PROTOCOL: 1042-CDD-3001

TITLE:	A Double-blind, Randomized, Placebo-controlled Trial of Adjunctive Ganaxolone Treatment in Children and Young Adults with Cyclin-dependent Kinase-like 5 (CDKL5) Deficiency Disorder (CDD) Followed by Long-term Open-label Treatment
DRUG:	Ganaxolone
IND:	44,020
EUDRACT NO.:	2018-001180-23
SPONSOR:	Marinus Pharmaceuticals, Inc. 5 Radnor Corporate Center 100 Matsonford Road, Suite 500 Radnor, PA 19087 USA
PRINCIPAL/ COORDINATING INVESTIGATOR:	
PROTOCOL HISTORY:	Original Protocol: 08 Jun 2018, version 1.0 Global Protocol Amendment 1.0: 05 May 2019 Global Protocol Amendment 2.0: 26 May 2020

PROTOCOL SIGNATURE PAGE

Sponsor's Approval

Signature: [redacted]	**Date:** June 2, 2020 | 11:28 AM PDT
[redacted] **MD** **Marinus Pharmaceuticals** [redacted]	

Investigator's Acknowledgement

I have read this protocol for Marinus Study 1042-CDD-3001.

Title: A Double-blind, Randomized, Placebo-controlled Trial of Adjunctive Ganaxolone Treatment in Children and Young Adults with Cyclin-dependent Kinase-like 5 (CDKL5) Deficiency Disorder (CDD) Followed by Long-term Open-label Treatment

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to the parent/caregiver/legally authorized guardian (LAR) in order to obtain consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Conference on Harmonisation guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Institution Name and Address: (please hand print or type)	

Signature: _____ **Date:** _____

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 2.0	**Amendment Date 26 May 2020**	**Global/Country/Site Specific** **Global**
Description of Change All additions to original text are in **Bold.**		**Section(s) Affected by Change**
Administrative changes: Minor changes involving grammar, wordsmithing, punctuation, and other editorial changes have been made throughout the document. All are clearly identified in the track-changes version of the revised protocol.		
Removed: [redacted]MD Marinus Pharmaceuticals [redacted] **Revised:** [redacted]MD Marinus Pharmaceuticals [redacted]		Protocol Signature Page
Removed: [redacted]**MD** [redacted] Office Telephone: [redacted] Mobile Telephone: [redacted](primary contact method/send text message if no immediate response) Email: [redacted] If sponsor's Medical Monitor cannot be reached in an emergency, the site should contact: Back-up Medical Monitor: [redacted]MD, PhD [redacted]		Sponsor Contacts, Emergency Contact Information, Section 6.3 Unblinding the Treatment Assignment

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 2.0	**Amendment Date 26 May 2020**	**Global/Country/Site Specific** **Global**
Mobile Telephone: [redacted] Email: [redacted] Sponsor Project Managers: [redacted] PhD [redacted] Office Telephone: [redacted] Mobile Telephone: [redacted] (primary contact method) Email: [redacted] **Revised:** [redacted] **MD FAAP** [redacted] Mobile Telephone: [redacted] (primary contact method/send text message if no immediate response) Email: [redacted] If sponsor's Medical Monitor cannot be reached in an emergency, the site should contact: [redacted] **MD** [redacted] Office Telephone: [redacted] Mobile Telephone: [redacted] Email: [redacted]		

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 2.0	**Amendment Date 26 May 2020**	**Global/Country/Site Specific** **Global**
Sponsor Project Managers: [redacted]**BS** [redacted] Office Telephone: [redacted] Mobile Telephone: [redacted](primary contact method) Email: [redacted]		
Removed: [redacted] Office Telephone: [redacted] Email: [redacted] [redacted] Office Telephone: [redacted] Email: [redacted] **Revised:** [redacted]PhD [redacted] Office Telephone: [redacted] Email: [redacted]		CRO Contacts; Section 6.3 Unblinding the Treatment Assignment

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[redacted] [redacted] Office Telephone: [redacted] Mobile: [redacted] Email: [redacted]		
Added: Dose changes including alternative dosing paradigm (e.g., lower dose during the daytime and higher dose in the evening) should be discussed with the sponsor medical monitor prior to making the change or within 48 hours of making the change. **The higher dose in the evening is expected to be better tolerated due to the proximity to bedtime, however, tolerability management and the final decision to adjust drug dosages lies with the principal investigator.**		Study Synopsis (Methodology and Investigational product, dose, and mode of administration), Section 3.1 Study Design and Flow Chart, Section 3.4 Discussion of Study Design, Including the Choice of Control Group, Section 6.2.3 Dosing
Added: (a) Molecular confirmation of a pathogenic or likely pathogenic CDKL5 variant, early onset, difficult to control seizures, and neurodevelopmental impairment are required. The principal investigator (PI) must review the results of the genetic analysis and confirm that gene mutation is likely to be the cause of the epilepsy syndrome. If the subject has a *de novo* variant of unknown significance (VUS) in the kinase domain of the CDKL5, parental testing is negative and meets all other inclusion criteria, then the subject can be included. Genetic mutations will be confirmed by the sponsor's chosen central laboratory. **In France, genetic mutations may be confirmed by an approved French organization, in compliance with French legislation prior to Screening Visit 1 (b)** Subjects must have (b) seizure onset by 1 year of age and (c) lack of independent ambulation by 2 years of age.		Synopsis (Inclusion Criteria); Section 4.1 Inclusion Criteria; Section 7.3.5 Genetic Testing
Added: Participants should be on a stable regimen of 0-4 anti-seizure medications **(including moderate or strong inducer or inhibitor anti-seizure medications e.g. carbamazepine, phenytoin, etc.)** for ≥ 1 month prior to the screening visit, without a foreseeable change in dosing for the duration of the double-blind phase. Vagus nerve stimulator (VNS), ketogenic diet, and		Synopsis (Inclusion Criteria); Section 4.1 Inclusion Criteria

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modified Atkins diet do not count towards this limit but must be unchanged for 3 months prior to screening.		
Removed: A new dosing syringe and adapter should be used every day. Dosing syringes should be cleaned with hot water rinse and air-drying between 1st, 2nd, and 3rd daily doses. ***Revised:*** The syringe should be replaced daily and cleaned between each dose that day by rinsing for 30 seconds using hot water and allowing it to air dry. The bottle adapter should stay in the bottle once it's inserted. It should not be removed.		Section 6.2.4 Dose Administration; Appendix 3: Dosing Instructions for Oral Suspension
Removed: In the event an Investigator deems it necessary to unblind a subject's treatment, the sponsor's Medical Monitor, or Back-up Medical Monitor/Sponsor Project Managers must be notified in a timely manner. Subjects who are unblinded during the double-blind phase will be discontinued from investigational drug treatment but asked to continue seizure charting until the completion of the double-blind phase. To initiate unblinding procedures anytime, please contact: ***Revised:*** **Prior to unblinding or immediately following, the sponsor's Medical Monitor must be contacted. The sponsor's Medical Monitor does not have to be contacted to initiate unblinding in the IWRS system.** Subjects who are unblinded during the double-blind phase will be discontinued from investigational drug treatment but asked to continue seizure charting until the completion of the double-blind phase. **If unblinding occurs, please contact:**		Section 6.3 Unblinding the Treatment Assignment
Original Text: **Primary Efficacy Endpoint** The primary efficacy endpoint is the percent change in 28-day primary seizure frequency through the end of the 17-week, double-blind treatment phase relative to the 6-week prospective baseline period. The primary seizure types include bilateral tonic (sustained motor activity ≥ 3 seconds), generalized tonic-clonic, bilateral clonic, atonic/drop seizures and focal to bilateral tonic-clonic.		Study Synopsis: Criteria for Evaluation; [redacted] Section 9.7.2 Key Secondary Efficacy Endpoints, Section 9.7.3.1 Secondary Efficacy: Seizure Control, Section 9.7.3.2 Secondary Efficacy: Behavioral/Neuropsychiatric,

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Secondary Efficacy Endpoints (Seizure control): Derived seizure secondary efficacy endpoints will be based on data through the end of the 17-week double-blind treatment phase relative to the 6-week prospective baseline period. • Arithmetic change in percentage of seizure-free days, based on primary seizure types • Percentage of subjects experiencing a ≥ 50% reduction in 28-day primary seizure frequency compared to the 6-week baseline • CGI-CSID: seizure intensity and duration **Secondary Efficacy Endpoints (Behavioral/Neuropsychiatric):** • CGICA • CGI-C in parent/caregiver/LAR identified behavioral target - potential domains include sociability, communication, irritability, and hyperactivity • CGI-I: overall improvement by both parent/caregiver/LAR and clinician [redacted]		

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 **Open-Label Phase Endpoints:** The analyses for the double-blind phase will be repeated for the open-label phase. **Revised:** Primary Efficacy Endpoint: The primary efficacy endpoint is the percentage change from baseline in 28-day primary seizure frequency **during** the 17-week, double-blind treatment phase. The primary seizure types include bilateral tonic (sustained motor activity ≥ 3 seconds), generalized tonic-clonic, bilateral clonic, atonic/drop seizures and focal to bilateral tonic-clonic. **Key Secondary Efficacy Endpoints:** • **Number (%) of subjects with a ≥50% reduction from baseline in primary seizure frequency.** • **Clinical Global Impression of Improvement (CGI-I) at the last scheduled visit in the 17-week DB treatment phase.**		

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Secondary Efficacy Endpoints (Seizure control): Derived seizure secondary efficacy endpoints will be based on data through the end of the 17-week double-blind treatment phase relative to the 6-week prospective baseline phase. • Change from baseline in the percentage of seizure-free days during the 17-week double-blind treatment phase, based on primary seizure types • CGI-CSID: seizure intensity and duration Secondary Efficacy Endpoints (Behavioral/Neuropsychiatric): • CGICA score • CGI-C in parent/caregiver/LAR identified behavioral target - potential domains include sociability, communication, irritability, and hyperactivity [redacted]		

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Amendment Number 2.0	**Amendment Date 26 May 2020**	**Global/Country/Site Specific** **Global**
 Open-Label Phase Endpoints: **Except for the changes in seizure frequency during the titration phase and during the maintenance phase, the same efficacy, exploratory, quality of life, and safety endpoints for the DB phase will also be used for the open-label phase. In addition, Tanner Staging, which is performed at Screening in the DB phase, will be repeated during the Open-Label phase and assessed as a Safety endpoint.**		
Removed: The Per-Protocol (PP) population includes all ITT subjects without major protocol violations (defined prior to database lock). ***Revised:*** The Per-Protocol (PP) population includes all ITT subjects **who received study drug for at least 6 weeks, provided at least 5 weeks of post-baseline seizure data, and without major protocol violations (defined prior to database lock).**		Study Synopsis: Statistical Method, Section 9.6 Study Population

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Amendment Number 2.0	**Amendment Date 26 May 2020**	**Global/Country/Site Specific** **Global**
Removed: (3) To explore the possibility that the effect of GNX compared to PBO is greater among subjects with low Allo-S levels. ***Revised:*** (3) To examine the effect of GNX compared to PBO among subjects with low Allo-S levels.		Study Synopsis: Statistical Method: Primary Endpoint: Definition and Analysis & Sensitivity Analyses Section 9.7.1 Primary Efficacy Endpoint Section 9.7.7 Sensitivity Analyses
Added: The following subgroup summarizations of the primary efficacy parameter are planned as outlined in the SAP: • Allo-S levels [(low (≤2.5 ng/mL), **middle (> 2.5 ng/mL and < 6.0 ng/mL) or** high (≥ 6.0 ng/mL)],		Study Synopsis & Section 9.7.5: Sub-group Analysis
Removed: All the analyses for the double-blind phase will be repeated for the open-label phase, with the following differences: • The results will be presented overall and also classified according to the double-blind treatment received by subjects. • The only sensitivity analysis to be performed is the analysis of the primary endpoint among subjects with low plasma allopregnanolone sulfate (Allo-S) levels. • The time points for the efficacy, exploratory, and quality of life endpoints will be at Weeks 21, 34, 52, and every 16 weeks thereafter of open-label treatment relative to the 6-week prospective baseline phase. For the seizure endpoints, this corresponds to the first 4, 17, 35, 51, etc. weeks from the start of the open-label phase • The differences between the double-blind treatment groups in the percent changes from baseline of the 28-day seizure frequencies will not be tested for statistical significance. The complete list of differences will be outlined in the SAP.		Study Synopsis & Section 9.7.8 Open-Label Analyses

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Revised: All the analyses for the double-blind phase will be repeated for the open-label phase, with the following differences: • The results will be presented overall and also classified according to the double-blind treatment received by subjects. • The post-baseline seizure endpoints will be derived starting from the first dosing day of OLE treatment • The only sensitivity analysis to be performed is the analysis of the primary endpoint among subjects with low plasma allopregnanolone sulfate (Allo-S) levels. • The seizure frequencies during the titration and maintenance phases will not be Analyzed separately • The time points for the efficacy, exploratory, and quality of life endpoints will be at Weeks 21, 34, 52, and every 16 weeks thereafter of open-label treatment relative to the 6-week prospective baseline phase. For the seizure endpoints, this corresponds to the first 4, 17, 35, 51, etc. weeks from the start of the open-label phase • The differences between the double-blind treatment groups in the percent changes from baseline of the 28-day seizure frequencies will not be tested for statistical significance. • No PP analyses will be performed • If a subject prematurely discontinues from the OLE phase, the EEG comparison to baseline at the Final OL/Taper Visit cannot be reassigned for analysis purposes since the EEG is performed only at that visit in the OLE phase; hence the tabulation at that visit will include all the subjects, regardless of whether they discontinued.(Taper Visit assessments among the subjects who prematurely discontinue from the DB phase are reassigned if possible; if they cannot be reassigned then they are not tabulated.)		

Protocol Amendments		
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Amendment Number 2.0	**Amendment Date 26 May 2020**	**Global/Country/Site Specific** **Global**
Added: Safety assessments include: • AEs • Clinical laboratory tests • Vital signs including temperature, blood pressure, pulse rate, and weight • 12-lead ECG • Physical, neurological and developmental examinations • Tanner staging (OL phase only) • **Concomitant AED levels (If available)**		Study Synopsis & Section 9.8: Safety Analysis
Added: 9.7.2 Key Secondary Efficacy Endpoints The key Secondary endpoints are: • Number (%) of subjects with a ≥50% reduction from baseline in primary seizure frequency. • Clinical Global Impression of Improvement (CGI-I) at the last scheduled visit in the 17-week DB treatment phase.		Section 9.7.2 Key Secondary Efficacy Endpoints
Removed: Subjects that fall below 80% compliance at 2 consecutive visits during the double-blind phase should be withdrawn from the study. ***Revised****:* Subjects that fall below 80% compliance at 2 consecutive visits during the double-blind phase will not be included in the per-protocol population.		Section 7.4.1 Seizure Type and Frequency

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Amendment Number 2.0	**Amendment Date 26 May 2020**	**Global/Country/Site Specific** **Global**
Removed: The clinical research associate (CRA)/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data. ***Revised:*** The clinical research associate (CRA)/study monitor will review all data in accordance with the clinical monitoring plan. If the data are unclear or contradictory to source data, queries are sent for corrections or verification of data.		Section 10.2.3.1 Electronic Case Report Form (eCRF)
Removed: The CRA/study monitor will verify the contents of the eDiary data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data. ***Revised:*** The CRA/study monitor will verify the contents of the eDiary data in accordance with the clinical monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.		Section 10.2.3.2 Electronic Seizure Diary (eDiary)

See Appendix 13 for protocol history, including all amendments.

EMERGENCY CONTACT INFORMATION

SERIOUS ADVERSE EVENT REPORTING:

In the event of a serious adverse event (SAE), the investigator must notify the Sponsor Medical Monitor and the Sponsor Project Manager by e-mail or fax the Marinus Safety Reporting Form within 24 hours to Marinus Safety Department at:

Email: safetyCDD3001@marinuspharma.com
Fax: +1 484-679-2138

SPONSOR CONTACTS:

Sponsor Medical Monitor:

[redacted] **MD, FAAP**
[redacted]
Mobile Telephone: [redacted] (primary contact method/send text message if no immediate response)Email: [redacted]

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ABBREVIATIONS

Term	Definition
ACTH	Adrenocorticotropic hormone
ADAMS	Anxiety, Depression, and Mood Scale
AE	adverse event
AED	antiepileptic drug
ANOVA	analysis of variance
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_t	area under the concentration versus time curve from time 0 to t hours
AUC_∞	area under the concentration versus time curve from time 0 to infinity
β-HCG	β-human chorionic growth hormone
BID	twice daily
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
CBD	cannabidiol
CDD	cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder
CDKL5	cyclin-dependent kinase-like 5
CGI-I	Clinical Global Impression Improvement
CGI-C	Caregiver Global Impression of Change
CGICA	Caregiver Global Impression of Change in Attention
CGI-CSID	Caregiver Global Impression of Change in Seizure Intensity/Duration
CL	clearance
C_{max}	maximum plasma concentration
CNS	central nervous system
CRA	clinical research associate
CRO	clinical research organization

Term	Definition
CSHQ	Children's Sleep Habit Questionnaire
CSWS	continuous spikes and waves during sleep
CYP 3A4	cytochrome P450 3A4
DB	double-blind
DMC	Data Monitoring Committee
eCRF	electronic case report form
EC	ethics committee
ECG	electrocardiogram
eDiary	electronic seizure diary
EEG	electroencephalogram
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FXS	Fragile X Syndrome
GABA	γ-Aminobutyric acid
$GABA_A$	γ-Aminobutyric acid type A
GCP	Good Clinical Practice
GGT	Gamma-gamma transferase
GNX	ganaxolone
HDPE	high-density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IRB	institutional review board
IS	infantile spasms
ITT	Intent-to-Treat Population
IWRS	interactive web response system

Term	Definition
LAR	legally authorized representative
LGS	Lennox Gastaut syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	Maximum Tolerated Dose
OL	open-label
PBO	placebo
PCDH19	protocadherin 19
PI	principal investigator
PK	Pharmacokinetic
PP	Per-Protocol
PRN	as needed
PSI	Parenting Stress Index
PTSD	post-traumatic stress disorder
PTZ	pentylenetetrazol
QI-Disability	Quality of Life Inventory-Disability
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIF/DRF	Seizure Identification and Diagnostic Review Form
SOC	standard of care
TEAE	Treatment-emergent adverse event
THC	tetrahydrocannabinol
TID	three times daily
t_{max}	time of maximum concentration
ULN	upper limit of normal
UK	United Kingdom
US	United States

Term	Definition
VAS	Visual Analog Scale
VNS	Vagus nerve stimulator
VUS	variant of unknown significance
WCBP	women of childbearing potential

STUDY SYNOPSIS

Protocol number: 1042-CDD-3001	**Drug:** ganaxolone
Title of the study: A double-blind, randomized, placebo-controlled trial of adjunctive ganaxolone treatment in children and young adults with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) followed by long-term open-label treatment	
Number of subjects (total and for each treatment arm): A sufficient number of CDKL5 patients will be screened to enroll 100 subjects, with a 1:1 randomization to either ganaxolone (GNX) or placebo (PBO).	
Investigators: Multicenter study	
Sites and Regions: Global, multicenter study to be conducted at up to 50 sites	
Study period (planned): [redacted]	**Clinical phase:** 3

Objectives:

Primary: To assess the efficacy of GNX compared with PBO as adjunctive therapy for the treatment of primary-type seizures in children and young adults with genetically confirmed CDD at the end of the 17-week double-blind phase.

Secondary:

- To assess behavioral/neuropsychiatric changes correlated with domains of attention, sleep, and a target behavior chosen by the parent/caregiver, using objective tests of central nervous system (CNS) function for GNX compared with PBO as adjunctive therapy at the end of the 17-week double-blind phase.
- To assess the safety and tolerability of GNX compared with PBO as adjunctive therapy at the end of the 17-week double-blind phase.
- To assess pharmacokinetic (PK) parameters in subjects receiving GNX doses up to 63 mg/kg/day (1800 mg/day maximum) throughout the study.
- To assess the long-term efficacy of GNX when administered as adjunctive therapy throughout the open-label phase.
- To assess the long-term safety and tolerability of GNX when administered as adjunctive therapy throughout the open-label phase.

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- [redacted]
- [redacted]
- [redacted]

Rationale:

Cyclin-dependent kinase-like 5 (CDKL5) deficiency- mediated early-onset infantile epileptic encephalopathy is a rare genetic disorder with approximately 1,600 documented cases world-wide (Loulou Foundation). The CDKL5 gene is on the X chromosome; consequently, the condition affects mainly girls, although boys can also be affected. The CDKL5 gene produces a protein that is important for neuronal morphogenesis and brain

development, (Fuchs et al., 2014) and helps regulate expression of genes involved in synaptic function, structure, and plasticity (Carouge et al., 2010; Kameshita et al., 2008).

Cyclin-dependent kinase-like 5 deficiency disorder is characterized by early onset intractable seizures, severe developmental delay, disturbed sleep and severe intellectual/gross motor impairment (Bahi-Buisson et al., 2008). Typically, the seizures are resistant to conventional antiepileptic medication. Treatment-resistant epilepsy can be fatal and patients are often treated with high doses of multiple antiepileptic drugs (AEDs) that worsen the cognitive, behavioral and physical consequences of the underlying disorder. Together, these children and young adults experience major impairments to quality-of life. Any therapy that can reduce the frequency, duration or severity of seizures can positively impact quality of life for the child and family (Müller et al., 2016).

Ganaxolone is the 3β-methylated synthetic analog of allopregnanolone, an endogenous allosteric modulator of CNS γ-Aminobutyric acid type A ($GABA_A$) receptors. Ganaxolone has potency and efficacy comparable to allopregnanolone (Carter et al., 1997) in activating synaptic and extrasynaptic $GABA_A$ receptors at a site distinct from benzodiazepines. GNX has protective activity in diverse rodent seizure models (Reddy and Rogwski, 2012; Bialer et al., 2010). Clinical studies have demonstrated GNX has anticonvulsant activity with an acceptable safety and tolerability profile in the dose range of 900 to 1800 mg per day in adults and children (Sperling et al., 2017; Laxer et al., 2000; Kerrigan et al., 2000; Pieribone et al., 2007). Further, GNX reduces seizures in children with infantile spasms (IS) and refractory pediatric epilepsy. In an open-label study, pediatric subjects aged 2 to 60 months with refractory seizures and a history of IS were treated with GNX doses up to 36 mg/kg for up to 3 months (Kerrigan et al., 2000). Sixteen of the 20 subjects completed treatment, 15 of whom had a history of IS. Five of the 15 subjects had a decrease from baseline in the number of spasms of ≥ 50%, 5 had a decrease of 25 to 50%, and 5 had a decrease of < 25%. One subject became spasm free and 1 non-responder (with a decrease of <25%) was spasm-free from weeks 2 to 7.

An anticonvulsant treatment effect signal of GNX in CDD has emerged from an ongoing open-label flexible-dose exploratory study (1042-0900) of GNX in children (age range 2-15 years) with rare genetic epilepsies (including CDKL5) with uncontrolled seizures despite multiple AED regimens (ClinicalTrials.gov Identifier: NCT02358538). Following the screening and baseline evaluations, consenting subjects enrolled into a 26-week study during which investigators were allowed to dose GNX flexibly up to 1,800 mg/day for subjects whose body weight was > 30 kg or up to 63 mg/kg /day for subjects whose body-weight was < 30 kg. The primary efficacy measure was the percent change from baseline in the 28-day seizure frequency count. Safety and tolerability assessments were among the secondary objectives. The median change in 28-day seizure frequency from baseline in the intent-to-treat (ITT) population (primary endpoint) was a decrease of 48% (n=7). The median change from baseline in seizure-free days in the ITT population (key secondary endpoint) was an increase of 78% (n=5; 2 subjects could not be calculated due to 0 baseline seizure-free days). The Clinical Global Impression-Improvement Scale scores rated by investigators and caregivers were consistent with seizure control for all the children. Children with a 43% or higher seizure reduction were rated as “much improved” or “very much improved” by the investigators and caregivers. Investigators and caregivers reported improvements in attention, mood, behavior and sleep via investigator narratives. Ganaxolone was generally safe and well tolerated with no serious adverse events (SAEs). To date, there have been no adverse event (AE) reports of somnolence or dizziness in the CDKL5 population. The safety and tolerability profile in these subjects was similar to earlier studies.

In addition to anticonvulsant activity, GNX has shown positive effects on anxiety, hyperactivity, and attention in children with fragile X syndrome (Ligsay et al., 2016). Similar behavior problems occur in children with CDKL5 mutations.

It is hypothesized that GNX treatment will increase and improve $GABA_A$ mediated signaling by boosting the signaling capacity of existing receptors and improve not only seizure control, but also other behavioral abnormalities in children with the CDKL5 mutation.

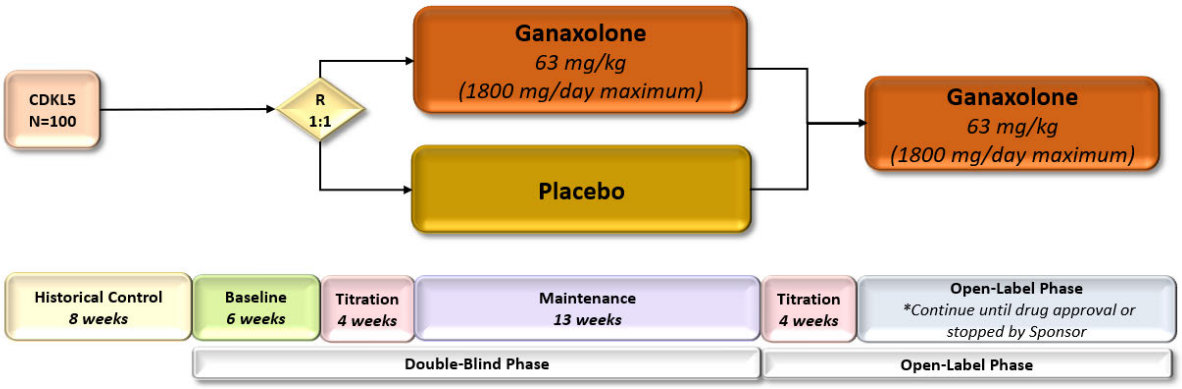
Methodology: This is a global, double-blind, randomized, PBO-controlled trial of adjunctive GNX treatment in children and young adults with CDD. The trial consists of a 6-week prospective baseline period to collect seizure data, followed by a 17-week double-blind treatment phase, which is then followed by a long-term open-label phase.

If available, a 2-month (8-week) daily historical seizure calendar will be reviewed at the screening visit to determine eligibility per inclusion/exclusion criteria. Acceptable historical seizure data must include seizure type, frequency, and denote seizure free days, with the historical seizure calendar starting at Week -14 (8-week historical + 6-week prospective = 14 weeks). Procedures specific to this protocol and not otherwise considered standard of care, will not be performed until written informed consent from the subject's parent or legally authorized representative (LAR) and/or subject assent has been appropriately obtained. In the event that parent/caregiver/LAR do not routinely maintain a daily seizure calendar per standard of care, written informed consent will be obtained from the parent/LAR and/or subject assent, and the subject will be asked to return to the clinic for the screening visit after they have maintained a 2-month (8 week) daily historical seizure calendar.

The double-blind phase includes 6 weeks prospective baseline, 4 weeks of titration followed by 13 weeks of dose maintenance. After meeting the eligibility criteria, approximately 100 children and young adults aged 2-21 years (inclusive) with CDD will be randomly assigned to receive GNX or PBO (1:1 ratio) for 17 weeks in addition to their standard anti-seizure treatment. Participants will be titrated to 63 mg/kg/day (max 1800 mg/day) over 4 weeks, and then maintained at that dose for another 13 weeks. Subjects who are not able to tolerate 63 mg/kg/day (or 1800 mg/day maximum) may be maintained on a lower dose after discussion with the sponsor. A minimum dose of 33 mg/kg/day or 900 mg/day is generally required during the double-blind phase unless a lower dose is agreed to with the sponsor.

Dose changes including alternative dosing paradigm (e.g., lower dose during the daytime and higher dose in the evening) should be discussed with the sponsor medical monitor prior to making the change or within 48 hours of making the change. The higher dose in the evening is expected to be better tolerated due to proximity to bedtime. However, tolerability management and the final decision to adjust drug dosages lies with the principal investigator. For any subject who is unable to be maintained at the minimum dose, the investigator should contact the sponsor to discuss continued investigational product dosing. Subjects who discontinue investigational product should undergo a 2-week taper period, unless otherwise medically indicated. Subjects who discontinue investigational product treatment before the completion of the double-blind phase will continue to be followed per protocol and at minimum maintain daily seizure electronic seizure diary (eDiary) entry until the double-blind phase is completed. These subjects will also return to the site 2 weeks after the taper for safety follow-up assessments.

After completing the initial 17-week, double-blind, PBO-controlled phase, all subjects will be treated with GNX in the open-label phase of the study. Ganaxolone subjects will continue GNX treatment and PBO subjects will titrate onto GNX. To maintain the blind, subjects initially randomized to GNX will undergo a false titration (increasing PBO doses) for 4 weeks, while PBO subjects will titrate up to 63 mg/kg/day GNX (1800 mg/day maximum) during the same time period. An interactive web response system (IWRS) will be used to randomize subjects, dispense drug, track treatment, and maintain the blind throughout the duration of the study. Any participant who discontinues from the open-label portion of the study will undergo a 2-week taper and return to the site 2 weeks later for safety follow-up assessments.



Participants will be required to complete an eDiary to determine GNX's effect on seizures. A variety of clinician

and caregiver administered instruments will be used to assess the efficacy of GNX in CDKL5, and include: Caregiver Global Impression of Change in Attention (CGICA), Caregiver Global Impression of Change (CGI-C) in parent/caregiver identified behavioral target- potential domains of sociability, communication, irritability, and hyperactivity, Clinical Global Impression of Improvement (CGI-I) by parent/caregiver and clinician, Caregiver Global Impression of Change in Seizure Intensity/Duration (CGI-CSID), Children's Sleep Habit Questionnaire (CSHQ), ADAMS, QI-Disability and PSI.

Inclusion and Exclusion criteria:

Inclusion Criteria:

1. (a) Molecular confirmation of a pathogenic or likely pathogenic CDKL5 variant, early onset, difficult to control seizures, and neurodevelopmental impairment are required. The principal investigator (PI) must review the results of the genetic analysis and confirm that gene mutation is likely to be the cause of the epilepsy syndrome. If the subject has a *de novo* variant of unknown significance (VUS) in the kinase domain of the CDKL5, parental testing is negative and meets all other inclusion criteria, then the subject can be included. Genetic mutations will be confirmed by the sponsor's chosen central laboratory. In France, genetic mutations may be confirmed by an approved French organization, in compliance with French legislation prior to Screening Visit 1. Subjects must have (b) seizure onset by 1 year of age and (c) lack of independent ambulation by 2 years of age.
2. Male or female subjects aged 2 through 21 years, inclusive.
3. Subject/parent or LAR willing to give written informed consent/assent, after being properly informed of the nature and risks of the study and prior to engaging in any study-related procedures.
4. Failure to control seizures despite appropriate trial of 2 or more anti-seizure mediations at therapeutic doses.
5. Have at least 16 seizures of primary seizure types: bilateral tonic (sustained motor activity ≥ 3 seconds), generalized tonic-clonic, atonic/drop, bilateral clonic or focal to bilateral tonic-clonic per 28 days in each 1-month period in the 2-month period prior to screening.
6. Subject must be approved to participate by sponsor and/or designee (i.e., Epilepsy Consortium) after review of medical history, genetic testing, seizure classification, and historical seizure calendars.
7. Participants should be on a stable regimen of 0-4 anti-seizure medications (including moderate or strong inducer or inhibitor anti-seizure medications e.g. carbamazepine, phenytoin, etc.) for ≥ 1 month prior to the screening visit, without a foreseeable change in dosing for the duration of the double-blind phase. Vagus nerve stimulator (VNS), ketogenic diet, and modified Atkins diet do not count towards this limit but must be unchanged for 3 months prior to screening.
8. Subjects with surgically implanted VNS will be allowed to enter the study provided that all of the following conditions are met:
    a. The VNS has been in place for ≥ 1 year prior to the screening visit.
    b. The settings must have remained constant for 3 months prior to the screening visit and remain constant throughout the double-blind phase.
    c. The battery is expected to last for the duration of the double-blind phase.
9. Felbamate: The use of felbamate is allowed provided that the subject has been maintained on a stable dose of felbamate for > 6 months and has had stable liver function (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) and hematology during the course of treatment and is expected to remain constant throughout the double-blind phase.
10. Parent/caregiver is able and willing to maintain an accurate and complete daily electronic seizure calendar for the duration of the study.
11. Able and willing to take investigational product with food 3 times daily. Ganaxolone must be administered with food.
12. Sexually active female of childbearing potential must be using a medically acceptable method of birth control and have a negative quantitative serum β-human chorionic growth hormone (β-HCG) test collected at the initial screening visit. 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 prior to screening, 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. Hormonal oral contraceptives must also be used when a condom is used. In subjects who are not sexually active, abstinence is an acceptable form.

Exclusion Criteria:

1. Previous exposure to GNX.
2. Pregnant or breastfeeding.
3. West Syndrome with hypsarrhythmia pattern on EEG or seizures predominantly of Infantile Spasms (IS) type; if EEG pattern/seizure type is uncertain, study inclusion should be reviewed and determined by the sponsor/sponsor delegate.
4. Concurrent use of adrenocorticotropic hormone (ACTH), prednisone or other glucocorticoid is not permitted, nor use of moderate or strong inducers or inhibitors of CYP3A4/5/7. A list of CYP3A4/5/7 inhibitors and inducers is included in Section 12.1. Moderate or strong inducer or inhibitor anti-epileptic drugs will be allowed (e.g., carbamazepine, phenytoin, etc.)
5. Subjects on ACTH, prednisone or other systemically (non-inhaled) administered steroids should be off the product greater than 28 days prior to screening. Concomitant PRN topical or intranasal steroids for dermatologic reactions and allergic rhinitis are allowed and do not warrant exclusion from the study.
6. Subjects with a positive result on tetrahydrocannabinol (THC) or cannabidiol (CBD) test (via urine or plasma drug screen) at the screening visit, and a positive result on THC or CBD test (via plasma) at the baseline visit without prescription for Epidiolex (may go by another name in countries outside the United States) in epilepsy will be excluded from the study. Concomitant Epidiolex (CBD) use will be allowed in the double-blind phase provided the subject has been on a stable dose for at least 1 month prior to screening and is expected to remain on a stable dose without a foreseeable change for the duration of the double-blind phase. THC and/or CBD will be allowed in the open-label phase.
7. Use of dietary supplements or herbal preparations are not permitted if subject has been using them consistently for less than 3 months prior to screening or does not plan on remaining on stable doses for the duration of the double-blind phase. Use of St. John's Wort is not permitted (See Section 12.1).
8. Changes in anti-epileptic drugs (AEDs) within the last month prior to screening. All AEDs must be stable in dose for at least 1-month prior to screening unless otherwise noted.
9. Have an active CNS infection, demyelinating disease, degenerative neurological disease, or CNS disease deemed progressive as evaluated by brain imaging (magnetic resonance imaging [MRI]).
10. Have any disease or condition (medical or surgical; other than CDKL5) at screening that might compromise the hematologic, cardiovascular, pulmonary, renal, gastrointestinal, or hepatic systems; or other conditions that might interfere with the absorption, distribution, metabolism, or excretion of the investigational product, or would place the subject at increased risk.
11. An AST (serum glutamic oxaloacetic transaminase [SGOT]) or ALT (serum glutamic pyruvic transaminase [SGPT]) greater than 3 times the upper limit of normal (ULN) at study entry. If AST or ALT increases > 3 times ULN during the study, subject should be followed with weekly laboratory repeat testing and continue in study if levels trending down. Subject will be discontinued if levels do not decline to under 3 x ULN.
12. Total bilirubin levels greater than ULN at study entry. In cases of documented, stable medical condition (i.e., Gilbert's Syndrome) resulting in levels of total bilirubin greater than ULN, the medical monitor can determine if a protocol exception can be made. If total bilirubin increases to 1.5 x ULN or more during study, the subject will be discontinued.
13. Subjects with significant renal insufficiency, estimated glomerular filtration rate (eGFR) < 30 mL/min (calculated using the Cockcroft-Gault formula or Pediatric GFR calculator or Bedside Schwartz), will be excluded from study entry or will be discontinued if the criterion is met post baseline.
14. Have been exposed to any other investigational drug within 30 days or less than 5 half-lives prior to screening.
15. Unwillingness to withhold grapefruit, Seville oranges or star fruit from diet during the entire clinical trial.
16. Unwillingness to withhold alcohol throughout the entire clinical trial.
17. 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.
18. Known sensitivity or allergy to any component in the investigational product(s), progesterone or other related steroid compounds.

19. Plasma allopregnanolone – sulfate (Allo-S) levels ≥ 6.0 ng/ml at the screening visit.

Number of subjects: A sufficient number of subjects will be screened to enroll 100 children and young adults aged 2-21 years (inclusive) with CDD

Investigational product, dose, and mode of administration: Ganaxolone is to be administered in increments of 15 mg/kg/day up to 63 mg/kg/day (1800 mg/day maximum) given as an oral suspension (50 mg/mL) with food. Subjects ≤ 28 kg will be dosed on an mg/kg basis. Ganaxolone is to be administered with food during the 4-week titration period of the double-blind phase of the study as follows:

Oral Suspension (50 mg/ml) Dosing for Subjects Weighing ≤ 28 kg

Dose	Total mg/kg/day	Days
6 mg/kg TID	18	1-7
11 mg/kg TID	33	8-14
16 mg/kg TID	48	15-21
21 mg/kg TID	63	22-28

TID = three times daily

Oral Suspension (50 mg/ml) Dosing for Subjects Weighing > 28 kg

Dose	ml per Dose	Total mg/day	Days
150 mg TID	3	450	1-7
300 mg TID	6	900	8-14
450 mg TID	9	1350	15-21
600 mg TID	12	1800	22-28

TID = three times daily

Any subject not tolerating the next dose step can be maintained at the lower dose step for additional days before advancing to the next dose. If the next dose is still not tolerated, the subject can drop back to the next lower dose step. A minimum dose of 33 mg/kg/day and 900 mg/day is generally required during the double-blind phase unless a lower dose is agreed to with the Sponsor. Dose changes, including alternative dosing paradigm ((e.g., lower dose during the daytime and higher dose in the evening), should be discussed with the sponsor medical monitor prior to making the change or within 48 hours of making the change. The higher dose in the evening is expected to be better tolerated due to proximity to bedtime. However, tolerability management and the final decision to adjust drug dosages lies with the principal investigator. Any subject who is unable to be maintained at the minimum dose should contact the sponsor to discuss continued investigational product dosing. Subjects who discontinue investigational product treatment before the completion of the double-blind phase will continue to be followed per protocol and at minimum maintain daily seizure eDiary entry until the double-blind phase is completed. These subjects will also return to the site 2 weeks after the taper for safety follow-up assessments.

During the open-label phase, all subjects will be treated with GNX. Subjects will receive the same GNX dose given in the 17-week double-blind phase in the open-label phase of the study. However, to maintain the study blind, GNX subjects will enter into a 4-week false titration phase by increasing PBO doses in addition to maintaining GNX. Subjects who received PBO in the 17-week double-blind phase will enter a 4-week, GNX titration period in the open-label phase of the study.

Reference Therapy, Dose and Mode of Administration: PBO is to be administered as an oral suspension with food during the 4-week, titration period of the double-blind phase of the study as follows:

- PBO TID -Days 1-7
- PBO TID -Days 8-14
- PBO TID - Days 15-21
- PBO TID - Days 22-28

Placebo will only be used in the open-label phase of the study during the 4-week false titration phase for those subjects who were originally randomized to GNX in the 17-week double-blind phase.

Duration of treatment: Eligible subjects will collect 6 weeks of prospective baseline seizure data. Subjects will be randomized (1:1) to a 17-week double-blind treatment phase with GNX or PBO (4 weeks titration and 13 weeks dose maintenance), followed by a long-term open-label treatment phase with GNX. Following the completion of the 17-week double-blind phase, subjects randomized to PBO will transition to GNX (using false titration), while subjects randomized to GNX will stay on 63 mg/kg/day suspension (1800 mg/day maximum), or their Maximum Tolerated Dose (MTD). Subjects will begin the 4-week blinded dose titration to 63 mg/kg/day or 1800 mg/day (or MTD) after completing the final double-blind visit. It is estimated that the maximum duration of subject participation in the double-blind phase will be 23 weeks, including the 17-week double-blind treatment phase and 6-week prospective baseline period, and approximately an additional 3 years for the long-term open-label phase. The open-label phase will continue until the sponsor terminates the development of the investigational product in CDD or GNX has been approved and marketed in the subjects' respective country.

Participants who complete the study or discontinue investigational product treatment before the end of the study will undergo a 2-week taper period, unless otherwise medically indicated, after which he/she will return to the study site for a safety follow up visit. Subjects who discontinue investigational product treatment before the completion of the double-blind phase will be followed per protocol and at minimum maintain the daily seizure eDiary until the double-blind phase is completed.

Criteria for Evaluation:

Seizures: All seizure types and frequency will be recorded daily in an eDiary. Days in which no seizures occur will also be noted. Subsets of seizure types will be defined below.

Primary Efficacy Endpoint: The primary efficacy endpoint is the percentage change from baseline in 28-day primary seizure frequency during the 17-week, double-blind treatment phase. The primary seizure types include bilateral tonic (sustained motor activity ≥ 3 seconds), generalized tonic-clonic, bilateral clonic, atonic/drop seizures and focal to bilateral tonic-clonic.

Key Secondary Efficacy Endpoints:

- Number (%) of subjects with a ≥50% reduction from baseline in primary seizure frequency.
- Clinical Global Impression of Improvement (CGI-I) at the last scheduled visit in the 17-week DB treatment phase.

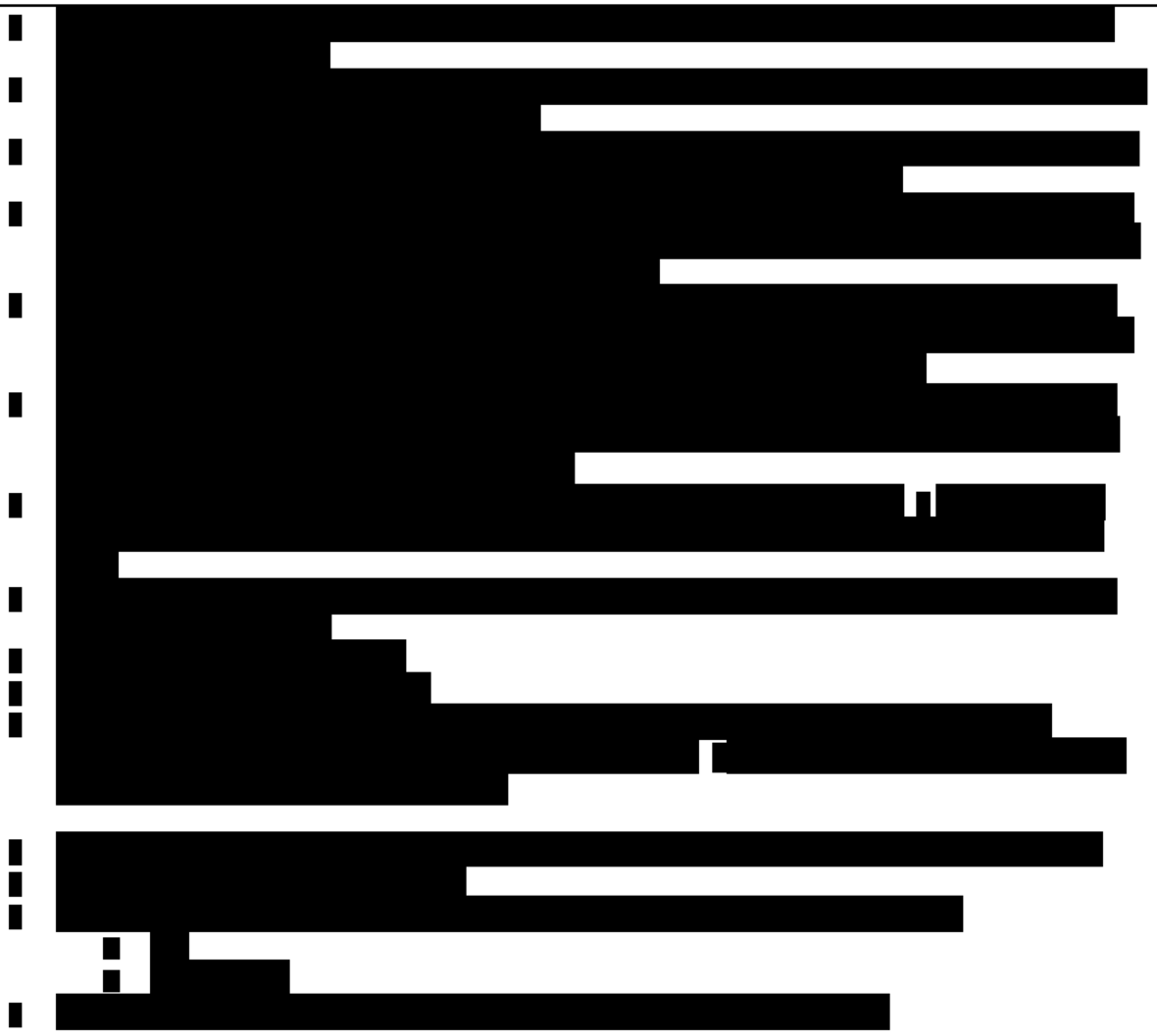
Secondary Efficacy Endpoints (Seizure control): Derived seizure secondary efficacy endpoints will be based on data through the end of the 17-week double-blind treatment phase relative to the 6-week prospective baseline phase.

- Change from baseline in the percentage of seizure-free days during the 17-week double-blind treatment phase, based on primary seizure types
- CGI-CSID: seizure intensity and duration

Secondary Efficacy Endpoints (Behavioral/Neuropsychiatric):

- CGICA score
- CGI-C in parent/caregiver/LAR identified behavioral target - potential domains include sociability, communication, irritability, and hyperactivity

[redacted]



Open-Label Phase Endpoints: Except for the changes in seizure frequency during the titration phase and during the maintenance phase, the same efficacy, exploratory, quality of life, and safety endpoints for the DB phase will also be used for the open-label phase. In addition, Tanner Staging, which is performed at Screening in the DB phase, will be repeated during the Open-Label phase and assessed as a Safety endpoint.

Pharmacokinetic Assessments:

The PK population will include all subjects who have received at least 1 dose and who have had at least 1 sample collected and a valid bioanalytical result obtained. Four samples will be drawn between 1 and 5 hours or between 4 and 8 hours after the last dose, the remaining samples will be drawn without specific time constraints. Exact date and time of sample draw and drug intake will be recorded in the electronic case report form (eCRF). Pharmacokinetic analyses will be limited to listing of concentrations because sufficient concentration-time data will not be available for noncompartmental analyses such as C_{max}, AUC or t_{max}. Pharmacokinetic data from this study may be used for a Population PK analyses to be conducted separately from this study and reported separately.

Safety and Tolerability Assessments:

Safety and tolerability will be assessed by monitoring vital signs (blood pressure [BP], heart rate [HR], respiratory rate [RR], body temperature, weight, and height), electrocardiograms (ECGs), clinical laboratory tests

(hematology, chemistry and urinalysis), physical, neurological, and developmental examinations, and frequency, type, and severity of AEs during the 17-week, double-blind phase and the open-label phase.

Statistical Methods:

The safety and ITT populations comprise all randomized subjects who received at least one dose of investigational product. In addition to being the population for safety and ITT analyses, it is the primary population for the efficacy analyses and for the neurosteroid level analyses. The Per-Protocol (PP) population includes all ITT subjects who received study drug for at least 6 weeks, provided at least 5 weeks of post-baseline seizure data, and without major protocol violations (defined prior to database lock). There will be no PP population for the open-label phase of the study. The primary analysis is in the ITT population; a supportive analysis in the PP population will also be conducted.

All endpoints will be assessed descriptively, by the double-blind treatment to which the subjects are randomized, with point estimates and 95% confidence intervals. Only the primary endpoint will be assessed in an inferential manner since it is unlikely the trial will be powered to achieve statistical significance regarding effects on these measures

The results of the primary, secondary and exploratory endpoints in the double-blind and open-label phases will be summarized separately. In both phases, the results will be summarized by the double-blind treatment to which the subjects were randomized and, for the open-label phase of the study, combined over the treatment groups. Subject demographics, characteristics, and medical history at randomization will be summarized using descriptive statistics.

Primary Endpoint: Definition and Analysis:

The primary efficacy endpoint is the percent change in 28-day primary seizure frequency at the end of the 17-week double-blind treatment phase relative to the baseline, based on the primary seizure types including bilateral tonic (sustained motor activity ≥ 3 seconds), generalized tonic-clonic, bilateral clonic, atonic/drop seizures and focal to bilateral tonic-clonic).

Post-baseline 28-day seizure frequency will be calculated as the total number of seizures in the 17-week double-blind treatment phase divided by the number of days with seizure data in the period, multiplied by 28. Baseline 28-day seizure frequency will be calculated as the total number of seizures in the baseline period divided by the number of days with seizure data in the period, multiplied by 28. The calculation for percent change from baseline in 28-day seizure frequency will be done as follows for each subject:

$$\left(\frac{[(\text{Post-baseline 28-day seizure frequency}) - (\text{Baseline 28-day seizure frequency})]}{(\text{Baseline 28-day seizure frequency})}\right)\times 100\%$$

The baseline, post-baseline, and arithmetic and percent changes from baseline in 28-day seizure frequency will be summarized using descriptive statistics.

The difference between the treatment groups in the percent changes will be tested for statistical significance. Since the percent differences are anticipated to display skewness and/or outliers, the test will be performed using the Wilcoxon Rank-Sum statistic using a 2-sided significance level of 0.05.

Three sensitivity analyses of the primary efficacy endpoint will be performed for subjects who stop recording their seizure counts (1) To examine the primary outcome measure when a subject stops recording measurements permanently prior to the end of the 17-week DB phase using the imputation approach outlined in the Statistical Analysis Plan (SAP), (2) to explore the possibility that subjects who stop recording seizure counts tend to have higher seizure counts than other subjects, and (3) To examine the effect of GNX compared to PBO among subjects with low Allo-S levels.

Sample Size:

Based on data from the 7 subjects in Study 1042-0900 evaluating GNX in CDKL5 patients, the standard deviation for the percent change in 28-day seizure frequency for seizure types tonic (sustained motor activity ≥ 3 seconds), tonic-clonic, atonic/drop, epileptic spasms, or clonic (generalized or unilateral) is estimated to be 44.5.

Therefore, when the percent change in 28-day seizure frequency on GNX minus that on PBO truly is 30%, then a trial with 100 subjects randomized in a 1:1 manner will have 92% power to detect this effect when using an analysis of variance (ANOVA) that preserves a (one-sided) 2.5% false positive error rate. (If the true difference in the percent changes is 35%, then the study will have 97.5% power.) The threshold for achieving statistical significance at the final analysis when 100 subjects have completed their 17-week double-blind treatment phase would be achieved with an estimate of the difference that is approximately 17.5%. (The actual analysis will use a Wilcoxon rank-sum test, which has approximately the same power as the ANOVA.)

Secondary and Exploratory Endpoints - Descriptive Evaluation:

All secondary and exploratory endpoints will compare GNX and PBO at the end of the 17-week double-blind treatment period relative to the 6-week prospective baseline period. The primary analyses of all secondary and exploratory analyses will be performed on the ITT population. All the endpoints will be included in data listings.

In addition to evidence about effects of GNX on 28-day seizure frequency, the clinical trial will provide substantive insights about its effects on several secondary endpoints that capture important symptoms and activities of daily living that are meaningfully compromised by CDD. The seizure-related secondary endpoints, along with the primary endpoint, should be the most influential in the assessment of anti-epileptic efficacy. The behavioral/neuropsychiatric secondary endpoints will provide information about the overall impact of GNX compared with PBO on the treatment of subjects with CDD. [redacted]

Subgroup Analysis

The following subgroup summarizations of the primary efficacy parameter are planned as outlined in the SAP:

- Allo-S levels [(low (≤2.5 ng/mL), middle (> 2.5 ng/mL and < 6.0 ng/mL) or high (≥ 6.0 ng/mL)],
- Gender

Since there may be a potentially greater treatment effect among subjects with low Allo-S levels, the subgroup with low levels will be analyzed as a sensitivity analysis.

Sensitivity Analyses

Three sensitivity analyses of the primary efficacy endpoint will be performed as outlined in the SAP:

- To examine the primary outcome measure when a subject stops recording measurements permanently prior to the end of the 17-week DB phase using the imputation approach outlined in the Statistical Analysis Plan.
- To explore the possibility that subjects who stop recording their seizure counts tend to have higher counts than the other subjects.
- To examine the effect of GNX compared to PBO among subjects with low Allo-S levels.

Open-Label Analyses

All the analyses for the double-blind phase will be repeated for the open-label phase, with the following differences:

- The results will be presented overall and also classified according to the double-blind treatment received by subjects.
- The post-baseline seizure endpoints will be derived starting from the first dosing day of OLE treatment

- The only sensitivity analysis to be performed is the analysis of the primary endpoint among subjects with low plasma allopregnanolone sulfate (Allo-S) levels.
- The seizure frequencies during the titration and maintenance phases will not be Analyzed separately
- The time points for the efficacy, exploratory, and quality of life endpoints will be at Weeks 21, 34, 52, and every 16 weeks thereafter of open-label treatment relative to the 6-week prospective baseline phase. For the seizure endpoints, this corresponds to the first 4, 17, 35, 51, etc. weeks from the start of the open-label phase
- The differences between the double-blind treatment groups in the percent changes from baseline of the 28-day seizure frequencies will not be tested for statistical significance.
- No PP analyses will be performed

If a subject prematurely discontinues from the OLE phase , the EEG comparison to baseline at the Final OL/Taper Visit cannot be reassigned for analysis purposes since the EEG is performed only at that visit in the OLE phase; hence the tabulation at that visit will include all the subjects, regardless of whether they discontinued. (Taper Visit assessments among the subjects who prematurely discontinue from the DB phase are reassigned if possible; if they cannot be reassigned then they are not tabulated.)

Safety Analysis: All safety analyses will be performed in the Safety Population. The results in the double-blind and open-label phases will be summarized separately. In both phases, the results will be summarized by the double-blind treatment received and, for the open-label phase of the study, combined over the treatment groups.

The number and percentage of days that subjects received investigational product, the highest percentage of the maximum allowable daily dose (1800 mg or 63 mg/kg) that subjects received, and the total amount of investigational product received will be summarized. For the open-label phase, they will be summarized over just the open-label phase as well as over the entire study (combined DB and OL phases) but the classification by the double-blind treatment applies only for the open-label phase summary. The summarization over the entire study will include the double-blind data only from subjects who were in the GNX group during the double-blind phase, regardless of whether they entered the open-label phase, and all the subjects from the open-label phase.

A subject data listing will be provided with full details of the study drug dispensation.

Safety assessments include:

- AEs
- Clinical laboratory tests
- Vital signs including temperature, blood pressure, pulse rate, and weight
- 12-lead ECG
- Physical, neurological and developmental examinations
- Tanner staging (OL phase only)
- Concomitant AED levels (If available)

Detailed analysis and complete listings will be outlined in the SAP.

Pharmacokinetic Analysis: A population PK approach addressing the relationship between GNX PK parameters and individual characteristics will be implemented in the double-blind and open-label phase as follows:

- Visit 3 (Week 5): between 1 and 5 hours since the last investigational product dosing.
- Visit 4 (Week 9): between 4 and 8 hours since the last investigational product dosing.
- Visit 7 (Week 21): between 1 and 5 hours since the last investigational product dosing.
- Visit 9 (Week 52): between 1 and 5 hours since the last investigational product dosing.

For all other PK draws, there is no specified time to draw the PK sample and can be drawn when convenient during the study visit for Visit 5 (Week 17), Visit 6 (Week 19), Visit 8 (Week 34), Visit 10 (Week 68), and every 16 weeks for the duration of the open-label phase.

Exact time of sample withdrawal and drug intake will be recorded in the electronic case report form (eCRF).

Neurosteroid serum and Concomitant AED levels:

A blood sample will be drawn at the screening visit to confirm the subject meets eligibility criteria and does not have plasma allopregnanolone – sulfate (Allo-S) levels ≥ 6.0 ng/ml.

Blood samples will also be drawn at Week 17 and the final open-label visit to measure neurosteroid levels allopregnanolone and related endogenous CNS-active steroids and sulfate metabolites. Concomitant AED levels will not be mandatory but will be conducted per sites' standard of care. If AED levels are available, the results, date and time of last AED dose and date and time of AED PK sample will be recorded in the eCRF.

Interim Analysis:

Formal interim analyses are planned, in addition to the final analysis, of treatment effect on the primary endpoint, in accordance with the SAP.

Data Monitoring Committee: Emerging study data will be reviewed on a regular basis by an independent Data Monitoring Committee (DMC). The mission of the DMC will be to safeguard the interests of study participants and to enhance the integrity and credibility of the trial. To enable the DMC to achieve their mission, the DMC will have ongoing access to unblinded efficacy and safety data and data regarding quality of trial conduct and will ensure the confidentiality of these data will be preserved. A DMC Charter will provide the principles and guidelines for the DMC process.

Table 1: Schedule of Assessment for the 17-week, Double-blind Treatment Phase of the Study

	Screen/Baseline			DB Titration + Maintenance					Final DB Visit
WEEK	**-14**	**-6 (Screening)**	**0 Baseline (Randomization)**	**3 days**	**1, 2, 3, 4**	**5**	**9**	**11, 13**	**17**
Visit Windows			**+6 days[n]**	**± 1 day**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**
	Historical Seizure frequency	**Visit 1**	**Visit 2**	**Phone Follow-up**	**Phone Follow-up**	**Visit 3**	**Visit 4**	**Phone Follow-up**	**Visit 5**
Screening and Diagnosis									
Informed Consent[a]	X[b]	X							
Demographics & Medical History		X	X[c]						
Historical Seizure Calendar Review		X							
Inclusion/Exclusion Criteria		X	X						
Genetic testing[d]		X							
Seizure Identification and Diagnostic Review Form (Epilepsy Study Consortium)		X	X						
Safety Assessments									
Vital signs (BP, HR, RR, and body temperature)		X[e]	X			X	X		X[f]
Physical/Neurological/ Developmental Exam		X				X			X
Physical/Neurological/ Developmental Exam Follow-up			X				X		
ECG		X	X			X			X
Clinical Laboratory		X	X			X	X		X

Table 1: Schedule of Assessment for the 17-week, Double-blind Treatment Phase of the Study

	Screen/Baseline			DB Titration + Maintenance					Final DB Visit
WEEK	**-14**	**-6 (Screening)**	**0 Baseline (Randomization)**	**3 days**	**1, 2, 3, 4**	**5**	**9**	**11, 13**	**17**
Visit Windows			**+6 days[n]**	**± 1 day**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**
	Historical Seizure frequency	**Visit 1**	**Visit 2**	**Phone Follow-up**	**Phone Follow-up**	**Visit 3**	**Visit 4**	**Phone Follow-up**	**Visit 5**
Tests[g]									
Urinalysis		X[h]	X[h]						X
Drug screen[i]		X							
Pregnancy Test (WCBP)[j]		X	X						
Tanner Staging		X							
Investigational Product PK						X[k]	X[k]		X
Concomitant AED Review and levels if per standard of care[l]		X	X			X	X		X
Neurosteroid levels		X							X
Adverse Event		X	X	X	X	X	X	X	X
Efficacy Assessments									
Seizure eDiary review		X	X	X	X	X	X	X	X
Caregiver Global Impression of Change in Attention (CGICA)		X[m]				X	X		X
Caregiver Global Impression of Change in parent/caregiver identified behavioral target (CGI-C)		X[m]				X	X		X

Table 1: Schedule of Assessment for the 17-week, Double-blind Treatment Phase of the Study

	Screen/Baseline			DB Titration + Maintenance					Final DB Visit
WEEK	**-14**	**-6 (Screening)**	**0 Baseline (Randomization)**	**3 days**	**1, 2, 3, 4**	**5**	**9**	**11, 13**	**17**
Visit Windows			**+6 days[n]**	**± 1 day**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**
	Historical Seizure frequency	**Visit 1**	**Visit 2**	**Phone Follow-up**	**Phone Follow-up**	**Visit 3**	**Visit 4**	**Phone Follow-up**	**Visit 5**
Caregiver Global Impression of Change in Seizure Intensity/Duration (CGI-CSID)						X	X		X
Clinical Global Impression Improvement (CGI-I) by parent/caregiver & clinician		X[m]				X	X		X
[redacted]									
[redacted]			[redacted]						[redacted]
[redacted]			[redacted]			[redacted]	[redacted]		[redacted]
[redacted]			[redacted]			[redacted]	[redacted]		[redacted]
[redacted]			[redacted]			[redacted]	[redacted]		[redacted]
[redacted]			[redacted]			[redacted]	[redacted]		[redacted]
Dispense Investigational Product			X			X	X		X

Table 1: Schedule of Assessment for the 17-week, Double-blind Treatment Phase of the Study

	Screen/Baseline			DB Titration + Maintenance					Final DB Visit
WEEK	**-14**	**-6 (Screening)**	**0 Baseline (Randomization)**	**3 days**	**1, 2, 3, 4**	**5**	**9**	**11, 13**	**17**
Visit Windows			**+6 days[n]**	**± 1 day**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**
	Historical Seizure frequency	**Visit 1**	**Visit 2**	**Phone Follow-up**	**Phone Follow-up**	**Visit 3**	**Visit 4**	**Phone Follow-up**	**Visit 5**

AED = antiepileptic drug; BP = blood pressure; CBD = cannabidiol; D/C = discontinuation; DB = double-blind; ECG = electrocardiogram; EEG = electroencephalogram; HR = heart rate; LAR = legally authorized representative; PK = pharmacokinetic; RR = respiratory rate; THC = tetrahydrocannabinol; WCBP = women of childbearing potential.

a. Written informed consent/assent must be obtained from subject, parent or LAR before any study assessments are performed.
b. Written informed consent/assent from subject, parent or LAR needed if 8-week historical control is not available and need to chart prospectively.
c. Review of medical history only.
d. Genetic testing to be performed to confirm pathogenic or likely pathogenic CDKL5 variant.
e. In addition, height and weight will be measured. If weight unable to be collected at Visit 1, may be collected at Visit 2.
f. In addition, weight will be measured.
g. Chemistry & Hematology (Section 12.2).
h. An attempt should be made to collect a urine sample for a urinalysis at screening. Otherwise, the urine sample can be collected at baseline for the urinalysis.
i. A drug screen (urine or plasma) will be performed to test for THC and CBD at screening. A negative drug test at screening meets the protocol eligibility criteria. If the screening drug test is positive, a plasma drug screen will be performed to test for THC and CBD at baseline. A positive drug test at baseline will exclude the subject from the study.
j. Serum pregnancy test is required for all girls/women of childbearing potential.
k. Population PK will be conducted at these visits (Visit 3: between 1-5 hours since last IP dosing, Visit 4: between 4-8 hours since the last IP dosing).
l. Concomitant AEDs or their dose must be stable for 1 month prior to screening and cannot be changed at any time prior to Visit 5 but may be adjusted during the open-label phase of the study.
m. During the Screening visit, the investigator and parent/caregiver/LAR will decide on a specific behavior that the patient exhibits that denotes assessment measured. This behavior will be used at subsequent visits to assess change after the initiation of investigational product.
n. Visit 2 to occur minimum of 6 weeks (42 days) after Visit 1 and maximum of 6 weeks + 6 days (48 days)

Table 2: Schedule of Assessments for Open-Label Phase

	Final DB Visit/ First OL Visit	Titration (4 weeks blinded)					Open-Label Maintenance (Visits will be every 16 weeks with a telephone follow up in-between after 52 weeks)						Final OL Visit or Taper	Safety Follow-up post
WEEK	**17**	**3 Days Post Visit 5**	**18**	**19**	**20**	**21**	**28**	**34**	**43**	**52**	**60**	**68 and X visit**	**X/ or early D/C**	**2 weeks post last**
Visit Windows		**± 1**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 3 days**
	Visit 5	**Phone follow-up**	**Phone follow-up**	**Visit 6**	**Phone follow-up**	**Visit 7**	**Phone follow-up**	**Visit 8**	**Phone follow-up**	**Visit 9**	**Phone follow-up**	**Visit 10 and Visit X**	**Visit X**	**Visit X**
Safety Assessments														
Vital signs (BP, HR, RR, and body temperature)[a]	X[a]			X		X		X[a b]		X[a b]		X[a]	X[a b]	X
Physical/Neurological/ Developmental Exam	X					X		X		X		X	X	
Physical/Neurological/ Developmental Exam Follow-up				X										X
ECG	X					X		X		X		X	X	
Clinical Laboratory Tests[c]	X			X		X		X		X		X	X	X
Urinalysis	X									X[e]			X	X[e]
Pregnancy Test (WCBP)[d]													X	X
Tanner Staging[e]										X			X	
Investigational Product PK	X			X		X[f]		X		X[f]		X	X	X
Concomitant AED Review and levels if per standard of care	X			X		X		X		X		X	X	X

Table 2: Schedule of Assessments for Open-Label Phase

	Final DB Visit/ First OL Visit	Titration (4 weeks blinded)					Open-Label Maintenance (Visits will be every 16 weeks with a telephone follow up in-between after 52 weeks)						Final OL Visit or Taper	Safety Follow-up post
WEEK	**17**	**3 Days Post Visit 5**	**18**	**19**	**20**	**21**	**28**	**34**	**43**	**52**	**60**	**68 and X visit**	**X/ or early D/C**	**2 weeks post last**
Visit Windows		**± 1**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 3 days**
	Visit 5	**Phone follow-up**	**Phone follow-up**	**Visit 6**	**Phone follow-up**	**Visit 7**	**Phone follow-up**	**Visit 8**	**Phone follow-up**	**Visit 9**	**Phone follow-up**	**Visit 10 and Visit X**	**Visit X**	**Visit X**
Neurosteroid Levels	X												X	
Adverse Event	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Assessments														
Seizure eDiary review	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Caregiver Global Impression of Change in Attention (CGICA)	X					X		X		X		X	X	
Caregiver Global Impression of Change (CGI-C) in parent/caregiver identified behavioral target	X					X		X		X		X	X	
Clinical Global Impression of Improvement (CGI-I) by parent/ caregiver & clinician)	X			X		X		X		X		X	X	

Table 2: Schedule of Assessments for Open-Label Phase

	Final DB Visit/ First OL Visit	Titration (4 weeks blinded)					Open-Label Maintenance (Visits will be every 16 weeks with a telephone follow up in-between after 52 weeks)						Final OL Visit or Taper	Safety Follow-up post
WEEK	**17**	**3 Days Post Visit 5**	**18**	**19**	**20**	**21**	**28**	**34**	**43**	**52**	**60**	**68 and X visit**	**X/ or early D/C**	**2 weeks post last**
Visit Windows		**± 1**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 3 days**
	Visit 5	**Phone follow-up**	**Phone follow-up**	**Visit 6**	**Phone follow-up**	**Visit 7**	**Phone follow-up**	**Visit 8**	**Phone follow-up**	**Visit 9**	**Phone follow-up**	**Visit 10 and Visit X**	**Visit X**	**Visit X**
Caregiver Global Impression of Change in Seizure Intensity/Duration Severity (CGI-CSID)	X					X		X		X		X	X	
[redacted]														
[redacted]	[redacted]												[redacted]	
[redacted]	[redacted]					[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	
[redacted]	[redacted]					[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	
[redacted]	[redacted]					[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	
[redacted]	[redacted]					[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	
[redacted]														

Table 2: Schedule of Assessments for Open-Label Phase

	Final DB Visit/ First OL Visit	Titration (4 weeks blinded)					Open-Label Maintenance (Visits will be every 16 weeks with a telephone follow up in-between after 52 weeks)						Final OL Visit or Taper	Safety Follow-up post
WEEK	**17**	**3 Days Post Visit 5**	**18**	**19**	**20**	**21**	**28**	**34**	**43**	**52**	**60**	**68 and X visit**	**X/ or early D/C**	**2 weeks post last**
Visit Windows		**± 1**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 3 days**
	Visit 5	**Phone follow-up**	**Phone follow-up**	**Visit 6**	**Phone follow-up**	**Visit 7**	**Phone follow-up**	**Visit 8**	**Phone follow-up**	**Visit 9**	**Phone follow-up**	**Visit 10 and Visit X**	**Visit X**	**Visit X**
Dispense Investigational Product	X			X		X		X		X		X	X	

AED = antiepileptic drug; BP = blood pressure; DB = double-blind; D/C = discontinuation; ECG = electrocardiogram; EEG = electroencephalogram; HR = heart rate; PK = pharmacokinetic; OL = open-label; RR = respiratory rate; WCBP = women of childbearing potential.

a. In addition, weight will be measured at every visit, except the safety follow-up visit.
b. In addition, height will be measured. Height will be measured annually after Visit 9 (Week 52), except the safety follow-up visit.
c. Chemistry & Hematology (Section 12.2).
d. Serum pregnancy test is required for all girls/women of childbearing potential.
e. Conduct annually and at the final open-label visit.
f. Population PK will be conducted at these visits: Visit 7: between 1-5 hours since last IP dosing and Visit 9: between 1-5 hours since last IP dosing

1. BACKGROUND INFORMATION

1.1. Indication and Current Treatment Options

The cyclin-dependent kinase-like 5 (CDKL5) gene is located on the X chromosome and was previously called STK9. Mutations in certain regions of the CDKL5 gene results in a rare X-linked disorder that manifests as early onset, difficult to control seizures, severe neuro-developmental impairment and behavioral abnormalities.

Most children affected by CDKL5 are already symptomatic in the perinatal period, presenting with irritability, early epilepsy including infantile spasms (IS), hand stereotypies, severely impaired psychomotor development and severe hypotonia. They may have a temporary regression in seizures in the first 1-2 years of life. They generally have poor eye contact, often due to cortical blindness, but have normal head circumference and generally normal autonomic function.

Other symptoms of a CDKL5 disorder often include limited or absent speech, 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 tendencies, apraxia, eating/drinking challenges, sleep difficulties and stereotypic movements and posturing such as sideways glances, and sitting with one leg crossed over the other.

Although previously called “atypical Rett Syndrome” or the “Hanefeld variant of Rett Syndrome,” since the discovery of the pathogenic gene mutations of CDKL5 by John Christodoulou and others, the ultra-rare pediatric epilepsy with encephalopathy now known as CDKL5 deficiency disorder (CDD) is considered an independent clinical entity associated with early-onset encephalopathy (Fehr et al., 2013). The median age of epilepsy onset is much earlier in females with the CDD (median 6.0 weeks) than Rett syndrome (median 4.9 years) and the risk of developing seizures is much greater in CDKL5 affected females.

CDKL5 deficiency disorder has also been mistaken for other epileptic encephalopathies grouped purely by seizure semiology and not via a common etiology, such as Lennox Gastaut Syndrome (LGS) and West syndrome. Table 3 summarizes the key differences between these other epilepsies associated with encephalopathy and the distinct entity CDD.

Table 3: Certain Pediatric Epilepsies with Encephalopathy

	CDD	Rett Syndrome	Lennox Gastaut	West Syndrome
Etiology	CDKL5 gene mutation X chromosome (catalytic domain)	MECP2 mutation of X chromosome	Multitude of etiologies including Perinatal birth injury, infection	Multitude but commonly hypoxia and tuberous sclerosis (overlaps with LGS)
Gender	Very predominantly female; males more severely impacted	Virtually exclusively female	Either	Either, but x-linked form more common in males than females (x-linked infantile spasms)
Seizure Types	Focal seizures first weeks to months, infantile spasms first months to 1-2 years. Brief "honeymoon" can occur followed by tonic and myoclonic seizures.	No specific pattern of development with mixed types including atonic, tonic, focal, absence, generalized tonic clonic	Many types including infantile spasms, atonic (drop), tonic, absence	Infantile spasms associated with hypsarrhythmia on EEG
Non-CNS Features	Scoliosis, severe GI issues	scoliosis	Uncommon	Uncommon

CDD = CDKL5 deficiency disorder; CDKL5 = cyclin-dependent kinase-like 5; CNS = central nervous system; EEG = electroencephalogram; GI = gastrointestinal; LGS = Lennox Gastaut Syndrome.
Source: Mangatt et al., 2016; Markand, 2003; NIH, 2017

In a subsequent 2016 review of 167 children with confirmed pathogenic mutation of the CDKL5 gene with CDD (median age 5.9 years), Mangatt et al, concluded, "This study captured a much clearer picture of the CDKL5 disorder than previously possible using the largest sample available to date. There were differences in the presentation of clinical features occurring in the CDKL5 disorder and in Rett syndrome, reinforcing the concept that CDKL5 is an independent disorder with its own distinctive characteristics" (Mangatt et al., 2016).

CDKL5 deficiency disorder is a genetically defined neonatal onset pediatric epilepsy with early encephalopathy that responds poorly to all available therapies including ketogenic diet. There is currently no standard of care for treating this epilepsy or the associated behavioral aberrations associated with the encephalopathy. In a 2016 review of the efficacy of 22 anti-epileptic drugs, ketogenic diet and steroids, the major finding was that seizure reduction was minor and short-lived. This led the authors to conclude that for now, even short-lived slight reductions in seizure frequency might improve both the patient's and parent's quality of life (Müller, 2016).

Preliminary clinical evidence has suggested that patients that are deficient in endogenous neurosteroids exhibit an improved efficacy response to ganaxolone when compared to patients that have normal/elevated levels. In specific, a Phase 2 study of ganaxolone in a genetic pediatric epilepsy similar to CDD, called PCDH19-related epilepsy, showed that patients with a baseline allopregnanolone-sulfate (Allo-S) level below 6.0 ng mL^{-1} had a greater antiseizure response when compared to those with baseline values greater than 6.0 ng mL^{-1}. An allopregnanolone deficiency in the PCDH19 population had previously been implicated as a potential cause of the epilepsy phenotype in PCDH19 patients. To date, no studies have

explored neurosteroid up/down-regulation in patients with CDD as a potential result of the gene mutation. Based on these preliminary data, the hypothesis that patients with a neurosteroid (e.g., Allo-S) deficiency experience an enhanced treatment effect is planned to be further studied.

1.2. Product Background and Clinical Information

Ganaxolone is the 3β-methylated synthetic analogue of the neuroactive steroid allopregnanolone, but it is designed not to activate nuclear (classical) progesterone receptors. Ganaxolone differs from other γ-Aminobutyric acid (GABA) agents by interacting with both synaptic and extra-synaptic γ-Aminobutyric acid type A ($GABA_A$) receptors and at binding sites distinct from benzodiazepines. Whereas benzodiazepines might lose their inhibitory action, GNX does not because it selectively binds to $GABA_A$ receptors containing the α and δ subunits. By enhancing $GABA_A$ receptor function, GNX provides an alternative mechanism in the treatment of seizures and could serve as effective therapy in the management of benzodiazepine-resistant seizure conditions, such as CDD.

The anticonvulsant activity of GNX was established in several *in vivo* models of seizure activity. Ganaxolone was effective at behaviorally non-toxic doses in rodent models of seizures induced by pentylenetetrazol (PTZ), bicucilline, aminophylline, strychnine, and t-butylbicyclophosphorothionate and antagonized 4-AP lethality in mice. Ganaxolone blocked tonic seizures induced by maximal electroshock in mice and rats but only at doses that produced ataxia on the rotarod test. Ganaxolone was a potent anticonvulsant against fully-kindled Stage-5 seizures induced by corneal kindling in the rat at doses well below those that resulted in ataxia. Seizure threshold, as determined by the dose of intravenously infused PTZ required to induce clonus, was significantly elevated by non-toxic doses of GNX in the mouse. These results indicate that GNX blocks seizure propagation and elevates seizure threshold (Carter et al., 1997; Kaminski et al., 2004; Reddy et al., 2004).

As of [redacted] 1557 unique subjects have received treatment with GNX in completed company-sponsored clinical trials ranging in duration from 1 day to more than 2 years, using doses from 50 to 2,000 mg/day. In addition, 30 subjects received GNX in an ongoing open-label Phase 2 study, and an estimated 65 subjects received GNX in ongoing Phase 2/3 double-blind studies.

Of these 1557 unique subjects, 319 healthy subjects have received GNX treatment in Phase 1 studies and 1238 subjects have received GNX treatment in Phase 2/3 studies. The completed trials include 20 Phase 1 studies in healthy subjects and 20 Phase 2/3 studies in adults with epilepsy, children with seizure disorders, children with FXS, adults with PTSD and adults with migraine.

Four company-sponsored clinical studies of GNX are ongoing and have enrolled over 200 unique subjects:

- Study 1042-0900 in pediatric epilepsies including female pediatric subjects with PCDH19 epilepsy and other rare genetic epilepsies including CDKL5 deficiency disorder, LGS and continuous spikes and waves during sleep (CSWS)
- Study 1042-SE-2001 in adolescents and adults with SE

- Study 1042-PPD-2002 in women with PPD (GNX IV and oral capsule multiple-dose escalation study)
- Study 1042-PPD-2003 in women with PPD

For these 4 ongoing clinical studies, enrollment is complete for Study 1042-0900, 1042-PPD-2002 and 1042-PPD-2003 and is ongoing for Study 1042-SE-2001.

In addition to the company-sponsored studies, 29 subjects were treated with GNX in completed studies not sponsored by Marinus. These included 16 subjects who received oral GNX doses from 400 mg/day to 1200 mg/day in a smoking cessation study and 10 subjects who received oral GNX in a postmenopausal depression study. One pediatric subject received oral GNX up to 63 mg/kg/day under a special access scheme in Australia for treatment of refractory seizures associated with PCDH19 genetic epilepsy. In addition, two pediatric subjects received GNX in separate emergency INDs to treat super-refractory status epilepticus: 1 subject received IV GNX up to a dose of 2880 mg/day and 1 subject received IV GNX infusion up to a dose of 192 mg/day and transitioned to a GNX oral suspension dose of 1260 mg/day that was tapered over 6 weeks.[SAE Section 5.6 IB]

Furthermore, 3 non-company-sponsored clinical studies are ongoing. In these studies, a total of 7 subjects continue to receive treatment with GNX through investigator-initiated INDs following participation in Marinus-sponsored studies as follows:

- In one study, 3 subjects received GNX following participation in Study 1042-0603 of adult subjects with drug-resistant partial-onset seizures.
- In one study, 3 subjects (2 subjects with PCDH19 epilepsy and 1 subject with LGS) received GNX following participation in Study 1042-0900.
- In another study, 1 subject with CDD received GNX following participation in Study 1042-0900

The overall frequency of treatment-emergent adverse events (TEAE) in company-sponsored PBO-controlled studies was 61.7% (613/993 subjects) in subjects who received GNX and 51.8% (330/637 subjects) in subjects who received PBO. The most frequently reported TEAEs in GNX-treated subjects were somnolence, dizziness, fatigue, and headache. All of these events, except for headache, occurred more frequently in GNX-treated subjects than PBO-treated subjects. Central nervous system (CNS)-related events appeared to be dose related, with the majority of these events occurring at doses ≥ 500 mg and were anticipated based on the mechanism of action of GNX.

The majority of TEAEs were anticipated based on the mechanism of action of GNX and were non-serious, mild to moderate in severity, and did not lead to discontinuation of treatment.

In the GNX development program overall, no clinically significant trends in electrocardiogram (ECG) intervals, vital signs, or physical or neurologic examinations have been noted, and no mean changes from baseline in clinical laboratory results have been identified. Overall, there have been only a few clinically significant individual changes from baseline in clinical laboratory measurements in clinical trials of GNX. In the completed PBO-controlled Phase 1, 2, and 3 studies, 0.3% of subjects treated with GNX and 0.5% of subjects treated with PBO exhibited elevated liver function tests during the study (aspartate aminotransferase or alanine

aminotransferase > 3 times the upper limit of normal [ULN]). There have been no cases of Hy's law considered to be related to GNX in the GNX development program. In controlled clinical trials of GNX, 1.1% of subjects receiving PBO and 1.7% of subjects receiving GNX reported an adverse event (AE) of rash suggesting there is no obvious imbalance between drug and PBO in terms of frequency of this AE. However, in PBO-controlled studies rash led to discontinuation in GNX-treated subjects in 6 cases (0.6%) compared to no cases (0%) in PBO-treated subjects. One of the events was also reported as an SAE and the event resolved after discontinuation of the study drug. In addition, in the ongoing study 1042-0900, an additional event of rash was reported as an SAE. There have been no cases of Stevens-Johnson syndrome, toxic epidermal necrolysis or any other clinically important rashes reported in the clinical development program. Marinus considers rash as a potential risk associated with GNX and continues to monitor the occurrence of this AE in the clinical development program.

Pediatric Safety

Marinus has completed 2 double blind, randomized trials and 5 open-label, uncontrolled clinical trials of GNX in the pediatric population. One additional pediatric trial, open-label Study 1042-0900 in children with various genetic epilepsies and LGS is ongoing. This study has enrolled 30 subjects of which 7 are subjects with the CDKL5 mutation.

Approximately 224 pediatric subjects aged 4 months to 17 years (data cutoff [redacted]) have received at least 1 dose of GNX. The largest cohorts received 12-54 mg/kg/day, although some subjects received doses as high as 63 mg/kg/day or 1800 mg/day for adolescents. As of [redacted] 4 subjects were treated ≥ 4 years, 9 subjects were treated ≥ 2 years, 39 subjects were treated ≥ 1 year and 66 subjects were treated ≥ 6 months.

The majority of the pediatric subjects were refractory epilepsy patients who had uncontrolled seizures despite trying other antiepileptic drugs (AEDs) (range 1-8). Overall, GNX was generally safe and well tolerated.

In the incomplete crossover Study 1042-0500 (N=56; all received GNX during the trial), 39 subjects with IS treated with GNX doses up to 54 mg/kg/day for up to 20 days reported at least 1 TEAE. The most frequently reported AEs (≥ 8% of subjects) were vomiting (7 subjects), somnolence (5 subjects), and cough (5 subjects). Most AEs were mild or moderate; 1 severe AE of lethargy occurred in 1 GNX subject. During the 8-day PBO-controlled treatment period, the most frequent AEs noted were vomiting (11% in both GNX and PBO groups) and cough (8% GNX, 5% PBO). Other AEs attributed to GNX included flatulence, insomnia, irritability, lethargy, and somnolence.

Adverse events reported in the other uncontrolled refractory pediatric epilepsy studies were consistent with the GABAergic mechanism of action or disease under study.

In another randomized, double-blind, PBO-controlled study of 59 subjects (aged 5-17 years) with fragile X syndrome who were treated with GNX up to 36 mg/kg/day (maximum 1800 mg/day) or PBO, the percentage of subjects who reported at least 1 TEAE was comparable between the treatment groups (85.2% versus 83.1% in the PBO and GNX treatment groups, respectively). The most frequently reported TEAEs among subjects who received GNX included fatigue (29/59 subjects; 49.2%), somnolence (20/59 subjects; 33.9%),condition aggravated (10/59

subjects; 16.9%), and upper respiratory tract infection (9/59 patients; 15.3%)Both fatigue (49.2% vs 20.4%) and somnolence (33.9% vs 5.6%) occurred more frequently in GNX-treated subjects compared with PBO. Among subjects who received PBO, headache (6 subjects; 11.1%) and agitation (8 subjects; 14.8%) were reported more frequently compared with GNX-treated subjects. Severe TEAEs were reported for 3/59 (5.1%) GNX subjects and 1/54 (1.9%) PBO subjects. Severe events in the GNX group were somnolence and fatigue in 1 subject each and agitation and aggression in 1 subject.

To date, AEs have been consistent with the GABAergic mechanism of GNX, disease understudy, or pediatric studies. There have not been any emerging safety concerns with respect to vital signs, ECG, physical/neurological examinations, or clinical laboratory measures.

2. STUDY OBJECTIVES AND PURPOSE

2.1. Rationale for the Study

Cyclin-dependent kinase-like 5 (CDKL5) deficiency- mediated early-onset infantile epileptic encephalopathy is a rare genetic disorder with approximately 1,600 documented cases world-wide (Loulou Foundation). The CDKL5 gene is on the X chromosome; consequently, the condition affects mainly girls, although boys can also be affected. The CDKL5 gene produces a protein that is important for neuronal morphogenesis and brain development, (Fuchs et al., 2014) and helps regulate expression of genes involved in synaptic function, structure, and plasticity (Carouge et al., 2010; Kameshita et al., 2008).

Cyclin-dependent kinase-like 5 deficiency disorder is characterized by early-onset intractable seizures, severe developmental delay, disturbed sleep and severe intellectual/gross motor impairment (Bahi-Buisson et al., 2008). Typically, the seizures are resistant to conventional antiepileptic medication. Treatment-resistant epilepsy can be fatal and patients are often treated with high doses of multiple AEDs that worsen the cognitive, behavioral and physical consequences of the underlying disorder. Together, these children and young adults experience major impairments to quality-of life. Any therapy that can reduce the frequency, duration or severity of seizures can positively impact quality of life for the child and family (Müller et al., 2016).

Ganaxolone is the 3β -methylated synthetic analog of allopregnanolone, an endogenous allosteric modulator of CNS $GABA_A$ receptors. GNX has potency and efficacy comparable to allopregnanolone (Carter et al., 1997) in activating synaptic and extrasynaptic $GABA_A$ receptors at a site distinct from benzodiazepines. GNX has protective activity in diverse rodent seizure models (Reddy and Rogwski, 2012; Bialer et al., 2010). Clinical studies have demonstrated GNX has anticonvulsant activity with an acceptable safety and tolerability profile in the dose range of 900 to 1800 mg in adults and children (Sperling et al., 2017; Laxer et al., 2000; Kerrigan et al., 2000; Pieribone et al., 2007). Further, GNX reduces seizures in children with IS and refractory pediatric epilepsy. In an open-label study, pediatric subjects aged 2 to 60 months with refractory seizures and a history of IS were treated with GNX doses up to 36 mg/kg for up to 3 months (Kerrigan et al., 2000). Sixteen of the 20 subjects completed treatment, 15 of whom had a history of IS. Five of the 15 subjects had a decrease from baseline in the number of spasms of ≥ 50%, 5 had a decrease of 25 to 50%, and 5 had a decrease of <25%. One subject became spasm free and 1 non-responder (with a decrease of <25%) was spasm-free from weeks 2 to 7.

An anticonvulsant treatment effect signal of GNX in CDD has emerged from an ongoing open-label flexible-dose exploratory study of GNX in children with rare genetic epilepsies (including CDKL5) with uncontrolled seizures despite multiple AED regimens (ClinicalTrials.gov Identifier: NCT02358538). Following screening and baseline evaluations, consenting patients enrolled into a 26-week study during which investigators were allowed to dose GNX flexibly up to 1,800 mg/day for patients whose body weight was > 30 kg, or up to 63 mg/kg/day for patients whose body-weight was < 30 kg. The primary efficacy measure was percent change from baseline in the 28-day seizure frequency count. Safety and tolerability were among secondary objectives. The median change in 28-day seizure frequency from baseline in the intent-to-treat (ITT) population (primary endpoint) was a decrease of 48% (n=7). The median change from

baseline in seizure-free days in the ITT population (key secondary endpoint) was an increase of 78% (n=5; two subjects cannot be calculated due to 0 baseline seizure-free days). The Clinical Global Impression Improvement Scale scores rated by investigators and caregivers were consistent with seizure control for all the children. Children with a 43% or higher seizure reduction were rated as "much improved" or "very much improved" by the investigators and caregivers. Investigators and caregivers reported improvements in attention, mood, behavior and sleep via investigator narratives. Ganaxolone was generally safe and well tolerated with no serious adverse events. To date, there have been no adverse event reports of somnolence or dizziness. The safety and tolerability profile in these patients was similar to earlier studies.

In addition to anticonvulsant activity, GNX has shown positive effects on anxiety, hyperactivity and attention in children with fragile X syndrome (Ligsay et al., 2016). Similar behavior problems occur in children with CDKL5 mutations.

It is hypothesized that GNX treatment will increase and improve $GABA_A$-mediated signaling by boosting the signaling capacity of existing receptors and improve not only seizure control, but also other behavioral abnormalities in children with the CDKL5 mutation.

This present study is planned to assess the efficacy, safety, and tolerability of GNX compared with PBO as adjunctive therapy to the subject's standard anti-seizure medication for the treatment of seizures in children and young adults with genetically confirmed CDD during the 17-week, double-blind phase. Pharmacokinetic (PK) assessments and population PK analyses will also be performed during this time. The 17-week, double-blind phase will be followed by an optional long-term open-label phase at which time all subjects will receive GNX as an adjunct to their standard anti-seizure medication. Efficacy, safety and tolerability, and PK assessments will continue to be performed.

2.2. Study Objectives

2.2.1. Primary Objective

The primary objective of this study is to assess the efficacy of GNX compared with PBO as adjunctive therapy for treatment of primary seizures in children and young adults with genetically confirmed CDD at the end of the 17-week double-blind phase.

2.2.2. Secondary Objectives

The secondary objectives of this study are the following:

- To assess behavioral/neuropsychiatric changes correlated with domains of attention, sleep, and a target behavior chosen by the parent/caregiver, using objective tests of CNS function for GNX compared with PBO as adjunctive therapy at the end of the 17-week double-blind phase.
- To assess the safety and tolerability of GNX compared with PBO as adjunctive therapy at the end of the 17-week double-blind phase.
- To assess PK parameters in subjects receiving GNX doses up to 63 mg/kg/day (1800 mg/day maximum) throughout the study.

- To assess the long-term efficacy of GNX when administered as adjunctive therapy throughout the open-label phase.
- To assess the long-term safety and tolerability of GNX when administered as adjunctive therapy throughout the open-label phase.

[redacted]

3. STUDY DESIGN

3.1. Study Design and Flow Chart

This is a global, double-blind, randomized, PBO-controlled trial of adjunctive GNX treatment in children and young adults with CDD. The trial consists of a 6-week prospective baseline period to collect seizure data, followed by a 17-week double-blind treatment phase, which is then followed by a long-term open-label phase.

If available, a 2-month (8-week) daily historical seizure calendar will be reviewed at the screening visit to determine eligibility per inclusion/exclusion criteria. Acceptable historical seizure data must include seizure type, frequency, and denote seizure free days, with the historical seizure calendar starting at Week -14 (8-week historical + 6-week prospective = 14 weeks). Procedures specific to this protocol and not otherwise considered standard of care, will not be performed until written informed consent from the subject's parent or legally authorized representative (LAR) and/or subject assent has been appropriately obtained. In the event that parent/caregiver/LAR do not routinely maintain a daily seizure calendar per standard of care, written informed consent will be obtained from the parent/LAR and/or subject assent, and the subject will be asked to return to the clinic for the screening visit after they have maintained a 2-month (8-week) daily historical seizure calendar.

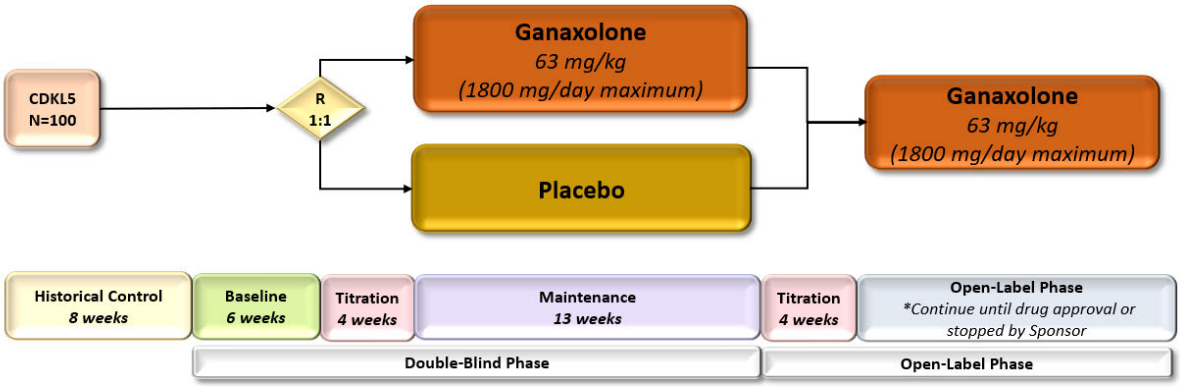
The double-blind phase includes 6 weeks prospective baseline, 4 weeks of titration followed by 13 weeks of dose maintenance. After meeting the eligibility criteria, approximately 100 children and young adults aged 2-21 years (inclusive) with CDD will be randomly assigned to receive GNX or PBO (1:1 ratio) for 17 weeks in addition to their standard anti-seizure treatment. Participants will be titrated to 63 mg/kg/day (max 1800 mg/day) over 4 weeks, and then maintained at that dose for another 13 weeks. Subjects who are not able to tolerate 63 mg/kg/day (or 1800 mg/day maximum) may be maintained on a lower dose after discussion with the sponsor. A minimum dose of 33 mg/kg/day or 900 mg/day is generally required during the double-blind phase unless a lower dose is agreed to with the Sponsor.

Dose changes, including alternative dosing paradigm, (e.g., lower dose during the daytime and higher dose in the evening) should be discussed with the sponsor medical monitor prior to making the change or within 48 hours of making the change. The higher dose in the evening is expected to be better tolerated due to the proximity to bedtime. However, tolerability management and the final decision to adjust drug dosages lies with the Principal Investigator. For any subject who is unable to be maintained at the minimum dose, the investigator should contact the sponsor to discuss continued investigational product dosing. Subjects who discontinue investigational product should undergo a 2-week taper period unless otherwise medically indicated. Subjects who discontinue investigational product treatment before the completion of the double-blind phase will continue to be followed per protocol and at minimum maintain daily seizure electronic diary (eDiary) entry until the double-blind phase is completed. These subjects will also return to the site 2 weeks after the taper for safety follow-up assessments.

After completing the initial 17-week, double-blind, PBO-controlled phase, all subjects will be treated with GNX in the open-label phase of the study. Ganaxolone subjects will continue GNX

treatment and PBO subjects will titrate onto GNX. To maintain the blind, subjects initially randomized to GNX will undergo a false titration (increasing PBO doses) for 4 weeks, while PBO subjects will titrate up to 63 mg/kg/day GNX (1800 mg/day maximum) during the same time period (Figure 1). An interactive web response system (IWRS) will be used to randomize subjects, dispense drug, track treatment, and maintain the blind throughout the duration of the study. Any participant who discontinues early from the study at any time will undergo a 2-week taper, unless otherwise medically indicated, and return to the site 2 weeks later for safety follow-up assessments.

Figure 1: Study Design



Participants will be required to complete a daily seizure calendar noting seizure type and frequency in an eDiary calendar to determine GNX's effect on seizures. In rare cases when an eDiary completion is not feasible, a paper seizure calendar will be used to log in daily seizure type and frequency. These cases will need approval by the sponsor. A variety of clinician and caregiver administered instruments will be used to assess the efficacy of GNX in CDKL5, and included: Caregiver Global Impression of Change in Attention (CGICA), Caregiver Global Impression of Change (CGI-C) in parent/caregiver identified behavioral target- potential domains of sociability, communication, irritability, and hyperactivity, Clinical Global Impression of Improvement (CGI-I) by parent/caregiver and clinician, Caregiver Global Impression of Change in Seizure Intensity/Duration (CGI-CSID), Children's Sleep Habit Questionnaire (CSHQ), ADAMS, QI-Disability, and PSI.

Safety and tolerability will be assessed by monitoring vital signs (blood pressure [BP], heart rate [HR], respiratory rate [RR], body temperature, weight, and height), ECGs, clinical laboratory tests (hematology, chemistry, and urinalysis), physical, neurological, and developmental examinations, and frequency, type, and severity of AEs during the 17-week, double-blind phase and the open-label phase.

3.2. Duration and Study Completion Definition

Eligible subjects after screening will collect 6 weeks of prospective baseline seizure data. Subjects will then be randomized into a 17-week, double-blind treatment phase. Participants

who complete the study or discontinue investigational product treatment before the end of the study will undergo a 2-week taper period, unless otherwise medically indicated, after which he/she will return to the site 2 weeks post last dose for a safety follow up visit. Subjects who discontinue investigational product treatment before the completion of the double-blind phase will continue to be followed per protocol and at minimum maintain daily seizure eDiary entry until the double-blind phase is completed. These subjects will also return to the site 2 weeks after the taper for safety follow-up assessments.

It is estimated that the maximum duration of subject participation in the double-blind phase will be 23 weeks, including the 17-week double-blind treatment phase and 6-week prospective baseline period, and approximately an additional 3 years for the long-term open label phase. The open-label phase will continue until the sponsor terminates the program or GNX has been approved and marketed the investigational product in the subjects' respective country.

3.3. Sites and Regions

This multicenter study is to be conducted globally, with up to 50 sites planned to participate.

3.4. Discussion of Study Design, Including the Choice of Control Group

Dosing will be based on doses that have been shown to be safe in children and adults in multiple studies with normal volunteers and individuals with epilepsy. In this current study, subjects will be randomized (1:1 ratio) to receive either GNX or PBO, prescribed in increments of 15 mg/kg/day up to 63 mg/kg/day (maximum 1800 mg/day), as an oral suspension for up to 17-weeks. The double-blind phase will be followed by an open-label phase in which all subjects will receive GNX up to an additional 3 years or more, providing long-term safety and tolerability data on GNX. Administration of GNX adjunctive therapy to background AEDs provides standard-of-care therapy in addition to any benefit that investigational product might provide.

Subjects will be randomized to receive either GNX or PBO, prescribed in increments of 15 mg/kg/day up to 63 mg/kg/day (maximum 1800 mg/day) as an oral suspension.

- 6 mg/kg three times daily (TID) (18 mg/kg/day) suspension -Days 1-7
- 11 mg/kg TID (33 mg/kg/day) suspension -Days 8-14
- 16 mg/kg TID (48 mg/kg/day) suspension - Days 15-21
- 21 mg/kg TID (63 mg/kg/day) suspension - Days 22-28

Any subject not tolerating the next dose step can be maintained at the lower dose step for additional days before advancing to next dose. If the next dose is still not tolerated, they can drop back to the next lower dose step. A minimum dose of 33 mg/kg/day and 900 mg/day must be maintained. Dose changes including alternative dosing paradigm (e.g., lower dose during the daytime and higher dose in the evening) should be discussed with the sponsor medical monitor prior to making the change or within 48 hours of making the change. The higher dose in the evening is expected to be better tolerated due to the proximity to bedtime. However, tolerability management and the final decision to adjust drug dosages lies with the Principal Investigator. Any subject who is unable to be maintained at the minimum dose should contact the sponsor to discuss continued investigational product dosing. Subjects who discontinue investigational

product should undergo a 2-week taper period unless otherwise medically indicated. Subjects who discontinue investigational product treatment before the completion of the double-blind phase will continue to be followed per protocol and at minimum maintain daily seizure diary entry until the double-blind phase is completed. These subjects should also return to the site after the taper for safety follow-up assessments.

4. STUDY POPULATION

Each subject's parent/LAR must participate in the informed consent process and provide written informed consent (and/or subject assent) before any procedures specified in the protocol are performed.

4.1. Inclusion Criteria

The subject will not be considered eligible for the study without meeting all the criteria below.

1. (a) Molecular confirmation of a pathogenic or likely pathogenic CDKL5 variant, early onset, difficult to control seizures, and neurodevelopmental impairment are required. The principal investigator (PI) must review the results of the genetic analysis and confirm that gene mutation is likely to be the cause of the epilepsy syndrome. If the patient has a *de novo* variant of unknown significance (VUS) in the kinase domain of the CDKL5, parental testing is negative and meets all other inclusion criteria, then the subject can be included. Genetic mutations will be confirmed by the sponsor's chosen central laboratory. In France, genetic mutations may be confirmed by an approved French organization, in compliance with French legislation prior to Screening Visit 1. Patients must have (b) seizure onset by 1 year of age and (c) lack of independent ambulation by 2 years of age.
2. Male or female patients aged 2 through 21 years, inclusive.
3. Subject/parent or LAR willing to give written informed consent/assent, after being properly informed of the nature and risks of the study and prior to engaging in any study-related procedures.
4. Failure to control seizures despite appropriate trial of 2 or more anti-seizure mediations at therapeutic doses
5. Have at least 16 seizures of primary seizure types: bilateral tonic (sustained motor activity ≥ 3 seconds), generalized tonic-clonic, bilateral clonic, atonic/drop or focal to bilateral tonic-clonic per 28 days in each 1-month period in the 2-month period prior to screening.
6. Subject must be approved to participate by sponsor and/or designee (i.e., Epilepsy Consortium) after review of medical history, genetic testing, seizure classification, and historical seizure calendars.
7. Participants should be on a stable regimen of 0-4 anti-seizure medications (including moderate or strong inducer or inhibitor anti-seizure medications e.g. carbamazepine, phenytoin, etc.) for ≥ 1 month prior to the screening visit, without a foreseeable change in dosing for the duration of the double-blind phase. Vagus nerve stimulator (VNS), ketogenic diet, and modified Atkins diet do not count towards this limit but must be unchanged for 3 months prior to screening.
8. Subjects with surgically implanted VNS will be allowed to enter the study provided that all of the following conditions are met:
    a. The VNS has been in place for ≥ 1 year prior to the screening visit.

b. The settings must have remained constant for 3 months prior to the screening visit and remain constant throughout the double-blind phase.
c. The battery is expected to last for the duration of the double-blind phase.

9. Felbamate: The use of felbamate is allowed provided that the subject has been maintained on a stable dose of felbamate for > 6 months and has had stable liver function (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) and hematology during the course of treatment, and is expected to remain constant throughout the double-blind phase.
10. Parent/caregiver is able and willing to maintain an accurate and complete daily electronic seizure calendar for the duration of the study.
11. Able and willing to take investigational product with food 3 times daily. Ganaxolone must be administered with food.
12. Sexually active female of childbearing potential must be using a medically acceptable method of birth control and have a negative quantitative serum β-human chorionic growth hormone (β-HCG) test collected at the initial screening visit. 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 prior to screening, 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. Hormonal oral contraceptives must also be used when a condom is used. In subjects who are not sexually active, abstinence is an acceptable form.

4.2. Exclusion Criteria

1. Previous exposure to GNX.
2. Pregnant or breastfeeding.
3. West Syndrome with hypsarrhythmia pattern on EEG or seizures predominantly of Infantile Spasm (IS) type; if EEG pattern/seizure type is uncertain, study inclusion should be reviewed and determined by the sponsor/sponsor delegate.
4. Concurrent use of adrenocorticotropic hormone (ACTH), prednisone or other glucocorticoid is not permitted, nor use of moderate or strong inducers or inhibitors of CYP3A4/5/7. A list of CYP3A4/5/7 inhibitors and inducers is included in Section 12.1. Moderate or strong inducer or inhibitor anti-epileptic drugs will be allowed (e.g., carbamazepine, phenytoin, etc.)
5. Patients on ACTH, prednisone or other systemically (non-inhaled) administered steroids should be off the product greater than 28 days prior to screening. Concomitant PRN topical or intranasal steroids for dermatologic reactions and allergic rhinitis are allowed and do not warrant exclusion from the study.
6. Subjects with a positive result on tetrahydrocannabinol (THC) or cannabidiol (CBD) test (via urine or plasma drug screen) at the screening visit, and a positive result on THC or CBD test (via plasma) at the baseline visit without prescription for Epidiolex (may go by another name in countries outside the United States) in epilepsy will be excluded from the study. Concomitant Epidiolex (CBD) use will be allowed in the double-blind phase

provided the subject has been on a stable dose for at least 1 month prior to screening and is expected to remain on a stable dose without a foreseeable change for the duration of the double-blind phase. THC and/or CBD will be allowed in the open-label phase.

7. Use of dietary supplements or herbal preparations are not permitted if subject has been using them consistently for less than 3 months prior to screening or does not plan on remaining on stable doses for the duration of the double-blind phase. Use of St. John's Wort is not permitted (See Section 12.1).
8. Changes in Anti-Epileptic Drugs (AEDs) within the last month prior to screening. All AEDs must be stable in dose for at least 1-month prior to screening unless otherwise noted.
9. Have an active CNS infection, demyelinating disease, degenerative neurological disease, or CNS disease deemed progressive as evaluated by brain imaging (magnetic resonance imaging [MRI]).
10. Have any disease or condition (medical or surgical; other than CDKL5) at screening that might compromise the hematologic, cardiovascular, pulmonary, renal, gastrointestinal, or hepatic systems; or other conditions that might interfere with the absorption, distribution, metabolism, or excretion of the investigational product, or would place the subject at increased risk.
11. An AST (serum glutamic oxaloacetic transaminase [SGOT]) or ALT (serum glutamic pyruvic transaminase [SGPT]) greater than 3 times the upper limit of normal (ULN) at study entry. If AST or ALT increases > 3 times ULN during the study, subject should be followed with weekly laboratory repeat testing and continue in study if levels trending down. Subject will be discontinued if levels do not decline to under 3 x ULN.
12. Total bilirubin levels greater than ULN at study entry. In cases of documented, stable medical condition (i.e., Gilbert's Syndrome) resulting in levels of total bilirubin greater than ULN, the medical monitor can determine if a protocol exception can be made. If total bilirubin increases to 1.5 x ULN or more during study, the subject will be discontinued.
13. Subjects with significant renal insufficiency, estimated glomerular filtration rate (eGFR) < 30 mL/min (calculated using the Cockcroft-Gault formula, Pediatric GFR calculator or Bedside Schwartz), will be excluded from study entry or will be discontinued if the criteria is met post baseline.
14. Have been exposed to any other investigational drug within 30 days or less than 5 half-lives prior to screening.
15. Unwillingness to withhold grapefruit, Seville oranges or star fruit from diet during the entire clinical trial.
16. Unwillingness to withhold alcohol throughout the entire clinical trial.
17. 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.
18. Known sensitivity or allergy to any component in the investigational product(s), progesterone or other related steroid compounds.

19. Plasma allopregnanolone – sulfate (Allo-S) levels ≥ 6.0 ng/ml at the screening visit.

4.3. Restrictions

Subjects must abstain from the use of alcohol and from consuming grapefruit, Seville oranges and starfruit until completion of the study.

4.4. Reproductive Potential

4.4.1. Female Contraception

Sexually active women of childbearing potential should be using a medically acceptable form of birth control. Women of childbearing potential must be advised to use medically acceptable birth control throughout the study period and for 30 days after the last dose of investigational product. If hormonal contraceptives are used, they should be administered per the package insert.

Women of childbearing potential who are not currently sexually active must agree to use acceptable contraception, as defined below, if they become sexually active during the period of the study and 30 days after the last dose of investigational product.

Female subjects should be:

- Premenarchal and either Tanner stage 1 or less than 9 years or age, *or*
- Surgically sterile (having undergone one of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy, or bilateral salpingectomy) and at least 6 weeks' post-sterilization, *or*
- Women of childbearing potential must have a negative serum pregnancy test prior to taking the first dose of investigational product and must agree to abstain from sexual activity that could result in pregnancy or agree to use a medically acceptable method of birth control.
- Abstinence is an acceptable method of birth control only if this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Medically acceptable methods of birth control include:
    a. Intrauterine device plus condoms
    b. Double-barrier methods (e.g., condoms and diaphragm with spermicidal gel or foam)
    c. Hormonal contraceptives (oral, patch, injectable, or vaginal ring), stabilized for at least 1 month prior to screening visit, plus condoms. Note: If a woman becomes sexually active during the study, she should use one of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days prior to screening visit. Hormonal oral contraceptives must also be used when a condom is used.

4.4.2. Male Contraception

Male participants must agree to take all necessary measures to avoid causing pregnancy in their sexual partners during the study and for 3 months after the last dose of investigational product. Medically acceptable contraceptives include surgical sterilization (such as a vasectomy) and a condom used with a spermicidal gel or foam. The female partner of a male subject must use hormonal oral contraceptives when the male subject uses a condom. Contraceptive measures such as Plan B™, sold for emergency use after unprotected sex, are not acceptable methods for routine use.

Male subjects should not donate sperm during the study and for 30 days after the last dose of investigational product.

4.5. Discontinuation of Subjects

A subject may withdraw — or their parent/LAR may withdraw the subject — from the study at any time for any reason without prejudice to their future medical care by the physician or at the hospital. The investigator or sponsor may withdraw the subject at any time (e.g., in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject from investigational product with the medical monitor when possible.

Subjects who discontinue investigational product treatment before the completion of the double-blind phase will continue to be followed per protocol and at minimum maintain daily seizure eDiary entry until the double-blind phase is completed. These subjects should also return to the site after the taper for safety follow-up assessments.

If the investigational product is discontinued at any time, subjects should follow the 2-week taper schedule. If the subject discontinues during the open-label phase, evaluations listed for Taper Visit are to be performed as completely as possible. Whenever possible, all subjects who discontinue should also undergo the protocol-specified Safety Follow-up Post Taper visit. Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for termination, date of stopping investigational product, and total amount of investigational product taken must be recorded in the electronic case report form (eCRF) and source documents. Discontinuation of investigational product due to AEs must also be reflected on the AE eCRF page.

4.5.1. Subject Withdrawal Criteria

All subjects or his/her parent/LAR reserve the right to withdraw from the clinical study at any time, as stated in the informed consent form. The investigator may discontinue subjects from the clinical study for any of the following reasons:

- Subject is found to have entered the study in violation of the protocol;
- Subject requires the use of a disallowed concomitant medication;
- 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;
- Subject or parent/LAR withdraws consent or assent to participate in the study;
- Subject is noncompliant with the procedures set forth in the protocol;

- Subject experiences an AE/SAE that warrants withdrawal from the study;
- Laboratory, medical, or clinical finding for which clinical intervention should take precedence over study participation; or
- It is the investigator's opinion that it is not in the subject's best interest to continue in the study.

Decisions to discontinue the study will be made at each participating site by the PI. If feasible, the reason for discontinuation should be discussed with the sponsor's medical monitor prior to subject discontinuation. Subjects who discontinue investigational product during the double-blind phase will continue to record daily seizure frequency at minimum until the completion of the double-blind phase.

If a subject must be abruptly discontinued from the investigational product (e.g., severe rash), careful attention should be paid for the possibility of withdrawal symptoms such as increase in seizure number or severity. Consideration should be made by the investigator for providing another GABA-A medication for 1-2 weeks such as clobazam to mitigate the potential risk of withdrawal from a positive modulator of GABA-A.

4.5.2. Reasons for Early Discontinuation

The reason for early discontinuation must be determined by the investigator and recorded in the subject's source documents and on the eCRF. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document and the most clinically relevant reason should be entered on the eCRF.

Reasons for early termination include but are not limited to the following:

- Adverse event in which the character, severity or frequency is new in comparison to the patient's existing risk profile with the exception of seizures.
- An Adverse Event that is associated with non-reversible target organ dysfunction, with the associated laboratory abnormalities as defined in exclusion criteria 11, 12 or 13. An allowance may be made for continued treatment if the abnormality is not medically significant (non-life-threatening or does not require ongoing treatment that could be life-threatening)
- A laboratory abnormality or vital sign change that is irreversible and considered medically significant, associated with use of the investigational product
- Protocol violation/protocol deviation
- Withdrawal by subject or parent/LAR
- Lost to follow-up
- Lack of efficacy
- Death
- Physician decision
- Pregnancy

- Other (must be specified in the subject source document and eCRF)

4.5.3. Subjects Lost to Follow-up Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgment of receipt request) asking that they return to the site for final safety evaluations and return any unused investigational product. If contact is made but the subject refuses or is unable to return to the site for the final safety follow-up visit, it should be documented in the eCRF.

4.6. Subject Numbering

During the screening visit, each subject will be assigned a unique 6-digit subject number by the Interactive Web Response System (IWRS). The subject number will consist of a 3-digit clinical investigational site number assigned by the sponsor, followed by a 3-digit subject number (e.g., 001) assigned by the study staff. This subject number will also serve as the screening number. A separate randomization number will be assigned once the subject is randomized, but the randomization number will not be used to track the subject. The unique 6-digit subject number will serve as the subject ID and be used to track the subject throughout the study. Each subject number will correspond with a treatment (active or PBO) as determined by the randomization schedule.

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

5. EXCLUDED, PRIOR, AND CONCOMITANT MEDICATIONS

The study physician should assess all concomitant medications at every visit, and at the screening visit in particular to ensure that the subject is not taking excluded medications.

5.1. Prior Medications

[redacted]

5.2. Concomitant Medications

Concomitant medications refer to all treatment taken between the date of the first dose of investigational product and the date of the last dose of investigational product. Concomitant treatment information must be recorded on the appropriate eCRF page. Concomitant as needed (PRN) topical and intranasal steroids for dermatologic reactions and allergic rhinitis are allowed and do not warrant exclusion from study. If the subject is currently taking an excluded medication at the time of the screening visit, then the subject must undergo a washout period equivalent to 5 half-lives of the drug before they may enter the prospective 6-week baseline period.

Use of dietary supplements or herbal preparations are permitted if subject has been using them consistently for more than 6 months prior to screening and does not plan on changing the dose for the duration of the double-blind phase. Use of St. John's Wort is not permitted (See Section 12.1).

Concomitant medications may be reduced or discontinued at the discretion of the investigator if medically warranted.

5.2.1. Concomitant AED Medications

Subjects participating in the study can take between 0-4 AEDs in addition to the investigational medication. Vagus nerve stimulator, ketogenic diet, and modified Atkins diet do not count towards this limit but must be unchanged for 3 months prior to the screening visit.

Subjects with surgically implanted VNS will be allowed to enter the study provided that all of the following conditions are met:

- The VNS has been in place for ≥ 1 year prior to the screening visit.
- The settings must have remained constant for 3 months prior to the screening visit and remain constant throughout the double-blind phase.
- The battery is expected to last for the duration of the double-blind phase.

Concomitant AEDs or their dose must be stable for 1 month prior to the screening visit and should not be changed at any time prior to Visit 5 in the double-blind phase but may be adjusted

during the open-label phase of the study. Concomitant AEDs may be reduced or discontinued at the discretion of the investigator if medically warranted.

Felbamate: The use of felbamate is allowed provided that the subject has been maintained on a stable dose of felbamate for > 6 months, and has had stable liver function (AST/ALT) and hematology during the course of treatment, and is expected to remain constant throughout the double-blind phase.

5.3. Rescue Medications

The use of rescue medication is allowed. The type, dose, date, and frequency will be recorded.

5.4. Excluded Medications

Excluded medications include all steroid medications, other investigational products, as well as ketoconazole. Concurrent use of ACTH, prednisone or other glucocorticoid is not permitted, nor use of moderate or strong inducers or inhibitors of CYP3A4/5/7. A list of CYP3A4/5/7 inhibitors and inducers is included in Section 12.1. Moderate or strong inducer or inhibitor anti-epileptic drugs will be allowed (e.g., carbamazepine, phenytoin, etc.) Concomitant PRN topical and intranasal steroids for dermatologic reactions and allergic rhinitis are allowed and do not warrant exclusion from the study.

Only Epidiolex (cannabidiol; GW Pharmaceuticals, may go by another name in countries outside the US) is allowed during the double-blind phase provided the subject has been on a stable dose for at least 1 month prior to screening and is expected to remain on a stable dose without a foreseeable change for the duration of the double-blind phase. Other products containing THC or CBD are excluded in the double-blind phase of the study but allowed in the open-label phase. Tetrahydrocannabinol or CBD should be washed out for at least 6 weeks. Subjects with a positive result on THC or CBD test (via urine or plasma drug screen) at the screening visit, and a positive result on THC or CBD test (via plasma) at the baseline visit will be excluded from the study.

6. INVESTIGATIONAL PRODUCT

6.1. Identity of Investigational Product

Drug name: GNX suspension

[redacted]

Vehicle: The suspension contains GNX (50 mg/mL), hydroxypropyl methylcellulose, polyvinyl alcohol, sodium lauryl sulfate, simethicone, methylparaben, propylparaben, sodium benzoate, citric acid, and sodium citrate at pH 3.8 to 4.2, and is sweetened with sucralose and flavored with artificial cherry.

Strength: 50 mg/mL suspension; 110 mL in 125 mL high-density polyethylene bottles

PBO suspension

[redacted]

Vehicle: The PBO suspension consists of titanium dioxide, microcrystalline cellulose, sodium lauryl sulfate, simethicone, methylparaben, propylparaben, sodium benzoate, citric acid, sodium citrate and is sweetened with sucralose and flavored with artificial cherry.

Both GNX and PBO will be packaged in high-density polyethylene (HDPE) bottles with a child resistant closure.

GNX will be supplied at a concentration of 50 mg/mL (GNX equivalent) in 125 mL bottles, containing 110 mL GNX. A PBO suspension, which is identical in taste and appearance, will be supplied at an equal volume.

6.1.1. Blinding the Treatment Assignment

The contents of each bottle will be blinded using labels with unique bottle numbers. Only the investigational product supplier and the sponsor's investigational product manager will be unblinded as to the bottle number and the contents of each bottle of investigational product.

6.2. Administration of Investigational Products

6.2.1. Interactive Response Technology for Investigational Product Management

For the double-blind phase and the titration period of the open-label phase and thereafter an IWRS will be utilized for the following investigational product tasks:

- Randomization
- Supply management
- Inventory management and supply ordering
- Expiration date tracking
- Emergency unblinding

6.2.2. Allocation of Subjects to Treatment

Subjects will be randomly assigned at a 1:1 ratio (GNX: PBO) based on a randomization schedule at Visit 2 (Week 0). Subjects will be stratified into 2 groups based on baseline seizure frequency. Only the investigational product supplier and the sponsor's investigational product manager will be unblinded as to the contents of each bottle of investigational product. Study staff as well as subject and caregiver will be blinded to treatment assignments.

An IWRS will centrally randomize subjects. The randomization schedule will be generated using a standard, validated method and maintained by the investigational product supplier and IWRS vendor. The investigator will be instructed by the IWRS, which numbered bottle to use to dose a subject. The investigator and research staff will be aware of the ascending dose design of the clinical investigation; however, the investigator, the research staff, and the subjects will be blinded with respect to who is receiving active drug versus PBO. The maximum PBO period is 17 weeks.

The contents of each bottle will be blinded using labels. The randomization schedule will match a subject number to a bottle number. Upon completion of baseline evaluations for each subject, the investigator or appropriate designee will log into the IWRS to receive a bottle number. Complete instructions for obtaining a bottle number will be provided to the clinical sites prior to initiating the study. The designated personnel at the clinical site will match the assigned bottle number with the correct bottle of investigational product and distribute the bottle to the investigator or designee.

6.2.3. Dosing

Ganaxolone will be prescribed in increments of 15 mg/kg/day up to 63 mg/kg/day (maximum 1800 mg/day) as an oral suspension. Subjects ≤ 28 kg will be dosed on an mg/kg basis.

For subjects weighing ≤ 28 kg

Subjects weighing 28 kg (61.6 lbs.) or less will be dosed according to the subject's weight in kilograms and use oral suspension (Table 4). All investigational product prescribed per day will be administered in 3 divided doses following a meal or snack.

Table 4: Oral Suspension (50 mg/ml) Dosing for Subjects Weighing ≤ 28 kg

Dose	Total mg/kg/day	Days
6 mg/kg TID	18	1-7
11 mg/kg TID	33	8-14
16 mg/kg TID	48	15-21
21 mg/kg TID	63	22-28

TID = three times daily

For subjects weighing > 28 kg

Subjects weighing greater than 28 kg (61.6 lbs.) will be dosed by mg/day using oral suspension (Table 5). Suspension dosing will be administered in 3 divided doses following a meal or snack.

Table 5: Oral Suspension (50 mg/ml) Dosing for Subjects Weighing > 28 kg

Dose	ml per Dose	Total mg/day	Days
150 mg TID	3	450	1-7
300 mg TID	6	900	8-14
450 mg TID	9	1350	15-21
600 mg TID	12	1800	22-28

TID = three times daily

The maximum allowable dose is 63 mg/kg/day or a maximum of 1800 mg a day. Any subject not tolerating the next dose step can be maintained at the lower dose step for additional days before advancing to next dose. If the next dose is still not tolerated, they can drop back to the next lower dose step. A minimum dose of 33 mg/kg/day and 900 mg/day is generally required during the double-blind phase unless a lower dose is agreed to with the Sponsor. Dose changes, including alternative dosing paradigm (e.g., lower dose during the daytime and higher dose in the evening), should be discussed with the sponsor medical monitor prior to making the change or within 48 hours of making the change. The higher dose in the evening is expected to be better tolerated due to the proximity to bedtime. However, tolerability management and the final decision to adjust drug dosages lies with Principal Investigator.

Investigational product may be stopped immediately and without down titration in the case of an emergency, although a down titration in the event of an early termination is recommended. Dose de-escalation will occur in decreasing increments of 15 mg/kg/day or 450 mg every 4 days over 2 weeks whenever feasible.

Open-Label

Following the completion of the 17-week, double-blind phase, subjects randomized to PBO will transition to GNX while subjects randomized to GNX will stay on 63 mg/kg/day suspension (maximum 1800 mg/day or Maximum Tolerated Dose [MTD]). Subjects will begin the 4-week blinded dose titration to 63 mg/kg/day or 1800 mg/day (or MTD) after completing Visit 5.

In order to maintain the blind of the double-blind phase, all subjects will be required to dose from 2 groups of bottles: Bottle Group A- maintenance and Bottle Group B- titration. In addition to the maintenance dose from Bottle Group A, subjects will be instructed to take a second dose from Bottle Group B. For subjects initially randomized to GNX, Bottle Group A will contain GNX while Bottle Group B will contain PBO. For subjects initially randomized to PBO, Bottle Group A will contain PBO while Bottle Group B will contain GNX.

Dosing from both Bottle Group A and Bottle Group B will begin at the end of Visit 5 (Week 17), the last visit in the double-blind phase, and continue until the end of the open-label 4-week titration period when subjects return to the site for evaluation (Visit 7, Week 21). Subjects will have an interim safety visit at Visit 6 (Week 19) 2 weeks after starting the open-label phase in which they will receive a new set of medication bottles (Table 6).

Table 6: Transition from Double-blind to Open-label: Oral Suspension (50 mg/ml) Dosing for Subjects ≤ 28 kg

Titration Day	**Bottle Group A- Maintenance**	**Bottle Group B- Titration**
	DB GNX: GNX bottle	*DB GNX: Placebo bottle*
	DB Placebo: Placebo bottle	*DB Placebo: GNX bottle*
	Bottle Group A Dose	**Bottle Group B Dose**
1-7	63 mg/kg/day (21 mg/kg TID)	18 mg/kg/day (6 mg/kg TID)
8-14	63 mg/kg/day (21 mg/kg TID)	33 mg/kg/day (11 mg/kg TID)
Visit 6, Week 19	Safety visit and new set of Group A and Group B bottles issued	
15-21	63 mg/kg/day (21 mg/kg TID)	48 mg/kg/day (16 mg/kg TID)
22-28	63 mg/kg/day (21 mg/kg TID)	63 mg/kg/day (21 mg/kg TID)
Visit 7, Week 21	One set of GNX bottles dispensed, return to dosing from 1 bottle at a time	
63 mg/kg/day (21 mg/kg TID)		

DB = double-blind; GNX = ganaxolone; TID = three times daily.

An example of the transition from double-blind to open-label dosing is shown in Table 7 for a 20 kg subject who was initially randomized to GNX during the double-blind phase.

Table 7: Example of Double-blind to Open-label: DB GNX Subject Weighing 20 kg-Suspension Dosing (50 mg/ml)

Titration Day	**Bottle Group A- Maintenance Treatment: GNX**	**Bottle Group B- Titration Treatment: Placebo**
Days 1-7	63 mg/kg/day (21 mg/kg TID)	18 mg/kg/day (6 mg/kg TID)
Day 1 morning dose	21 mg/kg; 8.4ml	6 mg/kg; 2.4ml
Day 1 afternoon dose	21 mg/kg; 8.4ml	6 mg/kg; 2.4ml
Day 1 evening dose	21 mg/kg; 8.4ml	6 mg/kg; 2.4ml
Continue dosing from Group A and B as above until the end of Day 7		
Days 8-14	63 mg/kg/day (21 mg/kg TID)	33 mg/kg/day (11 mg/kg TID)
Day 8 morning dose	21 mg/kg; 8.4ml	11 mg//kg; 4.4ml
Day 8 afternoon dose	21 mg/kg; 8.4ml	11 mg//kg; 4.4ml
Day 8 evening dose	21 mg/kg; 8.4ml	11 mg//kg; 4.4ml
Continue dosing from Group A and B as above until Visit 6, Week 19		
Visit 6, Week 19	Safety visit and receive new bottles	
Days 15-21	63 mg/kg/day (21 mg/kg TID)	48 mg/kg/day (16 mg/kg TID)
Day 15 morning dose	21 mg/kg; 8.4ml	16 mg//kg; 6.4ml
Day 15 afternoon dose	21 mg/kg; 8.4ml	16 mg//kg; 6.4ml
Day 15 evening dose	21 mg/kg; 8.4ml	16 mg//kg; 6.4ml
Continue dosing from Group A and B as above until the end of Day 21		
Days 22-28	63 mg/kg/day (21 mg/kg TID)	63 mg/kg/day (21 mg/kg TID)
Day 15 morning dose	21 mg/kg; 8.4ml	21 mg/kg; 8.4ml
Day 15 afternoon dose	21 mg/kg; 8.4ml	21 mg/kg; 8.4ml
Day 15 evening dose	21 mg/kg; 8.4ml	21 mg/kg; 8.4ml
Continue dosing from Group A and B as above until Visit 7, Week 21		
Visit 7, Week 21	One set of GNX bottles dispensed, return to dosing from 1 bottle at a time	
Day 29	63 mg/kg/day (21 mg/kg TID)	
Day 29 morning dose	21 mg/kg; 8.4ml	
Day 29 afternoon dose	21 mg/kg; 8.4ml	
Day 29 evening dose	21 mg/kg; 8.4ml	

DB = double-blind; GNX = ganaxolone; TID = three times daily.

An example of the transition from double-blind to open-label dosing is shown in Table 8 for a 20 kg subject who was initially randomized to PBO during the double-blind phase.

Table 8: Example of Double-blind to Open-label: Placebo Subject Weighing 20 kg-Suspension Dosing (50 mg/ml)

Titration Day	**Bottle Group A- Maintenance Treatment: Placebo**	**Bottle Group B- Titration Treatment: GNX**
Days 1-7	63 mg/kg/day (21 mg/kg TID)	18 mg/kg/day (6 mg/kg TID)
Day 1 morning dose	21 mg/kg; 8.4ml	6 mg/kg; 2.4ml
Day 1 afternoon dose	21 mg/kg; 8.4ml	6 mg/kg; 2.4ml
Day 1 evening dose	21 mg/kg; 8.4ml	6 mg/kg; 2.4ml
Continue dosing from Group A and B as above until the end of Day 7		
Days 8-14	63 mg/kg/day (21 mg/kg TID)	33 mg/kg/day (11 mg/kg TID)
Day 8 morning dose	21 mg/kg; 8.4ml	11 mg/kg; 4.4ml
Day 8 afternoon dose	21 mg/kg; 8.4ml	11 mg/kg; 4.4ml
Day 8 evening dose	21 mg/kg; 8.4ml	11 mg/kg; 4.4ml
Continue dosing from Group A and B as above until Visit 6, Week 19		
Visit 6, Week 19	Safety visit and receive new bottles	
Days 15-21	63 mg/kg/day (21 mg/kg TID)	48 mg/kg/day (16 mg/kg TID)
Day 15 morning dose	21 mg/kg; 8.4ml	16 mg/kg; 6.4ml
Day 15 afternoon dose	21 mg/kg; 8.4ml	16 mg/kg; 6.4ml
Day 15 evening dose	21 mg/kg; 8.4ml	16 mg/kg; 6.4ml
Continue dosing from Group A and B as above until the end of Day 21		
Days 22-28	63 mg/kg/day (21 mg/kg TID)	63 mg/kg/day (21 mg/kg TID)
Day 15 morning dose	21 mg/kg; 8.4ml	21 mg/kg; 8.4ml
Day 15 afternoon dose	21 mg/kg; 8.4ml	21 mg/kg; 8.4ml
Day 15 evening dose	21 mg/kg; 8.4ml	21 mg/kg; 8.4ml
Continue dosing from Group A and B as above until Visit 7, Week 21		
Visit 7, Week 21	One set of GNX bottles dispensed, return to dosing from 1 bottle at a time	
Day 29	63 mg/kg/day (21 mg/kg TID)	
Day 29 morning dose	21 mg/kg; 8.4ml	
Day 29 afternoon dose	21 mg/kg; 8.4ml	
Day 29 evening dose	21 mg/kg; 8.4ml	

GNX = ganaxolone; TID = three times daily.

Subjects weighing > 28 kg and dosed using suspension will follow the dosing schedule in Table 9.

Table 9: Transition from Double-blind to Open-label: Suspension (50 mg/ml) Dosing for Subjects > 28 kg

Titration Day	**Bottle Group A- Maintenance**	**Bottle Group B- Titration**
	DB GNX: GNX bottle	*DB GNX: Placebo bottle*
	DB Placebo: Placebo bottle	*DB Placebo: GNX bottle*
	Bottle Group A Dose	**Bottle Group B Dose**
1-7	1800 mg/day; 12 ml per dose TID	450 mg/day; 3 ml per dose TID
8-14	1800 mg/day; 12 ml per dose TID	900 mg/day; 6 ml per dose TID
Visit 6, Week 19	Safety visit and new set of Group A and Group B bottles issued	
15-21	1800 mg/day; 12 ml per dose TID	1350 mg/day; 9 ml per dose TID
22-28	1800 mg/day; 12 ml per dose TID	1800 mg/day; 12 ml per dose TID
Visit 7, Week 21	One set of GNX bottles dispensed, return to dosing from 1 bottle at a time	
1800 mg/day; 12 ml per dose TID		

DB = double-blind; GNX = ganaxolone; TID = three times daily.

An example of the transition from double-blind to open-label dosing is shown in Table 10 for a > 28 kg subject who was initially randomized to GNX during the double-blind phase using suspension.

Table 10: Example of Double-blind to Open-label: DB GNX Subject Weighing > 28 - Suspension Dosing (50 mg/ml)

Titration Day	**Bottle Group A- Maintenance Treatment: GNX**	**Bottle Group B- Titration Treatment: Placebo**
Days 1-7	1800 mg/day (600 mg TID)	450 mg/day (150 mg TID)
Day 1 morning dose	600 mg; 12ml	150 mg; 3ml
Day 1 afternoon dose	600 mg; 12ml	150 mg; 3ml
Day 1 evening dose	600 mg; 12ml	150 mg; 3ml
Continue dosing from Group A and B as above until the end of Day 7		
Days 8-14	1800 mg/day (600 mg TID)	900 mg/day (300 mg TID)
Day 8 morning dose	600 mg; 12ml	300 mg; 6ml
Day 8 afternoon dose	600 mg; 12ml	300 mg; 6ml
Day 8 evening dose	600 mg; 12ml	300 mg; 6ml
Continue dosing from Group A and B as above until Visit 6, Week 19		
Visit 6, Week 19	Safety visit and receive new bottles	
Days 15-21	1800 mg/day (600 mg TID)	1350 mg/day (450 mg TID)
Day 15 morning dose	600 mg; 12ml	450mg; 9ml
Day 15 afternoon dose	600 mg; 12ml	450mg; 9ml
Day 15 evening dose	600 mg; 12ml	450mg; 9ml
Continue dosing from Group A and B as above until the end of Day 21		
Days 22-28	1800 mg/day (600 mg TID)	1800 mg/day (600 mg TID)
Day 15 morning dose	600 mg; 12ml	600 mg; 12ml
Day 15 afternoon dose	600 mg; 12ml	600 mg; 12ml
Day 15 evening dose	600 mg; 12ml	600 mg; 12ml
Continue dosing from Group A and B as above until Visit 7, Week 21		
Visit 7, Week 21	One set of GNX bottles dispensed, return to dosing from 1 bottle at a time	
Day 29	1800 mg/day (600 mg TID)	
Day 29 morning dose	600 mg; 12ml	
Day 29 afternoon dose	600 mg; 12ml	
Day 29 evening dose	600 mg; 12ml	

DB = double-blind; GNX = ganaxolone; TID = three times daily.

An example of the transition from double-blind to open-label dosing is shown in Table 11 for a > 28 kg subject who was initially randomized to PBO during the double-blind phase using suspension.

Table 11: Example of Double-blind to Open-label: Placebo Subject Weighing > 28 kg- Suspension Dosing (50 mg/ml)

Titration Day	**Bottle Group A- Maintenance Treatment: Placebo**	**Bottle Group B- Titration Treatment: GNX**
Days 1-7	1800 mg/day (600 mg TID)	450 mg/day (150 mg TID)
Day 1 morning dose	600 mg; 12ml	150 mg; 3ml
Day 1 afternoon dose	600 mg; 12ml	150 mg; 3ml
Day 1 evening dose	600 mg; 12ml	150 mg; 3ml
Continue dosing from Group A and B as above until the end of Day 7		
Days 8-14	1800 mg/day (600 mg TID)	900 mg/day (300 mg TID)
Day 8 morning dose	600 mg; 12ml	300 mg; 6ml
Day 8 afternoon dose	600 mg; 12ml	300 mg; 6ml
Day 8 evening dose	600 mg; 12ml	300 mg; 6ml
Continue dosing from Group A and B as above until Visit 6, Week 19		
Visit 6, Week 19	Safety visit and receive new bottles	
Days 15-21	1800 mg/day (600 mg TID)	1350 mg/day (450 mg TID)
Day 15 morning dose	600 mg; 12ml	450mg; 9ml
Day 15 afternoon dose	600 mg; 12ml	450mg; 9ml
Day 15 evening dose	600 mg; 12ml	450mg; 9ml
Continue dosing from Group A and B as above until the end of Day 21		
Days 22-28	1800 mg/day (600 mg TID)	1800 mg/day (600 mg TID)
Day 15 morning dose	600 mg; 12ml	600 mg; 12ml
Day 15 afternoon dose	600 mg; 12ml	600 mg; 12ml
Day 15 evening dose	600 mg; 12ml	600 mg; 12ml
Continue dosing from Group A and B as above until Visit 7, Week 21		
Visit 7, Week 21	One set of GNX bottles dispensed, return to dosing from 1 bottle at a time	
Day 29	1800 mg/day (600 mg TID)	
Day 29 morning dose	600 mg; 12ml	
Day 29 afternoon dose	600 mg; 12ml	
Day 29 evening dose	600 mg; 12ml	

GNX = ganaxolone; TID = three times daily.

De-escalation Period

Any subject who completes the study or discontinues investigational product treatment should undergo a 2-week drug de-escalation (taper) period. The schedule will be dependent on the maintenance dose. Typically, doses will be reduced by 15 mg/kg/day or 450 mg/day every 3 days until the subject is completely off investigational product. Subjects should then return for a post-taper safety follow up visit.

Table 12: De-Escalation of Investigational Product

Formulation	Dose	Frequency
Suspension (weighing ≤ 28 kg)	Reduce 15mg/kg/day	Every 3 days
Suspension (weighing > 28 kg)	Reduce 450 mg/day	Every 3 days

6.2.4. Dose Administration

Investigational product will be provided as an oral suspension. **Ganaxolone must be taken with a meal or snack**. Note: grapefruit and grapefruit juice, Seville oranges and star fruit are prohibited during the study.

Ganaxolone oral suspension will be administered through an oral dosing syringe administered by parents/caregivers 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 12 hours. A missed dose of investigational product may be taken up to 4 hours before the next scheduled dose; otherwise, the missed dose should not be given.

Prior to each dose, the following instructions should be followed:

1. Manually shake bottle end to end, 2-3 times per second, for 1 minute
2. Allow the bottle to stand for 1 minute
3. Attach the dosing apparatus (adaptor with syringe), invert the bottle and remove the indicated dose
4. Administer dose as indicated

Use the bottle adapter and dosing syringes provided. Do not use a household spoon. The syringe should be replaced daily and cleaned between each dose that day by rinsing for 30 seconds using hot water and allowing it to air dry. The bottle adapter should stay in the bottle once it's inserted. It should not be removed.

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

6.2.5. Missing a Dose

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

Parents/caregivers should be instructed that if the subject misses 2 days in a row or more, the site should be contacted to determine whether any adjustment in investigational product is needed. The site will confer with the medical monitor to devise a dosing plan.

Parents/caregivers should be instructed to minimize the number of missed doses the subject experiences and be re-educated on proper dosing procedures at each visit to ensure that missed doses are avoided.

Table 13: Missed Dose of Investigational Product

Formulation	Proceed to Dose	DO NOT DOSE
Suspension	≥ 4 hours before next scheduled dose	< 4 hours before next scheduled dose

6.3. Unblinding the Treatment Assignment

If it is deemed necessary to unblind a subject's treatment in order to provide medical management of an AE or to provide emergency treatment, unblinding will be conducted through the IWRS. Unblinding should only occur if necessary, for the medical management of the subject. Prior to unblinding or immediately following, the sponsor's Medical Monitor must be contacted. The sponsor's Medical Monitor does not have to be contacted to initiate unblinding in the IWRS system. Subjects who are unblinded during the double-blind phase will be discontinued from investigational drug treatment but asked to continue seizure charting until the completion of the double-blind phase. If unblinding occurs, please contact:

SPONSOR CONTACTS:

Sponsor Medical Monitor

[redacted] **MD, FAAP**
[redacted]
Mobile Telephone: [redacted] (primary contact method/send text message if no immediate response) Email: [redacted]

If sponsor's Medical Monitor cannot be reached in an emergency, the site should contact:

Back-up Medical Monitor:
mailto: [redacted] **MD**
[redacted]
Office Telephone: [redacted]

Mobile Telephone: [redacted]
Email: [redacted]

Sponsor Project Managers:

[redacted]
Office Telephone: [redacted]
Mobile Telephone: [redacted] primary contact method)
Email: [redacted]

[redacted] **BS**
[redacted]
Office Telephone: [redacted]
Mobile Telephone: [redacted](primary contact method)
Email:[redacted]

CRO CONTACTS:

[redacted]
mailto:
[redacted] **PhD**
[redacted]
Office Telephone: [redacted]
Email: [redacted]

[redacted]
[redacted]
Office Telephone: [redacted]
Mobile Telephone: [redacted]
Email: [redacted]
Global Clinical Trials (GCT): Russia

[redacted]
[redacted]
Mobile Telephone : [redacted]
Email: [redacted]

6.4. Labeling, Packaging, Storage, and Handling

6.4.1. Labeling

Labels containing study information and bottle identification are applied to the investigational product container.

All investigational product is labeled with a minimum of the following: protocol number, medication identification number (if applicable), dosage form (including product name and quantity in pack), directions for use, storage conditions, batch number and/or packaging reference, the statements "For investigational use only" and/or "Caution: New Drug—Limited by Federal (or US) Law to Investigational Use" and "Keep out of reach of children," and the sponsor's name and address.

Additional labels may, on a case-by-case basis, be applied to the investigational product in order to satisfy local or hospital requirements, but must not:

- Contradict the clinical study label
- Obscure the clinical study label
- Identify the study subject by name, without consultation with the sponsor

Additional labels may not be added without the sponsor's prior full agreement.

6.4.2. Packaging

Ganaxolone and PBO oral suspension formulation will be provided to the site as individual suspension bottles containing 110 mL in 125-mL HDPE bottles. Ganaxolone will be supplied at a concentration of 50 mg/mL.

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the sponsor.

6.4.3. Storage

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. Investigational products are distributed by the pharmacy or by a nominated member of the study team.

Ganaxolone and PBO suspension should be stored at room temperature 15°C to 25°C (59°F to 77°F).

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring of the investigational product is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by an in-house system, by a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over

a specific time period can be recorded and retrieved as required. Such a device (i.e., certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), such as fumigation of a storage room.

6.5. Investigational Product Accountability

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for administering/dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (e.g., a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or their designee (as documented by the investigator in the applicable study delegation of authority form) will administer and/or dispense the investigational product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his or her treatment assignment. All administered and/or dispensed investigational product will be documented on the eCRFs and/or other investigational product record. The investigator is responsible for ensuring the retrieval of all investigational product and study supplies from subjects.

The subject's parent/caregiver must be instructed to save and bring their unused investigational product and empty/used investigational product packaging to the clinic and final follow-up visit or to ship it back to the site via secure courier. Investigational product accountability must be assessed at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (e.g., bottles) or at the individual count level for opened containers/packaging. The pharmacist/nominated person will record details on the investigational product accountability form.

No investigational product stock or returned inventory from a Marinus-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records.

At the end of the study, or as instructed by the sponsor, all unused stock, subject-returned, or expired investigational product are either to be sent to a nominated contractor on behalf of the sponsor for destruction or are to be destroyed by the site. Investigational products being returned to the sponsor's designated contractors or approved to be destroyed by the site counted/measured and verified will be reconciled by clinical site personnel and the sponsor (or designated CRO). Shipment return forms, when used, will be signed prior to shipment from the site. Returned investigational products will be packed in a tamper-evident manner to ensure product integrity. Shipment of all returned investigational product must comply with local, state, and national laws.

With the written agreement of the sponsor, unused stock, subject-returned, and expired investigational product may be destroyed at the site or a local facility. In this case, destruction records identifying what was destroyed, when, and how must be obtained with copies provided to the sponsor. Destruction of investigational products must be in accordance with local, state, and national laws.

Based on entries in the site's drug accountability forms, it must be possible to reconcile investigational products delivered with those used and returned. All investigational products must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.

6.6. Subject Compliance

Subject compliance will be tracked through the electronic seizure and medication diary. Parent/caregiver are to record daily seizure frequency and type in addition to study medication and non-study AED administration throughout the study including the prospective 6-wk baseline seizure-charting period. Compliance with investigational product treatment will be assessed by inspecting the electronic seizure and medication diary entries and returned supplies with queries as necessary. Parent/caregiver will be re-educated on the importance of adhering to daily seizure, investigational product and non-study AED recording as needed. Subjects that fall below 80% compliance at 2 consecutive visits during the double-blind phase will not be included in the per-protocol population.

7. STUDY PROCEDURES

7.1. Study Assessments

See Schedule of Assessments (Table 1 and Table 2) for details regarding scheduled assessments and procedures in this study.

7.2. Study Procedures (Double-blind Phase)

7.2.1. Screening Period

7.2.1.1. Historical Seizure Type and Frequency (Week -14)

Potential subjects will have already been pre-identified by the site because of confirmed or suspected CDKL5 genetic mutation testing as part of their standard of care epilepsy work-up.

It is also very common that parents/caregivers/LARs of CDKL5 patients maintain daily seizure calendars, which capture both seizure type and frequency and days when no seizures occur as part of their standard of care treatment regimen. A 2-month (8-week) daily historical seizure calendar will be reviewed at the screening visit to determine eligibility per inclusion/exclusion criteria. Acceptable daily historical seizure calendars will need to denote seizure types, frequency, and days that no seizures occurred. Procedures specific to this protocol and not otherwise considered standard of care, will not be performed until written informed consent/assent from the subject's parent or legal guardian has been appropriately obtained. In the event that parents/caregivers/LAR do not routinely maintain a daily seizure calendar per standard of care, written informed consent will be obtained, and the subject will be asked to return to the clinic for the Screening (Visit 1) after they have maintained a 2-month (8-week) daily historical seizure calendar.

7.2.1.2. Screening (Visit 1, Week -6)

Additional procedures/assessments to be completed during the screening period may include the following:

- Informed consent from parent/LAR (or subject assent)
- Demographics and medical history
- Historical seizure calendar review
- Review of inclusion/exclusion criteria
- Genetic testing to confirm pathogenic or likely pathogenic CDKL5 variant
- Seizure Identification and Diagnostic Review Form (SIF/DRF) (Epilepsy Study Consortium)
- Vital signs (to include BP, HR, RR, body temperature, weight, and height)
- Physical, neurological, and developmental examination
- ECG

- Clinical laboratory tests (to include complete blood count [CBC] with automated differential, creatinine, blood urea nitrogen, and comprehensive metabolic panel)
- Urinalysis (An attempt should be made to collect a urine sample at this screening visit. Otherwise, the urine sample can be collected at baseline.)
- Drug screen (urine or plasma)
- Investigator and parent/caregiver/LAR establish baseline patient behavior for CGICA, CGI-C and CGI-I
- Serum pregnancy test for girls/women of childbearing potential
- Tanner staging
- Concomitant AED review and levels if per standard of care (SOC)
- Neurosteroid level sample draw
- Adverse events
- Electronic seizure and medication diary set up and review

A screen failure is a subject for whom informed consent has been obtained and has failed to meet the inclusion criteria and/or met at least 1 of the exclusion criteria and has not been administered the investigational product.

7.2.1.3. Baseline (Visit 2, Week 0 + 6 days, Randomization)

The following study procedures/assessments must be completed, the results must be received, and the investigator must ensure the subject meets all inclusion and exclusion criteria prior to investigational product administration. Visit 2 must occur a minimum of 6 weeks (42 days) after Visit 1 and no later than 6 weeks + 6 days (48 days) after Visit 1:

- Review of inclusion/exclusion criteria
- Medical history review
- SIF/DRF (Epilepsy Study Consortium) approval
- Vital signs (to include BP, HR, RR, and body temperature. Weight will only be collected if unable to collect at Visit 1)
- Physical, neurological, and developmental follow-up examination
- ECG
- Clinical laboratory tests (to include CBC with automated differential, creatinine, blood urea nitrogen, and comprehensive metabolic panel)
- Urinalysis (If the urine sample was not collected at screening, it must be collected at baseline in order to complete the study-related procedures per protocol.)
- Serum pregnancy test for girls/women of childbearing potential
- Concomitant AED review and levels if per SOC

- Adverse events
- Seizure and medication diary review
- EEG
- CSHQ
- ADAMS
- QI-Disability
- PSI
- Dispense investigational product

7.2.2. Titration + Maintenance (3 Days, Weeks 1, 2, 3, 4, 5, 9, and 13)

7.2.2.1. Telephone Follow-up (Day 3 ± 2 days and Weeks 1, 2, 3, and 4 ± 3 days)

A telephone follow-up visit will be conducted at Day 3 ± 2 days and Weeks 1, 2, 3, and 4 to assess the following:

- Adverse events
- Seizure and medication diary review

7.2.2.2. Titration + Maintenance (Visits 3 and 4, Weeks 5 ± 3 days and 9± 3 days)

The following study procedures/assessments will be completed at Weeks 5 and 9 of the double-blind phase:

- Vital signs (to include BP, HR, RR, and body temperature)
- Physical, neurological, and developmental examination (Visit 3, Week 5 only)
- Physical, neurological, and developmental follow-up examination (Visit 4, Week 9 only)
- ECG (Visit 3, Week 5 only)
- Clinical laboratory tests (to include CBC with automated differential, creatinine, blood urea nitrogen, and comprehensive metabolic panel)
- Investigational Product PK (population PK at Visit 3:1-5 hours post dose and Visit 4: 4-8 hours post dose)
- Concomitant AED review and levels if per SOC
- Adverse events
- Seizure and medication diary review
- CGICA
- CGI-C (parent/caregiver/LAR identified behavioral target)

- CGI-I (parent/caregiver/LAR and clinician)
- CGI-CSID
- CSHQ
- ADAMS
- QI-Disability
- PSI
- Dispense investigational product

7.2.2.3. Telephone Follow-up Visit (Weeks 11, 13 ± 3 days)

A telephone follow-up visit will be conducted at Weeks 11 and 13 to assess the following:

- Adverse events
- Seizure and medication diary review

7.2.3. Final Double-blind Visit /First Open-label Visit (Visit 5, Week 17 ± 3 days)

The following study procedures/assessments will be completed during the final double-blind visit or taper visit or at the time of early termination:

- Vital signs (to include BP, HR, RR, body temperature, and weight)
- Physical, neurological, and developmental examination
- ECG
- Clinical laboratory tests (to include CBC with automated differential, creatinine, blood urea nitrogen, and comprehensive metabolic panel)
- Urinalysis
- Investigational Product PK
- Concomitant AED review and levels if per SOC
- Neurosteroid level sample draw
- Adverse events
- Seizure and medication diary review
- CGICA
- CGI-C (parent/caregiver/LAR identified behavioral target)
- CGI-I (parent/caregiver/LAR and clinician)
- CGI-CSID
- EEG
- CSHQ

- ADAMS
- QI-Disability
- PSI
- Dispense investigational product

7.2.4. Telephone Follow-up (3 days after Visit 5 ± 1 day, Weeks 18 and 20 ± 3 days)

A telephone follow-up visit will be conducted 3 days after Visit 5 and at Weeks 18 and 20 to assess the following:

- Adverse events
- Seizure and medication diary review

7.2.5. Open-Label Blinded Titration (Visit 6, Week 19 ± 3 days)

The following study procedures/assessments will be completed at the Open-label Blinded Titration (Visit 6) in the open-label phase of the study:

- Vital signs (to include BP, HR, RR, and body temperature)
- Physical, neurological, and developmental follow-up examination
- Clinical laboratory tests (to include CBC with automated differential, creatinine, blood urea nitrogen, and comprehensive metabolic panel)
- Investigational Product PK
- Concomitant AED review and levels if per SOC
- Adverse events
- Seizure and medication diary review
- CGI-I (clinician and parent/caregiver/LAR)
- Dispense Investigational Product

7.2.5.1. Open-Label Blinded Titration (Visit 7, Week 21 ± 3 days)

- Vital signs (to include BP, HR, RR, and body temperature)
- Physical, neurological, and developmental examination
- ECG
- Clinical laboratory tests (to include CBC with automated differential, creatinine, blood urea nitrogen, and comprehensive metabolic panel)
- Investigational Product PK (population PK between 1-5 hours post dose)

- Concomitant AED review and levels if per SOC
- Adverse events
- Seizure and medication diary review
- CGICA
- CGI-C (parent/caregiver/LAR identified behavioral target)
- CGI-I (parent/caregiver/LAR and clinician)
- CGI-CSID
- CSHQ
- ADAMS
- QI-Disability
- PSI
- Dispense Investigational Product

7.2.6. Open-Label Maintenance (Weeks 28-68; ± 7 days window for each visit)

7.2.6.1. Telephone Follow-up (Weeks 28, 43 and 60; ± 7 days window for each visit)

A telephone follow-up visit will be conducted at Weeks 28, 43, and 60 of the open-label phase to assess the following:

- Adverse events
- Review and medication seizure diary

7.2.6.2. Open-Label Maintenance (Visits 8, 9, and 10, Weeks 34, 52 and 68; ± 7 days window for each visit)

The following study procedures/assessments will be completed at Weeks 34, 52 and 68 and every 16 weeks thereafter for the duration of the open-label phase:

- Vital signs (All Visits: to include BP, HR, RR, and body temperature; Visits 8, 9, and 10: to include weight; Visits 8 and 9: to include height)
- Physical, neurological, and developmental examination
- ECG
- Clinical laboratory tests (to include CBC with automated differential, creatinine, blood urea nitrogen and comprehensive metabolic panel)
- Urinalysis (Visit 9, Week 52 only)
- Tanner staging (Visit 9, Week 52 only)
- Investigational Product PK (Visit 9 only: population PK draw between 1-5 hours post dose)

- Concomitant AED review and levels if per SOC
- Adverse events
- Seizure and medication diary review
- CGICA
- CGI-C (parent/caregiver/LAR identified behavioral target)
- CGI-I (parent/caregiver/LAR and clinician)
- CGI-CSID
- CSHQ
- ADAMS
- QI-Disability
- PSI
- Dispense investigational product

7.2.6.3. Visit X - Additional Maintenance Visits in the Open-Label Phase (every 16 weeks with a telephone follow-up in between ± 7 days window for each visit)

If the subject continues in the open-label phase beyond Week 68, the subject must return for a clinic visit every 16 weeks to complete the following study procedures/assessments:

- Vital signs (All Visits: to include BP, HR, RR, body temperature, and weight; only height will be measured annually)
- Physical, neurological, and developmental examination
- ECG
- Clinical laboratory tests (to include CBC with automated differential, creatinine, blood urea nitrogen, and comprehensive metabolic panel)
- Urinalysis (annually)
- Tanner staging (annually)
- Investigational Product PK
- Concomitant AED review and levels if per SOC
- Adverse events
- Seizure and medication diary review
- CGICA
- CGI-C (parent/caregiver/LAR identified behavioral target)
- CGI-I (Parent/caregiver/LAR and clinician)
- CGI-CSID

- CSHQ
- ADAMS
- QI-Disability
- PSI
- Dispense investigational product

If the subject continues in the open-label phase beyond Week 68, a telephone follow-up visit will occur in between every clinic visit (8 weeks after each clinic visit) to assess the following:

- Adverse events
- Review and medication seizure diary

7.2.7. Final Open-Label Visit or Taper Visit; ± 7 days (or at time of Early Termination)

The timing of the final open-label visit is not defined at this time, as the study is anticipated to continue until either the investigational product is approved and marketed or the sponsor discontinues development of investigational product in CDD (approximately an additional 3 years). The following study procedures/assessments to be completed during the final open-label visit or taper visit at the time of early termination:

- Vital signs (to include BP, HR, RR, body temperature, weight, and height)
- Physical, neurological, and developmental examination
- ECG
- Clinical laboratory tests (to include CBC with automated differential, creatinine, blood urea nitrogen, and comprehensive metabolic panel)
- Urinalysis
- Serum pregnancy test for girls/women of childbearing potential
- Tanner staging
- Investigational Product PK
- Concomitant AED review and levels if SOC
- Neurosteroid level sample draw
- Adverse events
- Seizure and medication diary review
- CGICA
- CGI-C (parent/caregiver/LAR identified behavioral target)
- CGI-I (parent/caregiver/LAR and clinician)
- CGI-CSID

- EEG
- CSHQ
- ADAMS
- QI-Disability
- PSI
- Dispense investigational product

7.2.8. Safety Follow-up Post-taper (2 Weeks; ± 3 days Post Investigational Product Taper)

The following study procedures/assessments to be completed during the safety follow-up post-taper visit:

- Vital signs (to include BP, HR, RR, and body temperature)
- Physical, neurological, and developmental follow-up examination
- Clinical laboratory tests (to include CBC with automated differential, creatinine, blood urea nitrogen and comprehensive metabolic panel)
- Urinalysis
- Serum pregnancy test for women of childbearing potential
- Investigational Product PK
- Concomitant AED review and levels if SOC
- Adverse events
- Seizure and medication diary review

7.3. Screening and Diagnosis

Potential subjects will be pre-identified by the site because of confirmed or suspected CDKL5 genetic mutation testing as part of their standard of care epilepsy work-up. Potential subjects will have historical seizure diary charting 2 months prior to screening. Eligible historical seizure diary will need to include daily logs of seizure types and frequency and denote the absence of seizures on those days where no seizures occurred.

7.3.1. Informed Consent

Procedures specific to this protocol and not otherwise considered standard of care, will not be performed until written informed consent from the parent/caregiver/LAR has been appropriately obtained.

7.3.2. Drug Screen

A drug screen (urine or plasma) will be performed to test for THC and CBD at Visits 1 (screening) and Visit 2 (baseline). Concomitant use of Epidioloex (may go by another name in

countries outside the US) will be allowed in the double-blind phase provided the subject has been on a stable dose for at least 1 month prior to screening and is expected to remain on a stable dose without a foreseeable change for the duration of the double-blind phase. THC and/or CBD will be allowed in the open-label phase. All other THC and CBD products will not be allowed in the double-blind phase. Therefore, a negative drug test at Visit 1 meets the protocol eligibility criteria. If the screening drug test is positive, a plasma drug screen will be performed to test for THC and CBD at Visit 2 (baseline) if a prescription for Epidiolex (CBD) in epilepsy is not available. A positive drug test at Visit 2 will exclude the subject from the study. Dosing should not commence until confirmation of a negative drug screen from Visit 2.

7.3.3. Demographics and Medical History

Demographics including age, gender, ethnicity and race will be collected.

In addition to the genetic confirmation of pathogenic or likely pathogenic CDKL5 variant, relevant medical history including but limited to the age of seizure onset, other physical disabilities such as scoliosis, visual impairment, sensory problems and gastrointestinal difficulties will also be assessed. The subject's developmental history will also be assessed, as the subject will have to lack independent ambulation by 2 years of age. Demographics and Medical History will be reviewed and collected at the Visit 1 (screening). A review of the subject's Medical History will be performed again at Visit 2 (baseline).

7.3.4. Historical Seizure Calendar Review

It is very common for parent/caregivers/LARs to maintain daily seizure calendars for this patient population, which capture both seizure type and frequency. A 2-month historical seizure calendar will be reviewed at the screening visit to determine eligibility per inclusion/exclusion criteria. Acceptable historical seizure calendars will need to denote both seizure type and frequency and days that no seizures occur.

In the event the participant is not able to provide eligible historical seizure diary (2-months prior to screening), the informed consent will need to be obtained and the parent/caregiver will need to chart prospectively.

7.3.5. Genetic Testing

Genetic testing to confirm pathogenic or likely pathogenic CDKL5 variant will be confirmed by the sponsor's central genetic laboratory. In France, genetic mutations may be confirmed by an approved French organization, in compliance with French legislation prior to Screening Visit 1. If the subject has a *de novo* VUS in the kinase domain of the CDKL5 gene, parental testing is negative and meets all other inclusion criteria, then the subject is eligible for enrollment. If subject already has confirmation of pathogenic or likely pathogenic CDKL5 variant that has been confirmed by the sponsor's selected central genetic laboratory and can provide documentation that the same panel was used, this genetic testing will be waived.

Instructions for genetic testing sample collection and processing can be found in the laboratory manual.

7.3.6. Seizure Identification and Diagnostic Review

Per the inclusion criteria, enrollment into the study will be based on the presence and frequency of the primary seizure types which includes bilateral tonic (sustained motor activity ≥ 3 seconds), generalized tonic-clonic, bilateral clonic, atonic/drop or seizures or focal to bilateral tonic-clonic seizures.

To standardize seizure identification and classification in the study, a SIF/DRF will be submitted and reviewed by the Epilepsy Study Consortium. Approval of the SIF/DRF will be required prior to randomization. In addition to this form, videos of the subject's seizure types will also be reviewed to confirm proper classification provided that the parent/caregiver is able to capture video of these seizure types, parents/caregivers are able to provide videos to the site for upload onto a secure encrypted server in a manner consistent with ICH/GCP and if local IRB/EC regulations grants approval for collection of such videos. Parents/caregivers must make every effort to capture one example of each of the primary seizure types that their child experiences. Although it is acknowledged that drop seizures may be more difficult to capture on video, this information will provide valuable verification of this seizure type and the attempt should be made.

Instructions for completion of the SIF/DRF and submission of videos can be found in the Investigator Site File.

7.4. Efficacy Assessments

Efficacy as determined by a reduction in seizures will be evaluated by collecting daily seizure type and frequency in an electronic seizure diary. Changes in seizure intensity/duration, CGI-I, as well as changes in behavior and neuropsychiatric symptoms will be assessed by a variety of clinician and caregiver administered instruments.

7.4.1. Seizure Type and Frequency

Parent/caregiver/LAR will record daily seizure frequency denoting seizure type and frequency in an electronic seizure diary (eDiary). Seizures will be noted as occurring as individual seizures, seizures occurring in a cluster with countable seizures or seizures occurring in a cluster with uncountable seizures. In rare cases when an eDiary completion is not feasible, a paper seizure calendar will be used to log in daily seizure type and frequency. These cases will need approval by the sponsor. Primary seizure types of bilateral tonic (sustained motor activity ≥ 3 seconds), generalized tonic-clonic, bilateral clonic, atonic/drop or focal to bilateral tonic-clonic seizures will be counted towards the primary endpoint.

Subjects or parent/caregiver/LAR are to record administration of investigational product and background AEDs in the eDiary/seizure calendar. Compliance with investigational product treatment will be assessed by inspecting the subjects' eDiary/seizure calendar and returned supplies with queries as necessary. Subjects that fall below 80% compliance at 2 consecutive visits during the double-blind phase will not be included in the per-protocol population.

7.4.2. Caregiver Global Impression of Change in Seizure Intensity/ Duration (CGI-CSID)

The CGI-CSID is a 7-point Likert scale in which the parent/caregiver/LAR assesses change in seizure intensity and/or duration after initiation of investigational product relative to baseline (prior to treatment with investigational product). The scale ranges from 1- very much improved, 2- much improved, 3-minimally improved, 4- no change, 5- minimally worse, 6- much worse, and 7- very much worse (Section 12.6). CGI-CSID will be assessed at Visit 3 (Week 5), Visit 4 (Week 9), Visit 5 (Week 17) in the double-blind phase, and will be assessed at Visit 7 (Week 21), Visit 8 (Week 34), Visit 9 (Week 52), Visit 10 (Week 68) and will continue to be assessed every 16 weeks for the duration of the open-label phase and at the Final open-label (OL) Visit.

7.4.3. Caregiver Global Impression of Change in Attention (CGICA)

The CGICA is a 7-point Likert scale in which the parent/caregiver/LAR assesses change in attention after the initiation of investigational product relative to baseline (prior to treatment with investigational product). During the screening visit, the investigator and parent/caregiver/LAR will decide on a specific behavior that the patient exhibits that denotes attention. This behavior will be used at subsequent visits to assess change after the initiation of investigational product. The scale ranges from 1- very much improved, 2- much improved, 3-minimally improved, 4- no change, 5- minimally worse, 6- much worse, and 7- very much worse (Section 12.4).

CGICA will be assessed at Visit 3 (Week 5), Visit 4 (Week 9), Visit 5 (Week 17) in the double-blind phase, and will be assessed at Visit 7 (Week 21), Visit 8 (Week 34), Visit 9 (Week 52), Visit 10 (Week 68) and will continue to be assessed every 16 weeks for the duration of the open-label phase and at the Final OL Visit.

7.4.4. Caregiver Global Impression of Change (CGI-C– target behavior)

The CGI-C in target behavior is a 7-point Likert scale in which the caregiver chooses one domain from possible domains of sociability, communication, irritability, and hyperactivity to assess change in target behavior after the initiation of investigational product relative to baseline (prior to treatment with investigational product). This domain should be chosen based on behavior the parent/caregiver/LAR identifies to be the most impactful. During the screening visit, the investigator and parent/caregiver/LAR will decide on a domain and identify the specific behavior that the patient exhibits that denotes the domain. This behavior will be used at subsequent visits to assess change after the initiation of investigational product. The scale ranges from 1- very much improved, 2- much improved, 3-minimally improved, 4- no change, 5 - minimally worse, 6- much worse, and 7- very much worse (Section 12.5).

CGI-C – target behavior will be assessed at Visit 3 (Week 5), Visit 4 (Week 9), Visit 5 (Week 17) in the double-blind phase, and will be assessed at Visit 7 (Week 21), Visit 8 (Week 34), Visit 9 (Week 52), Visit 10 (Week 68) and will continue to be assessed every 16 weeks for the duration of the open-label phase and at the Final OL Visit.

7.4.5. Clinical Global Impression of Improvement (CGI-I)

The CGI-I is a 7-point Likert scale that the parent/caregiver/LAR and clinician uses to rate the change in overall seizure control, behavior, safety and tolerability after initiation of investigational product relative to baseline (prior to treatment with investigational product). The subject will be rated as follows: 1- very much improved, 2- much improved, 3-minimally improved, 4- no change, 5- minimally worse, 6- much worse, and 7- very much worse (Section 12.7).

CGI-I will be assessed at Visit 3 (Week 5), Visit 4 (Week 9), Visit 5 (Week 17) in the double-blind phase, and will be assessed at Visit 6 (Week 19), Visit 7 (Week 21), Visit 8 (Week 34), Visit 9 (Week 52), Visit 10 (Week 68) and will continue to be assessed every 16 weeks for the duration of the open-label phase and at the Final OL Visit.

[redacted]

7.6. Safety Assessments

Safety will be evaluated by collecting the assessments detailed in the sections below.

Baseline is defined as the last non-missing value obtained before the first double-blind treatment. If any of the baseline safety assessments are outside of normal limits, and the investigator feels is medically significant, the subject may not be randomized. Assessments performed at multiple post-baseline time points will be summarized at each time point for which they are scheduled, but the listings will also include any assessments performed at unscheduled time points.

7.6.1. Adverse Events

Details regarding AEs and SAEs are provided in Section 8.

7.6.2. Vital Signs

Vital signs including HR (bpm), RR (breaths/minute), body temperature (C/F), BP (mmHg) will be collected at every clinic visit. Height will be collected at Visit 1 (screening), Visit 8 (Week 34), Visit 9 (Week 52), annually thereafter, and at the Final OL Visit. Weight will be collected at Visit 1 (screening), Visit 5 (Week 17), Visit 8 (Week 34), and every clinic visit thereafter, including the Final OL Visit.

7.6.3. Physical/Neurological/Developmental Examinations

The full physical examination will include the following systems:

- General appearance
- Head (eyes, ears, nose and throat)
- Cardiovascular
- Respiratory
- Gastrointestinal
- Genitourinary
- Musculoskeletal
- Endocrine/Metabolic
- Hematologic/lymphatic
- Skin
- Other systems as appropriate

The full neurological examination will include:

- Cranial nerves
- Motor exam
- Sensory exam
- Reflexes
- Coordination/Cerebellar

The full developmental examination will include:

- Speech/language
  - Makes identifiable sounds for specific objects/people
  - Repeats sounds
  - Single words
  - Multiple words
  - Makes a sentence
  - Replies to question in an identifiable sound, single word, multiple word, sentence
  - Other abilities
- Motor
  - Sits with support
  - Sits independently

  - Crawls
  - Stands with support
  - Stands independently
  - Takes steps with assistance
  - Walks independently
  - Other abilities
- Social
  - Smiles appropriately to situation
  - Makes eye contact

Follow up physical, neurological, and developmental examinations are abbreviated examinations that ask whether there have been clinically significant changes or new abnormalities in the subject's physical, neurological, and developmental examinations since the last full examination.

7.6.4. ECG

Electrocardiograms will be performed to collect the electrical activity of the heart throughout the study to monitor safety. An evaluation of normal by a physician must be obtained before the subject is randomized to the double-blind phase. A third party will provide central ECG services for this study including provision of equipment to clinical sites, project management, site training and education, data analysis as well as delivery of clean quality data. Complete details regarding the third party's ECG services will be provided in the Investigator Site File.

ECGs will be performed at Visit 1 (screening), Visit 2 (baseline), Visit 3 (Week 5), Visit 5 (Week 17) in the double-blind phase, and will be assessed at Visit 7 (Week 21), Visit 8 (Week 34), Visit 9 (week 52), Visit 10 (Week 68) and will continue to be assessed every 16 weeks for the duration of the open-label phase and at the Final OL Visit.

7.6.5. Clinical Laboratory Tests

Laboratory safety assessments will be collected at every clinic visit throughout the study to monitor subject safety. Clinical laboratory tests are listed in Section 12.2 will be collected per the schedule listed in Table 1 and Table 2. These clinical laboratory assessments will include CBC with automated differential, creatinine, blood urea nitrogen, and eGFR calculation, comprehensive metabolic panel, as well serum pregnancy test for all women of childbearing potential.

The following liver function and eGFR tests will be monitored throughout the study as follows.

- If AST or ALT increases > 3 times ULN during the study, subject should be followed with weekly laboratory repeat testing and continue in study if levels trending down. Subject will be discontinued if levels do not decline to under 3 x ULN.
- If total bilirubin increases to 1.5 x ULN or more during study, the subject will be discontinued.

- Subjects with significant renal insufficiency, eGFR < 30 mL/min (calculated using the Cockcroft-Gault formula or Pediatric GFR calculator or Bedside Schwartz) will be discontinued if the criterion is met post baseline.

If any of the criteria above are deemed clinically significant by the investigator, then the sponsor's medical monitor should be contacted.

Due to the difficulty in obtaining urine samples, urinalysis will be conducted at Visit 1 (screening) or baseline (Visit 2), Week 17 (Visit 5), Week 52 (Visit 9), and annually thereafter or at the safety follow up visit if investigational product is discontinued. An attempt will be made to collect a urine sample at screening in order to perform the study-related urinalysis. Otherwise, the urine sample for the urinalysis can be collected at baseline.

7.6.6. Tanner Staging

The Tanner scale (also known as the Tanner stages) is a scale of physical development in children, adolescents and adults. The scale defines physical measurements of development based on external primary and secondary sex characteristics. Subjects will be evaluated and rated as Tanner I, Tanner II, Tanner III, Tanner IV, and Tanner V. Tanner staging will occur at Visit 1 (screening), Visit 9 (Week 52) and will continue to be assessed annually for the duration of the subject's participation in the open-label phase and at the Final OL Visit.

7.6.7. Investigational Product PK

Please refer to Section 7.7 for additional details regarding Pharmacokinetic Assessments.

7.6.8. Concomitant AED levels

Concomitant AED levels are not mandatory but will be collected per sites' standard of care. If AED levels are available for Visit 1 (screening), Visit 2 (baseline), Visit 3 (Week 5), Visit 4 (Week 9) and Visit 5 (Week 17), and throughout the open-label phase of the study at the timepoints noted in Table 1 and Table 2, the results, date and time of last AED dose and date and time of AED PK sample will be recorded in the eCRF.

7.6.9. Neurosteroid levels

A blood sample will be drawn at the screening visit to confirm the subject meets eligibility criteria and does not have plasma allopregnanolone – sulfate (Allo-S) levels ≥ 6.0 ng/ml.

Additional blood samples will be drawn at Visit 5 (Week 17) and at the Final OL Visit. The goal of this assessment is to measure levels of various neurosteroids.

Instructions for neurosteroid sample collection and processing can be found in the laboratory manual.

7.6.10. Adverse Events

Details regarding AEs and SAEs are provided in Section 8.

8. ADVERSE AND SERIOUS ADVERSE EVENT ASSESSMENTS

8.1. Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject who has been administered a pharmaceutical product; it does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (International Conference on Harmonisation [ICH] Guidance E2A March 1995).

All AEs are collected from the time the informed consent is signed until the defined follow-up period. This includes events occurring during the screening phase of the study, regardless of whether or not the investigational product has been administered. All AEs reported after the initiation of investigational product will be considered treatment-emergent AEs. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the eCRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE eCRF page.

All AEs must be followed to closure (the subject's health has returned to baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization is achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1. Severity Categorization

The severity of AEs must be recorded during the course of the event, including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pretreatment events, after initiation of the investigational product, must be recorded as new AEs (e.g., if a subject experiences mild intermittent dyspepsia prior to dosing of the investigational product, but the dyspepsia becomes severe and more frequent after the first dose of the investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate eCRF page).

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, that significantly affects clinical status, or that may require intensive therapeutic intervention.

8.1.2. Relationship Categorization

A physician/investigator must make the assessment of relationship between the investigational product and each AE. The investigator should decide whether, in their medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, the AE should be classified as "not related." If a relationship between the AE and the investigational product is at least reasonably possible (i.e. the relationship cannot be ruled out) the AE should be considered "related." The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship definition
Related	The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not related	The event can be readily explained by other factors, such as the subject's underlying medical condition, concomitant therapy, or accident, and no plausible temporal or biologic relationship exists between the investigational product and the event.

8.1.3. Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the eCRF. Outcomes are as follows:

- Fatal
- Not recovered/not resolved
- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Unknown

8.1.4. Symptoms of the Disease Under Study

Symptoms of the disease under study should not be classified as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE.

8.1.5. Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory, vital sign, ECG assessment can represent an AE if the change is clinically significant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to an abnormal value, or there is a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range (either while continuing treatment or after the end of treatment with the investigational product), and the range of variation of the respective parameter within its reference range must be taken into consideration.

If, at the end of the treatment phase, there are abnormal clinical laboratory, vital sign, or ECG values that were not present in the pretreatment findings observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (e.g., concomitant disease) is found for the abnormal values.

The investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory, vital sign, or ECG parameter is clinically significant and therefore represents an AE.

8.1.6. Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period.

Any report of pregnancy for any female study participant or the partner of a male study participant must be reported within 24 hours to the Marinus Safety Department or its delegate using the Pregnancy Report Form. A copy of the Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the CRO/Marinus medical monitor using the details specified in the emergency contact information section at the beginning of the protocol. The pregnant female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days after delivery.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported as outlined in Section 8.2.2 of the protocol using the Marinus Clinical Study Serious Adverse Event Form. Non-serious AEs are to be reported as per clinical eCRF guidelines. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE to the Marinus Safety Department or delegate as outlined in Section 8.2.2 of the protocol using the Marinus Clinical Study Serious Adverse Event Form. The test date of the first positive serum/urine β-human chorionic gonadotropin test or ultrasound result will determine the pregnancy onset date.

8.1.7. Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error must be reported to the sponsor per the SAE reporting procedure whether or not it results in an AE/SAE as described in Section 8.2.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse**: Persistent or sporadic intentional intake of an investigational product for a nonmedical purpose (e.g., to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society.
- **Misuse:** Intentional use of an investigational product other than as directed or indicated at any dose. (Note: This includes a situation in which the investigational product is not used as directed at the dose prescribed by the protocol.)
- **Overdose:** Intentional or unintentional intake of a dose of an investigational product exceeding a prespecified total daily dose of the product.
- **Medication error:** An error made in prescribing, dispensing, administering, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

Medication errors should be collected and reported for the investigational product under investigation.

The administration and/or use of an expired investigational product should be considered as a reportable medication error.

All investigational product provided to pediatric subjects should be supervised by the parent/caregiver/LAR.

8.2. Serious Adverse Event Procedures

8.2.1. Reference Safety Information

The reference for safety information for this study is the GNX Investigator's Brochure, which the sponsor has provided under separate cover to all investigators.

8.2.2. Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Marinus Safety Department or its delegate *and* the CRO/Marinus medical monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless they result in an SAE.

The investigator must complete, sign, and date the Marinus Clinical Study Serious Adverse Event Form and verify the accuracy of the information recorded on the form with the

corresponding source documents (Note: Source documents are not to be sent unless requested) and fax or e-mail the form to the Marinus Safety Department or its delegate. A copy of the Marinus Clinical Study Serious Adverse Event Form (and any applicable follow-up reports) must also be sent to the CRO/Marinus medical monitor using the details specified in the emergency contact information section of the protocol.

8.2.3. Serious Adverse Event Definition

An SAE is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for preexisting conditions that have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, a complication resulting from a hospitalization for an elective or previously scheduled surgery that meets serious criteria must be reported as an SAE.
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAEs when, based on appropriate medical judgment, they 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.

8.2.4. Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the parent/caregiver/LAR signs the informed consent until the defined follow-up period stated and must be reported to the Marinus Safety Department *and* the CRO/Marinus medical monitor within 24 hours of the first awareness of the event.

In addition, any SAE considered "related" to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Marinus Safety Department within 24 hours of the first awareness of the event.

8.2.5. Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the date the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.6. Fatal Outcome

Any SAE that results in the subject's death (i.e., the SAE was noted as the primary cause of death) must have fatal checked as an outcome, with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another investigational product action was previously taken (e.g., the drug was interrupted, reduced, or withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received the investigational product). The investigational product action of "withdrawn" should not be selected solely as a result of the subject's death.

8.2.7. Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The sponsor is responsible for notifying the relevant regulatory authorities in the United States (US) and the CRO is responsible for notifying the relevant regulatory authorities in rest of world of related, unexpected SAEs.

In addition, the sponsor or the CRO is responsible for notifying active sites and central institutional review boards (IRBs) of all related, unexpected SAEs occurring during all interventional studies across the GNX program.

The investigator is responsible for notifying the local IRBs, local ethics committee (EC), or the relevant local regulatory authority of all SAEs that occur at their site as required.

8.3. Adverse Events of Special Interest

8.3.1. Reference Safety Information

The following represent the Adverse Events of Special Interest:

- Rash
- Adverse Events that would be classified under reproductive system and breast disorders system organ class

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1. Data Collection

The investigator's authorized site personnel must enter the information required by the protocol on the eCRF. A study monitor will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the eCRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is screened, it is expected that site personnel will complete the eCRF entry within approximately 7 business days of the subject's visit.

The subject's parent/caregiver/LAR must enter the information required by the protocol in the eDiary. A study monitor will review all seizure diary entries in accordance with the monitoring plan for completeness and accuracy. Discrepancies will be addressed by the subjects' parent/caregiver/LAR and qualified site personnel. When a data discrepancy warrants correction, the correction will be made by the subjects' parent/caregiver/LAR and authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once the subject's parent/caregiver/LAR signs informed consent, it is expected that all eDiary entries will be made daily and no longer than 48 hours after each day.

Telephone Follow-up visits are allowed to be conducted via secure email per institutional policy if granted by individual sites IRB/EC.

9.2. Clinical Data Management

Data will be entered into a clinical database as specified in the CRO data management plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database.

Data will be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections will be documented in an auditable manner.

9.3. Statistical Analysis Process

The study will be analyzed by the sponsor or its agent. The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information, such as subject disposition, demographics, and baseline characteristics; investigational product exposure; and prior and concomitant medications. The SAP will also include a description of how missing data will be addressed.

To preserve the integrity of the statistical analysis and study conclusions, the SAP will be finalized prior to database lock.

All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC 27513).

9.4. Data Monitoring Committee

The emerging study data will be reviewed on a regular basis by an independent Data Monitoring Committee (DMC). The mission of the DMC will be to safeguard the interests of study participants and to enhance the integrity and credibility of the trial. To enable the DMC to achieve their mission, the DMC will have ongoing access to unblinded efficacy and safety data and data regarding quality of trial conduct and will ensure the confidentiality of these data will be protected. A DMC charter will provide the principles and guidelines for the DMC process.

9.5. Sample Size Calculation and Power Considerations

Based on data from the 7 patients in Study 1042-0900 evaluating GNX in CDKL5 patients, the standard deviation for the percent change in 28-day seizure frequency for seizure types tonic (sustained motor activity ≥ 3 seconds), tonic-clonic, atonic/drop, epileptic spasms, or clonic (generalized or unilateral) is estimated to be 44.5. Therefore, when the percent change in 28-day seizure frequency on GNX minus that on PBO truly is 30%, then a trial with 100 subjects randomized in a 1:1 manner will have 92% power to detect this effect when using an analysis of variance (ANOVA) that preserves a (one-sided) 2.5% false positive error rate. (If the true difference in the percent changes is 35%, then the study will have 97.5% power.) The threshold for achieving statistical significance at the final analysis when 100 subjects have completed their 17-week double-blind treatment period would be achieved with an estimate of the difference that is approximately 17.5%. (The actual analysis will use a Wilcoxon rank-sum test, which has approximately the same power as the ANOVA.)

9.6. Study Population

The Safety and Intent to Treat (ITT) populations comprise all randomized subjects who received at least one dose of investigational product. In addition to being the population for the safety and ITT analyses, it is the primary population for the efficacy analyses and for the concomitant AED level and neurosteroid level analyses.

The Per-Protocol (PP) population consists of ITT subjects who received study drug for at least 6 weeks, provided at least 5 weeks of post-baseline seizure data, and had no major protocol violations (defined prior to database lock). A supportive analysis of the primary and secondary efficacy endpoints will be conducted in this population. There will be no PP population for the OL period of the study.

The results of the primary, secondary and exploratory endpoints in the double-blind and open-label phases will be summarized separately. In both phases, the results will be summarized by the double-blind treatment to which the subjects were randomized and, for the open-label phase of the study, combined over the treatment groups.

Subject demographics, characteristics, and medical history at randomization will be summarized using descriptive statistics.

9.7. Efficacy Analyses

All endpoints will be assessed descriptively, by the double-blind treatment to which the subjects are randomized, with point estimates and 95% confidence intervals. Only the primary endpoint will be assessed in an inferential manner since it is unlikely the trial will be powered to achieve statistical significance regarding effects on these measures.

9.7.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the percent change in 28-day primary seizure frequency through the end of the 17-week, double-blind treatment phase relative to the 6-week prospective baseline period. The primary seizure types include bilateral tonic (sustained motor activity ≥ 3 seconds), generalized tonic-clonic, bilateral clonic, atonic/drop seizures or focal to bilateral tonic-clonic.

The baseline, post-baseline, and arithmetic and percent changes from baseline in 28-day seizure frequency will be summarized using descriptive statistics. The difference between the treatment groups in the percent changes will be tested for statistical significance. Since the percent differences are anticipated to display skewness and/or outliers, the test will be performed using the Wilcoxon Rank-Sum statistic using a 2-sided significance level of 0.05.

Three sensitivity analyses of the primary efficacy endpoint will be performed (1) To examine the primary outcome measure when a subject stops recording measurements permanently prior to the end of the 17-week DB phase using the imputation approach outlined in the Statistical Analysis Plan, (2) to explore the possibility that subjects who stop recording seizure counts tend to have higher counts than other subjects, and (3) To examine the effect of GNX compared to PBO among subjects with low Allo-S levels.

9.7.2. Key Secondary Efficacy Endpoints

The key Secondary endpoints are:

- Number (%) of subjects with a ≥50% reduction from baseline in primary seizure frequency.
- Clinical Global Impression of Improvement (CGI-I) at the last scheduled visit in the 17-week DB treatment phase.

9.7.3. Secondary Efficacy Endpoints

In addition to evidence about effects of GNX on 28-day seizure frequency, the clinical trial will provide substantive insights about its effects on several secondary endpoints that capture important symptoms and activities of daily living that are meaningfully compromised by CDD. The seizure-related secondary endpoints, along with the primary endpoint, should be the most influential in the assessment of anti-epileptic efficacy. The behavioral/neuropsychiatric secondary endpoints will provide information about the overall impact of GNX compared with PBO on the treatment of subjects with CDD. The CGICA, CGI-C, CGI-CSID, and the CGI-I are all 7-point scales, and the number and percentage of subjects with each score will be summarized. The scores range from 1=very much improved to 7=very much worse.

Since the CGI-I at the last scheduled visit in the 17-week DB treatment phase has been identified as a key secondary endpoint, the score at the last visit in the 17-week DB treatment phase will be analyzed using ordinal logistic regression. Proportional odds modelling will be carried out by including treatment group as a factor. The estimated odds ratios (GNX vs. placebo), 95% CI for the odds ratios, and the p-value testing the null hypothesis that the odds ratio is equal to 1, will be presented.

Derived seizure secondary efficacy endpoints will be based on data through the end of the 17-week double-blind treatment period relative to the 6-week prospective baseline period.

9.7.3.1. Secondary Efficacy: Seizure control

- Change baseline in the percentage of seizure-free days during the 17-week DB treatment phase, based on the primary seizure types
- Caregiver Global Impression of Change in Seizure Intensity/Duration (CGI-CSID)

9.7.3.2. Secondary Efficacy: Behavioral/Neuropsychiatric

- Caregiver Global Impression of Change in Attention (CGICA) score
- CGI-C in parent/caregiver identified behavioral target- potential domains include sociability, communication, irritability and hyperactivity

[redacted]

9.7.5. Subgroup Analyses

The following subgroup summarizations of the primary efficacy parameter are planned as outlined in the Statistical Analysis Plan:

- Allo-S levels [(low (≤2.5 ng/mL), middle (> 2.5 ng/mL and < 6.0 ng/mL) or high (≥ 6.0 ng/mL)],
- Gender

Since there may be a potentially greater treatment effect among subjects with low Allo-S levels, the subgroup with low levels will be analyzed as a sensitivity analysis.

9.7.6. Analysis of Weeks 5 and 9

In order to explore the time course of GNX on non-seizure endpoints, the analyses of those endpoints will be repeated using the data from the scheduled Week 5 and Week 9 visits.

9.7.7. Sensitivity Analyses

Three sensitivity analyses of the primary efficacy endpoint will be performed for subjects who stop recording their seizure counts as outlined in the Statistical Analysis Plan:

- To examine the primary outcome measure when a subject stops recording measurements permanently prior to the end of the 17-week DB phase using the imputation approach outlined in the Statistical Analysis Plan.
- To explore the possibility that subjects who stop recording seizure counts tend to have higher counts than other subjects.
- To examine the effect of GNX compared to PBO among subjects with low Allo-S levels.

9.7.8. Open-Label Analyses

All the analyses for the double-blind phase will be repeated for the open-label phase, with the following differences:

- The results will be presented overall and also classified according to the double-blind treatment received by subjects.
- The post-baseline seizure endpoints will be derived starting from the first dosing day of OLE treatment
- The only sensitivity analysis to be performed is the analysis of the primary endpoint among subjects with low plasma allopregnanolone sulfate (Allo-S) levels.
- The seizure frequencies during the titration and maintenance phases will not be Analyzed separately
- The time points for the efficacy, exploratory, and quality of life endpoints will be at Weeks 21, 34, 52, and every 16 weeks thereafter of open-label treatment relative to the 6-week prospective baseline phase. For the seizure endpoints, this corresponds to the first 4, 17, 35, 51, etc. weeks from the start of the open-label phase
- The differences between the double-blind treatment groups in the percent changes from baseline of the 28-day seizure frequencies will not be tested for statistical significance.
- No PP analyses will be performed
- If a subject prematurely discontinues from the OLE phase, the EEG comparison to

  baseline at the Final OL/Taper Visit cannot be reassigned for analysis purposes since the EEG is performed only at that visit in the OLE phase; hence the tabulation at that visit will include all the subjects, regardless of whether they discontinued.(Taper Visit assessments among the subjects who prematurely discontinue from the DB phase are reassigned if possible; if they cannot be reassigned then they are not tabulated.)

9.8. Safety Analyses

All safety analyses will be performed in the Safety Population. The results in the double-blind and open-label phases will be summarized separately. In both phases, the results will be

summarized by the double-blind treatment actually received and, for the open-label phase of the study, combined over the treatment groups.

The number and percentage of days that subjects received investigational product, the highest percentage of the maximum allowable daily dose (1800 mg or 63 mg/kg) that subjects received, and the total amount of investigational product received will be summarized. The denominator for the percentage of days of study drug is the number of days in the phase. For the open-label phase, they will be summarized over just the open-label phase as well as over the entire study (combined DB and OL phases) but the classification by the double-blind treatment applies only for the open-label phase summary. The summarization over the entire study will include the double-blind data only from subjects who were in the GNX group during the double-blind phase, regardless of whether they entered the open-label phase, and all the subjects from the open-label phase.

A subject data listing will be provided with full details of the study drug dispensation.

Safety assessments include:

- AEs
- Clinical laboratory tests
- Vital signs including temperature, blood pressure, pulse rate, and weight
- 12-lead ECG
- Physical, neurological and developmental examinations
- Tanner staging (OL phase only)
- Concomitant AED levels (If available)

Detailed analysis and complete listings will be outlined in the SAP.

9.9. Other Analyses

Concomitant AED levels will be analyzed according to the SAP.

9.10. Pharmacokinetic Analyses

The PK population will include all subjects who have received at least 1 dose and who have had at least 1 sample collected and a valid bioanalytical result obtained. Four samples will be drawn between 1 and 5 hours or between 4 and 8 hours after the last dose, the remaining samples will be drawn without specific time constraints. Exact date and time of sample draw and drug intake will be recorded in the electronic case report form (eCRF). Pharmacokinetic analyses will be limited to listing of concentrations because sufficient concentration-time data will not be available for noncompartmental analyses such as Cmax, AUC or tmax. Pharmacokinetic data from this study may be used for a Population PK analyses to be conducted separately from this study and reported separately.

9.11. Interim Analysis

A formal interim analysis is planned, in addition to the final analysis, of treatment effect on the primary endpoint in accordance with the SAP.

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, European Union (EU) Directive 2001/20/EC and its updates, and local ethical and legal requirements.

The name and address of each third-party vendor (e.g., CRO) used in this study will be maintained in the investigators' and sponsor's files, as appropriate.

10.1. Sponsor's Responsibilities

10.1.1. Good Clinical Practice (GCP) Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH GCP Guideline E6 (1996), and EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, eDiaries/seizure calendars and eCRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

10.1.2. Public Posting of Study Information

The sponsor, or their designee, is responsible for posting appropriate study information on applicable websites such as ClinicalTrials.gov. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.3. Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance.

10.1.4. Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies, and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study that has been posted to a designated public website will be updated accordingly.

10.2. Investigator's Responsibilities

10.2.1. Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained personnel are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub-investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

A coordinating PI is appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the PI (single-site study) or coordinating PI (multicenter study), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

10.2.2. Protocol Adherence and Investigator Agreement

The investigator and any sub-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by international regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or, for multicenter studies, the coordinating PI according to national provisions and will be documented in the investigator agreement.

10.2.3. Documentation and Retention of Records

10.2.3.1. Electronic Case Report Forms (eCRF)

The eCRFs are supplied by the CRO and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. eCRFs must be completed by the investigator or designee as stated in the site delegation log.

All data will have separate source documentation; no data will be recorded directly onto the eCRF.

All data sent to the sponsor must be endorsed by the investigator.

The clinical research associate (CRA)/study monitor will review all data in accordance with the clinical monitoring plan. If the data are unclear or contradictory to source data, queries are sent for corrections or verification of data.

Incorrect entries must be crossed with a single line as to not obscure the original entry. Corrections must be made adjacent to the item to be altered, initialed, and dated by an authorized investigator or designee as stated in the site delegation log. Overwriting of this information or use of liquid correction fluid is not allowed.

10.2.3.2. Electronic Seizure Diaries (eDiary)

The eDiaries are supplied by the Sponsor designee and should be handled in accordance with instructions from the sponsor.

All data collected and sent to the sponsor must be endorsed by the investigator.

The CRA/study monitor will verify the contents of the eDiary data in accordance with the clinical monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.3.3. Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to, the subject's medical file, the subject's electronic or paper seizure diaries, and original clinical laboratory reports.

All key data must be recorded in the subject's medical records.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The CRA/study monitor (and auditors, IRB/EC, or regulatory inspectors) may check the eCRF entries against the source documents. The consent form includes a statement by which the subject agrees to allow the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC to have access to source data (e.g., subject's medical file, appointment books, original laboratory reports, EEGs, ECGs, etc.).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (e.g., the US Food and Drug Administration [FDA], European Medicines Agency [EMA], United Kingdom [UK] Medicines and Healthcare Products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.3.4. Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the UK Medicines and Healthcare Products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.3.5. Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries, such as a grant to fund ongoing research, compensation in the form of equipment, or retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; and any significant equity interest in the sponsor or subsidiaries as defined in 21 Code of Federal Regulations 54 2(b) (1998).

10.3. Ethical Considerations

10.3.1. Informed Consent

It is the responsibility of the investigator to obtain written informed consent from the subject's parent/LAR for all study subjects prior to any study-related procedures, including screening assessments. As the disease under consideration is a condition for which the subjects will not be capable of signing consent/assent for themselves, a parent/caregiver/LAR will be required to sign upon identification of the subject for participation.

All consent documentation must be in accordance with applicable regulations and GCP. Each subject's parent/ LAR, as applicable, is requested to sign and date the subject's informed consent form or a certified translation, if applicable, after they have received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (i.e., a complete set of subject information sheets and fully executed signature pages) must be given to the subject's parent/ LAR, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

Site personnel should document providing instruction for and understanding by the parent/ LAR of the safe, responsible storage and administration of the oral investigational product.

The PI provides the sponsor with a copy of the consent form that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the

study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (i.e., sponsor or coordinating PI) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2. Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information, and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the CRO has received written IRB/EC approval of and copies of revised documents.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC informed of the progress of the study and of any changes made to the protocol, but in any case at least once a year. This can be done by the sponsor or investigator for sites within the EU, or for multicenter studies, it can be done by the coordinating PI, according to national provisions. The investigator must also keep the local IRB/EC informed of any SAEs and significant AEs.

10.4. Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with Health Insurance Portability and Accountability Act (HIPAA) of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the CRO.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After the subject's parent/caregiver/LAR have consented to take part in the study, the sponsor and/or its representatives review the medical records and data collected during the study. These records and data may, in addition, be reviewed by others, including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market GNX; national or local regulatory authorities; and the IRB/EC that gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are each assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor in verifying the accuracy of the data (e.g., to confirm that laboratory results have been assigned to the correct subject).

The results of studies—containing subjects' unique identifying numbers, relevant medical records, and possibly initials and dates of birth—will be recorded. They may be transferred to, and used in, other countries that may not afford the same level of protection that applies within the countries where this study is conducted. The purposes of any such transfer would include to support regulatory submissions, to conduct new data analyses to publish or present the study results, and to answer questions asked by regulatory or health authorities.

10.5. Study Results/Publication Policy

Marinus will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Marinus adheres to external guidelines (e.g., Good Publication Practices 2) when forming a publication steering committee, which may be done for large, multicenter Phase 2 to 4 and certain other studies as determined by Marinus. The purpose of the publication steering committee is to act as a noncommercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Marinus products or projects must undergo appropriate technical and intellectual property review, with Marinus agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the PI will own (or share with other authors) the copyright on his/her publications. To the extent that the PI has such sole, joint, or shared rights, the PI grants the sponsor a perpetual, irrevocable, royalty-free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure, including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral, or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Marinus, the hospital and PI shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the

study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single-site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors current standards. Participation as an investigator does not confer any rights to authorship of publications.

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12. APPENDICES

12.1. Appendix 1: CYP3A4/5/7 Inhibitors and Inducers

Strong Inhibitors of CYP3A[a]	Strong Inducers of CYP3A[e]
boceprevir	rifampin[f]
clarithromycin[b]	St John's wort[f]
conivaptin[b]	
grapefruit juice[c]	
indinavir	
itraconazole[b]	
ketoconazole[b]	
lopinavir/ritonavir[b] (combination drug)	
mibefradil[d]	
nefazodone	
nelfinavir	
posaconazole	
ritonavir[b]	
saquinavir	
telaprevir	
telithromycin	
voriconazole	

a. A strong inhibitor for CYP3A is defined as an inhibitor that increases the AUC of a substrate for CYP3A by ≥ 5-fold.
b. In vivo inhibitor of P-glycoprotein.
c. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).
d. Withdrawn from the United States market because of safety reasons.
e. A strong inducer for CYP3A is defined as an inducer that results in ≥ 80% decrease in the AUC of a substrate for CYP3A.
f. In vivo inducer of P-glycoprotein.

Note: The list of drugs in these tables is not exhaustive. Any questions about drugs not on this list should be addressed to the medical monitor of the protocol.

Source: FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Web link Accessed 21 January 2015:
http://www fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664 htm#inVivo

12.2. Appendix 2: Clinical Laboratory Tests

Clinical Chemistry	**Hematology**	**Urinalysis**
Total Bilirubin	Hemoglobin	pH
AST (SGOT)[1]	Hematocrit	Color
ALT (SGPT)[2]	Erythrocytes	Clarity
BUN[3]	Leukocytes + differential	Specific Gravity
Glucose	Thrombocytes (platelet count)	Urobilinogen
Potassium		Ketones
Sodium		Protein
Calcium		Glucose
Alkaline Phosphatase		Bilirubin
Chloride		Blood
Creatinine		Leukocyte esterase
CO_2		Nitrite
eGFR[4]		
		Drug screen[5]
Quantitative serum β-human chorionic growth hormone (β-HCG) serum pregnancy		

[1]ALT = alanine aminotransferase
[2]AST = aspartate aminotransferase
[3]BUN = blood urea nitrogen
[4]eGFR = estimated glomerular filtration rate
[5]Urine or plasma drug screen for THC, CBD

12.3. Appendix 3: Dosing Instructions for Oral Suspension

GANAXOLONE 1042-CDD-3001 STUDY
DOSING INSTRUCTIONS FOR ORAL SUSPENSION
(DOUBLE-BLIND DOSE TITRATION, DOUBLE-BLIND AND OPEN-LABEL MAINTENACE AND TAPER)

Name: _____

Next Appointment: _____

These are your dosing instructions for Ganaxolone Oral Suspension from ____ / _____ / _____ (start date) to ____ / _____ / _____ (end date), until your next visit.

Take the study medication three times each day with a meal or snack, plus approximately 4 - 8 oz of water.

Example 1:

Dose Titration / Dose Maintenance / Dose Taper (Please circle phase)

For a 15 kg child, please dose the following

Date___/___/___ to Date ___/___/___	**Dose (mg/kg)**	**Number of mls to take at EACH DOSE x 3 TIMES/DAY**
9/23/18-9/29/18; Days 1-7	6	1.8
9/30/18-10/6/18; Days 8-14	11	3.3
10/7/18-10/13/18; Days 15-21	16	4.8
10/14/18-10/20/18; Days 22-28	21	6.3

Example 2:
For a 15 kg child, please dose the following

Dose Titration / Dose Maintenance / Dose Taper (Please circle phase)

Date___/___/___ to Date___/___/___	**Dose (mg/kg)**	**Number of mls to take at EACH DOSE x 3 TIMES/DAY**
10/21/18 to 1/20/19	21	6.3

Please take the study medication as outlined below:

Dose Titration / Dose Maintenance / Dose Taper (Please circle phase)

Date___/___/___ to Date___/___/___	**Dose (mg/kg)**	**Number of mls to take at EACH DOSE x 3 TIMES/DAY**

SHAKE THE BOTTLE WELL BEFORE DISPENSING

Prior to each dose, the following instructions should be followed:

1. Manually shake bottle end to end, 2-3 times per second, for 1 minute
2. Allow the bottle to stand for 1 minute
3. Attach the dosing apparatus (adaptor with syringe), invert the bottle and remove the indicated dose
4. Administer dose as indicated

Use the bottle adapter and dosing syringes provided. Do not use a household spoon. The syringe should be replaced daily and cleaned between each dose that day by rinsing for 30 seconds using hot water and

allowing it to air dry. The bottle adapter should stay in the bottle once it's inserted. It should not be removed.

Each dose should be separated by at least 4 hours and not more than 12 hours. An example schedule would be one dose at 8 am after breakfast, the next dose at 3 pm with a snack, and the third dose at 9 pm with a snack before bed.

If you forget one dose and there is less than 4 hours before the next dose, skip that dose.

If you miss two days of dosing or more, call the study doctor for instructions how to restart.

Do not consume alcohol, grapefruit or grapefruit juice, Seville oranges, or starfruits during the study because it could interact with the study medication.

Study medication should be stored at room temperature (59°F-77°F / 15°C-25°C) in a safe place.

Save all empty, partially used and unused bottles of the investigational product and return the bottles at your next visit.

Some people may report feeling dizzy or tired, or experiencing other problems after taking the study medication, ganaxolone. These side effects usually go away after 2 or 3 days. If you experience any side effects from the study medication that interfere with your daily activities or if you 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: _____

GANAXOLONE 1042-CDD-3001 STUDY
DOSING INSTRUCTIONS FOR ORAL SUSPENSION
(DOUBLE-BLIND TO OPEN-LABEL TRANSITION)

Name: _____

Next Appointment: _____

These are your dosing instructions for Ganaxolone Oral Suspension from ____ / _____ / _____ (start date) to ____ / _____ / _____ (end date), until your next visit.

Take the study medication three times each day with a meal or snack, plus approximately 4 - 8 oz of water.

Study Drug Group A and B Dosing Instructions: Transition to active study medication

Your child is receiving bottles to Study Drug Group A and B during the transition to active study medication. During the next few weeks, the dosage of Study Drug B will be increased. The dosage of Study Drug A will remain the same. The following items will be discussed below:

- Bottle numbers to Study Drug Group A and B
- The amount of Study Drug A and B to be given each day

Example 1:

For a 15 kg child, please dose the following

Date___/___/___ to Date ___/___/___	**Study Drug A** mls 3 times/day	**Study Drug B** mls 3 times/ day
9/23/18-9/29/18; Days 1-7	6.3	1.8
9/30/18-10/6/18; Days 8-14	6.3	3.3
Visit 6, Week 19	Safety visit and new set of Study Drug A and B bottles issued	
10/7/18-10/13/18; Days 15-21	6.3	4.8
10/14/18-10/20/18; Days 22-28	6.3	6.3

Please take the study medication as outlined below:

Study Drug Group Bottle A Number(s)_____

Study Drug Group Bottle B Number(s)_____

Date___/___/___ to Date___/___/___	**Study Drug A** mls 3 times/day	**Study Drug B** mls 3 times/ day

SHAKE THE BOTTLE WELL BEFORE DISPENSING.

Prior to each dose, the following instructions should be followed:

1. Manually shake bottle end to end, 2-3 times per second, for 1 minute
2. Allow the bottle to stand for 1 minute
3. Attach the dosing apparatus (adaptor with syringe), invert the bottle and remove the indicated dose
4. Administer dose as indicated

Use the bottle adapter and dosing syringes provided. Do not use a household spoon. The syringe should be replaced daily and cleaned between each dose that day by rinsing for 30 seconds using hot water and allowing it to air dry. The bottle adapter should stay in the bottle once it's inserted. It should not be removed.

Each dose should be separated by at least 4 hours and not more than 12 hours. An example schedule would be one dose at 8 am after breakfast, the next dose at 3 pm with a snack, and the third dose at 9 pm with a snack before bed.

If you forget one dose and there is less than 4 hours before the next dose, skip that dose.

If you miss two days of dosing or more, call the study doctor for instructions how to restart.

Do not consume alcohol, grapefruit or grapefruit juice, Seville oranges, or starfruits during the study because it could interact with the study medication.

Study medication should be stored at room temperature (59°F-77°F / 15°C-25°C) in a safe place.

Save all empty, partially used and unused bottles of the investigational product and return the bottles at your next visit.

Some people may report feeling dizzy or tired, or experiencing other problems after taking the study medication, ganaxolone. These side effects usually go away after 2 or 3 days. If you experience any side effects from the study medication that interfere with your daily activities or if you 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: Caregiver Global Impression of Change in Attention (CGICA)

Date:_____ Subject No:_____

Rater Initials:_____ Subject Initials:_____

Behavior that denotes attention: _____

Rate the change in attention after the start of investigational product. Please circle the appropriate number.

1. **Very much improved**
2. **Much improved**
3. **Minimally improved**
4. **No change**
5. **Minimally worse**
6. **Much worse**
7. **Very much worse**

12.5. Appendix 5: Caregiver Global Impression of Change (CGI-C) – Target Behavior

Date:_____ Subject No:_____

Rater Initials:_____ Subject Initials:_____

Choose one from the following domains (please circle): sociability, communication, irritability, hyperactivity

Behavior that denotes target domain: _____

Rate the change in target domain after the start of investigational product. Please circle the appropriate number.

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: Caregiver Global Impression of Change in Seizure Intensity/Duration (CGI-CSID)

Date:_____ Subject No:_____

Rater Initials:_____ Subject Initials:_____

Rate the change in seizure intensity and/or duration after the start of investigational product. Please circle the appropriate number.

1. **Very much improved**
2. **Much improved**
3. **Minimally improved**
4. **No change**
5. **Minimally worse**
6. **Much worse**
7. **Very much worse**

12.7. Appendix 7: Clinical Global Impression - Improvement (CGI-I)

For the Clinician:

Date:_____ Subject No:_____

Rater Initials:_____ Subject Initials:_____

Rate the overall global impression of change after the start of investigational product relative to baseline (prior to investigational product). Please circle the appropriate number.

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) for the Caregiver

Date:_____ Subject No:_____

Rater Initials:_____ Subject Initials:_____

Rate the overall global impression of change after the start of investigational product relative to baseline (prior to investigational product). Please circle the appropriate number.

1. **Very much improved**
2. **Much improved**
3. **Minimally improved**
4. **No change**
5. **Minimally worse**
6. **Much worse**
7. **Very much worse**

12.8. Appendix 8: Children's Sleep Habit Questionnaire (CSHQ)

Child's Sleep Habits
(Preschool and School-Aged)
(Abbreviated Version)

_____
Coding

The following statements are about your child's sleep habits and possible difficulties with sleep. Think about the past week in your child's life when answering the questions. If last week was unusual for a specific reason (such as your child had an ear infection and did not sleep well or the TV set was broken), choose the most recent typical week. Answer USUALLY if some hing occurs **5 or more times** in a week; answer SOMETIMES if it occurs **2-4 times** in a week; answer RARELY if something occurs **never or 1 time** during a week. Also, please indicate whether or not the sleep habit is a problem by circling "Yes," "No," or "Not applicable (N/A)".

Bedtime

Write in child's bed ime: _____

	3 Usually (5-7)	2 Sometimes (2-4)	1 Rarely (0-1)	Problem?		
1) Child goes to bed at the same time at night **(R)**	☐	☐	☐	Yes	No	N/A
2) Child falls asleep within 20 minutes after going to bed **(R)**	☐	☐	☐	Yes	No	N/A
3) Child falls asleep alone in own bed **(R)**	☐	☐	☐	Yes	No	N/A
4) Child falls asleep in parent's or sibling's bed	☐	☐	☐	Yes	No	N/A
5) Child needs parent in the room to fall asleep	☐	☐	☐	Yes	No	N/A
6) Child struggles at bedtime (cries, refuses to stay in bed, etc.)	☐	☐	☐	Yes	No	N/A
7) Child is afraid of sleeping in he dark	☐	☐	☐	Yes	No	N/A
8) Child is afraid of sleep alone	☐	☐	☐	Yes	No	N/A

Sleep Behavior

Child's usual amount of sleep each day: _____ hours and _____ minutes
(combining nighttime sleep and naps)

	3 Usually (5-7)	2 Sometimes (2-4)	1 Rarely (0-1)	Problem?		
9) Child sleeps too little	☐	☐	☐	Yes	No	N/A
10) Child sleeps the right amount **(R)**	☐	☐	☐	Yes	No	N/A
11) Child sleeps about the same amount each day **(R)**	☐	☐	☐	Yes	No	N/A
12) Child wets the bed at night	☐	☐	☐	Yes	No	N/A
13) Child talks during sleep	☐	☐	☐	Yes	No	N/A
14) Child is restless and moves a lot during sleep	☐	☐	☐	Yes	No	N/A
15) Child sleepwalks during he night	☐	☐	☐	Yes	No	N/A
16) Child moves to someone else's bed during he night (parent, brother, sister, etc)	☐	☐	☐	Yes	No	N/A
17) Child grinds teeth during sleep (your dentist may have told you this)	☐	☐	☐	Yes	No	N/A
18) Child snores loudly	☐	☐	☐	Yes	No	N/A

CSHQ Abbreviated

Coding

Sleep Behavior (continued)

	3 Usually (5-7)	2 Sometimes (2-4)	1 Rarely (0-1)	Problem?		
19) Child seems to stop breathing during sleep	☐	☐	☐	Yes	No	N/A
20) Child snorts and/or gasps during sleep	☐	☐	☐	Yes	No	N/A
21) Child has trouble sleeping away from home (visiting relatives, vacation)	☐	☐	☐	Yes	No	N/A
22) Child awakens during night screaming, sweating, and inconsolable	☐	☐	☐	Yes	No	N/A
23) Child awakens alarmed by a frightening dream	☐	☐	☐	Yes	No	N/A

Waking During the Night

	3 Usually (5-7)	2 Sometimes (2-4)	1 Rarely (0-1)	Problem?		
24) Child awakes once during the night	☐	☐	☐	Yes	No	N/A
25) Child awakes more than once during the night	☐	☐	☐	Yes	No	N/A

Write he number of minutes a night waking usually lasts: _____

Morning Waking/Daytime Sleepiness

Write in the time of day child usually wakes in the morning: _____

	3 Usually (5-7)	2 Sometimes (2-4)	1 Rarely (0-1)	Problem?		
26) Child wakes up by him/herself **(R)**	☐	☐	☐	Yes	No	N/A
27) Child wakes up in negative mood	☐	☐	☐	Yes	No	N/A
28) Adults or siblings wake up child	☐	☐	☐	Yes	No	N/A
29) Child has difficulty getting out of bed in the morning	☐	☐	☐	Yes	No	N/A
30) Child takes a long time to become alert in the morning	☐	☐	☐	Yes	No	N/A
31) Child seems tired	☐	☐	☐	Yes	No	N/A

Child has appeared very sleepy or fallen asleep during the following (check all that apply):

	1 Not Sleepy	2 Very Sleepy	3 Falls Asleep
32) Watching TV	☐	☐	☐
33) Riding in car	☐	☐	☐

12.9. Appendix 9: Anxiety, Depression, and Mood Scale (ADAMS) - Baseline

Instructions

The Anxiety Depression and Mood Scale (ADAMS) contains a list of behaviors that can be found among individuals with intellectual disability. Please describe the individual's behavior over the last 6 months

0 behavior has not occurred, or is not a problem
1 behavior occurs occasionally, or is a mild problem
2 behavior occurs quite often, or is a moderate problem
3 behavior occurs a lot, or is a severe problem

		not a problem	mild problem	moderate problem	severe problem
1.	Nervous	0	1	2	3
2.	Problems initiating communication	0	1	2	3
3.	Does not relax or settle down	0	1	2	3
4.	Has periods of over-activity	0	1	2	3
5.	Sleeps more than normal	0	1	2	3
6.	Withdraws from other people	0	1	2	3
7.	Tense	0	1	2	3
8.	Engages in ritualistic behaviors	0	1	2	3
9.	Depressed mood	0	1	2	3
10.	Sad	0	1	2	3
11.	Worried	0	1	2	3
12.	Has developed difficulty staying on task or completing work	0	1	2	3
13.	Shy	0	1	2	3
14.	Easily fatigued (not due to being overweight)	0	1	2	3
15.	Anxious	0	1	2	3
16.	Repeatedly checks items	0	1	2	3
17.	Easily distracted	0	1	2	3
18.	Lacks energy	0	1	2	3
19.	Avoids others, spends much of time alone	0	1	2	3
20.	Easily upset if ritualistic behaviors are interrupted	0	1	2	3
21.	Lacks emotional facial expressions	0	1	2	3
22.	Has shown difficulty in starting routine tasks	0	1	2	3
23.	Listless	0	1	2	3
24.	Experiences panic attacks	0	1	2	3
25.	Avoids eye contact	0	1	2	3
26.	Trembles when frightening situations are not present	0	1	2	3
27.	Avoids peers	0	1	2	3
28.	Tearful	0	1	2	3

12.10. Appendix 10: Anxiety, Depression, and Mood Scale (ADAMS) – Post Baseline Visits

Instructions

The Anxiety Depression and Mood Scale (ADAMS) contains a list of behaviors that can be found among individuals with intellectual disability. Please describe the individual's behavior since the last visit (post-baseline visits).

4 behavior has not occurred, or is not a problem
5 behavior occurs occasionally, or is a mild problem
6 behavior occurs quite often, or is a moderate problem
7 behavior occurs a lot, or is a severe problem

		not a problem	mild problem	moderate problem	severe problem
1.	Nervous	0	1	2	3
2.	Problems initiating communication	0	1	2	3
3.	Does not relax or settle down	0	1	2	3
4.	Has periods of over-activity	0	1	2	3
5.	Sleeps more than normal	0	1	2	3
6.	Withdraws from other people	0	1	2	3
7.	Tense	0	1	2	3
8.	Engages in ritualistic behaviors	0	1	2	3
9.	Depressed mood	0	1	2	3
10.	Sad	0	1	2	3
11.	Worried	0	1	2	3
12.	Has developed difficulty staying on task or completing work	0	1	2	3
13.	Shy	0	1	2	3
14.	Easily fatigued (not due to being overweight)	0	1	2	3
15.	Anxious	0	1	2	3
16.	Repeatedly checks items	0	1	2	3
17.	Easily distracted	0	1	2	3
18.	Lacks energy	0	1	2	3
19.	Avoids others, spends much of time alone	0	1	2	3
20.	Easily upset if ritualistic behaviors are interrupted	0	1	2	3
21.	Lacks emotional facial expressions	0	1	2	3
22.	Has shown difficulty in starting routine tasks	0	1	2	3
23.	Listless	0	1	2	3
24.	Experiences panic attacks	0	1	2	3
25.	Avoids eye contact	0	1	2	3
26.	Trembles when frightening situations are not present	0	1	2	3
27.	Avoids peers	0	1	2	3
28.	Tearful	0	1	2	3

12.11. Appendix 11: Quality of Life Inventory – Disability (QI-Disability)

Quality of Life Inventory-Disability (QI-Disability)
Questionnaire for children and adolescents
Parent Version

These questions are about your child's life over the past month. We would like to know how you observe your child respond to a range of life experiences.

There are no right or wrong answers - please provide your best answers for your child.

For each question, please reflect on your observations of your child's well-being and enjoyment of life over the past month.

Health and well-being

Over the past month, how often has your child…	Never	Rarely	Sometimes	Often	Very often
1. Had enough energy to participate in daily routines and activities	☐	☐	☐	☐	☐
2. Kept in good general health (e.g. avoided coughs, colds, fever)	☐	☐	☐	☐	☐
3. Slept well during the night	☐	☐	☐	☐	☐
4. Been alert and aware during the day	☐	☐	☐	☐	☐

Feelings and emotions

Over the past month, how often has your child…	Never	Rarely	Sometimes	Often	Very often
5. Been in a good mood	☐	☐	☐	☐	☐
6. Smiled or brightened their facial expression	☐	☐	☐	☐	☐
7. Showed happiness through body language (e.g. making eye contact, body facing others)	☐	☐	☐	☐	☐
8. Showed cheeky or comical mannerisms (e.g. laughed, giggled)	☐	☐	☐	☐	☐
9. Been unsettled without an apparent reason	☐	☐	☐	☐	☐
10. Showed aggression (e.g. hitting, kicking, using offensive language, being destructive)	☐	☐	☐	☐	☐
11. Appeared upset or angry (e.g. crying, screaming, moving or stiffening the body)	☐	☐	☐	☐	☐
12. Become withdrawn with a low mood	☐	☐	☐	☐	☐
13. Deliberately hurt themselves	☐	☐	☐	☐	☐
14. Expressed discomfort with changes in routine (e.g. carers, school, respite, out-of-home care)	☐	☐	☐	☐	☐
15. Showed signs of being anxious or agitated (e.g. teeth grinding, fast breathing, avoidance)	☐	☐	☐	☐	☐

Family and friends

Over the past month, how often has your child…	Never	Rarely	Sometimes	Often	Very often
16. Expressed happiness when they were understood	☐	☐	☐	☐	☐
17. Appeared relaxed when making eye contact	☐	☐	☐	☐	☐
18. Initiated greetings with people verbally or nonverbally (e.g. eye contact)	☐	☐	☐	☐	☐
19. Enjoyed being included	☐	☐	☐	☐	☐
20. Enjoyed the social experiences of meal times	☐	☐	☐	☐	☐
21. Responded positively when others paid attention to them (e.g. your child smiled, showed interest)	☐	☐	☐	☐	☐
22. Showed pleasure or excitement when looking forward to activities (e.g. going to school, outings, events)	☐	☐	☐	☐	☐

Activities and the outdoors

Over the past month, how often has your child…	Never	Rarely	Sometimes	Often	Very often
23. Enjoyed moving their body (e.g. crawling, walking, swinging, swimming)	☐	☐	☐	☐	☐
24. Enjoyed feeling steady or stable during physical activities (e.g. sitting, standing, bike riding)	☐	☐	☐	☐	☐
25. Enjoyed physical activities (e.g. going out for a walk, swimming, swinging, dancing)	☐	☐	☐	☐	☐
26. Enjoyed going on outings in the community (e.g. shopping, party, sports, theatre)	☐	☐	☐	☐	☐

27. Enjoyed spending time outdoors (e.g. contact with water, grass, wind, sunshine)	☐	☐	☐	☐	☐

Daily life

Over the past month, how often has your child…	Never	Rarely	Sometimes	Often	Very often
28. Expressed their needs (e.g. hunger, thirst, toileting)	☐	☐	☐	☐	☐
29. Made their own choices for activities or things they enjoy (e.g. DVDs, toys)	☐	☐	☐	☐	☐
30. Helped to complete routine activities (e.g. dressing, feeding)	☐	☐	☐	☐	☐
31. Enjoyed making things with their hands – can be with help (e.g. building blocks, painting, cooking)	☐	☐	☐	☐	☐
32. Enjoyed using technology (e.g. computer, tablet, applications on phones)	☐	☐	☐	☐	☐

Comments: _____

_____

_____

_____

_____

_____

12.12. Appendix 12: Parenting Stress Index (PSI)

Tool 1: Parental Stress Scale (questionnaire attached)

Component being measured:

- Attempts to measure the levels of stress experienced by parents.
- Takes into account positive and negative aspects of parenting.

Why this outcome matters?

Higher levels of parental stress related to:

- Lower levels of parental sensitivity to the child
- Poorer child behaviour
- Lower quality of parent – child relationship.

In particular, provides evidence related to Children's Centres work to 'improve parenting' and Core Purpose goal of 'improving parenting skills'

Tool details:

- Developed by Berry and Jones (1995) as an alternative to the 101-item Parenting Stress Index.
- Provides a measure that considers positive aspects of parenting as well as the negative, 'stressful' aspects traditionally focused on.

Format of the tool:

- 18 – item self report scale – items represent positive (e.g. emotional benefits, personal development) and negative (demands on resources, restrictions) themes of parenthood.
- Respondents agree or disagree in terms of their typical relationship with their child or children
- 5 – Point scale; strongly disagree, disagree, undecided, agree, strongly agree.

Use of the tool:

What can the tool help to assess?

- Changes in parental stress levels for parents/carers who have accessed targeted support, such as family support, parenting courses and one to one parenting support.
- The outcomes of services or areas of work focused on improving parents/carers parenting capacity.

Practical administration:

- Self completion or could be administered as an interview.
- The scale is relatively short and easy to administer – can be completed in less than 10 minutes.
- Can be used as a before and after measure.

Scoring the tool :
We want a low score to signify a low level of stress, and a high score to signify a high level of stress.

Parental Stress Scale

The following statements describe feelings and perceptions about the experience of being a parent. Think of each of the items in terms of how your relationship with your child or children typically is. Please indicate the degree to which you agree or disagree with the following items by placing the appropriate number in the space provided.

1 = Strongly disagree 2 = Disagree 3 = Undecided 4 = Agree 5 = Strongly agree

1	I am happy in my role as a parent	
2	There is little or nothing I wouldn't do for my child(ren) if it was necessary.	
3	Caring for my child(ren) sometimes takes more time and energy than I have to give.	
4	I sometimes worry whether I am doing enough for my child(ren).	
5	I feel close to my child(ren).	
6	I enjoy spending time with my child(ren).	
7	My child(ren) is an important source of affection for me.	
8	. Having child(ren) gives me a more certain and optimistic view for the future.	
9	The major source of stress in my life is my child(ren).	
10	Having child(ren) leaves little time and flexibility in my life.	
11	Having child(ren) has been a financial burden.	
12	. It is difficult to balance different responsibilities because of my child(ren).	
13	The behaviour of my child(ren) is often embarrassing or stressful to me.	

Range of Validated quantitative tools and scales that can be used to measure the outcomes of children's centre work 2013 2

14	. If I had it to do over again, I might decide not to have child(ren).	
15	I feel overwhelmed by the responsibility of being a parent.	
16	Having child(ren) has meant having too few choices and too little control over my life.	
17	I am satisfied as a parent	
18	I find my child(ren) enjoyable	

APPENDIX 13 - PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific	
Original Protocol	08 Jun 2018	Global version 1.0	
Original Protocol	30 Aug 2018	UK version 1.1	
Original Protocol	11 Nov 2018	DE version 1.2	
	Protocol Amendment 1.0	05 May2019	Global Amendment 1.0
	Protocol Amendment 1.0	09 Sep 2019	IT version 1.1
	Protocol Amendment 1.0	31 Oct 2019	FR Version 1.2
	Protocol Amendment 2.0	26 May 2020	Global Amendment 2.0