits have been added. Study Assessments Added: • Additional study drug PK samples and concomitant AED samples to be drawn at existing blood draw at Week 26. Administrative Changes: • Study Title has been updated. • Sponsor Contact information has been updated. • Clarifying statements that the screening and baseline visit can be combined.
V5.1	September 30, 2015	Local Amendment – (Site #006) • Stiripentol has been added as an Exclusion Criteria in section 9.3.3 and to the list in Appendix 3 of "**Prohibited Strong and Moderate CYP 3A4 Inhibitors"**

V 6.0	April 2016	Local Amendment (Site #001) See Appendix 6 for Summary of Changes • Inclusion of other genetic epilepsies. These include, but are not limited to children with PCDH19 mutation, CDKL5 Disorder, Dravet Syndrome and other epileptic syndromes such as LGS, CSWS, and other potential genetic or clinical conditions with or without corresponding genetic condition (referred as genetic epilepsies) in an open-label proof-of-concept study. • Inclusion of additional EEG assessments • Addition of the Visual Analogue Scale (VAS-Targeted Behavior) at baseline, Visits 5, Visit 7, Visit 9 and Visit 10. • Stiripentol (Italy specific) has been added as an Exclusion Criteria in section 9.3.3 • Stiripentol (not sold in the US) has been added to the list in Appendix 3 of **"Prohibited Strong and Moderate CYP 3A4 Inhibitors"** • Visual Analogue Scale (VAS-Target Behavior) has been added to Appendix 7

13.6 Appendix 6: Amendment #5.2 Summary of Changes

There is one major revision to this protocol.

Addition of LGS, CSWS, encephalopathic epilepsy and other potential genetic epilepsies subjects. Despite trying multiple AEDs, many of these patients still do not have adequate seizure control. Since ganaxolone does have a unique mechanism of action and the safety and efficacy of ganaxolone has been well studied, it is reasonable to believe that ganaxolone could be beneficial to these subjects as well.

A number of sections have been revised to accommodate the addition of these epilepsies. In addition, administrative information has been updated. The revisions to the updated sections are described below:

Section 9.3.2 Inclusion Criteria

#3 Revised to include LGS, CSWS, or other genetic epilepsies and reads as follows:

"In the opinion of the investigator have confirmed PCH19 genetic mutation, confirmed CDKL5 genetic mutation or Dravet Syndrome confirmed by a SCN1A mutation, **or genetic epilepsy testing confirming a LSG or CSWS condition associated with this genetic phenotype. Refractive cases of LGS or CSWS that remain idiopathic or have prior history of steroid or ACTH response can also be entered if documentation confirms specific genetic defects are not found and prior steroid response clinically occurred**"

#4 Revised to include seizure criteria relevant for LGS, CSW and other genetic epilepsies and reads as follows:

a. "Have uncontrolled cluster seizures (3 or more seizures over the course of 12 hours) every 6 weeks or less during baseline, **or bouts of status epilepticus on intermittent basis, or"**
b. No revisions made
c. No revisions made
d. **Have subclinical CSWS syndrome with or without clinical events on EEG**

Section 9.3.3 Exclusion Criteria

#6 Revised to include stiripentol as an exclusionary medication for subjects with Dravet Syndrome enrolled in Italy and reads as follows:

For Dravet Syndrome subjects the following are also excluded: phenytoin, fosphenytoin, carbamazepine, oxcarbazepine, lamotrigine, rufinamide and stiripentol (Italy specific).

#6 Revised to include criteria for the use of cannabadiol and epidolex for LGS, CSWS or other genetic epilepsies per standard practice and reads as follows:

"**Patients on cannabadiol (CBD) products that have shown <75 improvement must be withdrawn from CBD and be off product >28 days before Visit 2**"
"**Patients on CBD products that have shown ≥75% improvement and have completed or discontinued from the blinded clinical study, are on maintenance CBD for >6 months or taking epidolex with stable laboratory values and no SAEs will, on a case by case basis, be considered for enrollment. The decision to taper or leave the patient on the drug before adding ganaxolone will be made, if it is believes to be unethical to take the patient off drug and promote status epilepticus or loss of gained >75% improvement of seizure control. The patient will need to meet criteria for current entry seizure frequency for the ganaxolone study**."

#10 Revised to include conditions for subjects who are on a ketogenic diet and reads as follows:

"**Are planning to follow a ketogenic diet. If on ketogenic diet more than 6 months with stable laboratory values and seizure control then enrollment will be made on a case by case basis**"

Section 9.5.5 Schedule of Study Procedures and Appendix 2 Schedule of Events

EEG added to Visit 4, Visit 6, Visit 8, Visit 9 and Visit 10

Visual Analogue Scale (VAS-Target Behavior) added at baseline, Visit 5, Visit 7, Visit 9 and Visit 10

Section 13.7 Appendix 7

Section 13.7.4 Visual Analogue Scale (VAS-Target Behavior) added

Administrative Change

- Sponsor Contact information has been updated

13.7 Appendix 7: Seizure Calendar & Ratings

13.7.1: Clinical Global Impression of Improvement: Clinician &
Clinical Global Impression of Improvement: Patient/Caregiver
13.7.2: Columbia-Suicide Severity Rating Scale Baseline & Visit
13.7.3: Subject Seizure Calendar & Investigator Instructions
13.7.4: Visual Analogue Scale (VAS-Targeted Behavior)

13.7.1 Clinical Global Impression of Improvement: Clinician & Clinical Global Impression of Improvement: Patient/Caregiver

Clinical Global Impression–Improvement (CGI-I) - Clinician

Circle the appropriate response that adequately describes how the subject's symptoms have improved or worsened relative to baseline before the beginning of the study (ie. before study drug was taken).

1=very much improved
2= much improved
3= minimally improved
4= no change
5= minimally worse
6= much worse
7= very much worse

Clinical Global Impression–Improvement (CGI-I) - Patient/Caregiver

Circle the appropriate response that adequately describes how your (or your child's) symptoms have improved or worsened relative to baseline before the beginning of the study (ie. before study drug was taken).

1=very much improved
2= much improved
3= minimally improved
4= no change
5= minimally worse
6= much worse
7= very much worse

13.7.2 Columbia Suicide Severity Scale: Baseline/Screening (Version 6/23/10)
Columbia Suicide Severity Scale: Children's Since Last Visit (Version 6/23/10)

13.7.3 Seizure Calendar and Investigator Instructions

13.7.4 Visual Analogue Scale (VAS-Target Behavior)