PROTOCOL: 1042-PCDH19-3002

TITLE:	A double-blind, randomized, placebo-controlled trial of adjunctive ganaxolone treatment in female children with protocadherin 19 (PCDH19)-related epilepsy followed by long-term open-label treatment
DRUG:	Ganaxolone
IND:	044020
EUDRACT NO.:	2018-004496-12
SPONSOR:	Marinus Pharmaceuticals, Inc. 5 Radnor Corporate Center, 100 Matsonford Road, Suite 500 Radnor, PA 19087 USA
PRINCIPAL/ COORDINATING INVESTIGATOR:	
PROTOCOL HISTORY:	Protocol Amendment 5: 20 January 2021: Version 6.0 Protocol Amendment 4: 30 June 2020: Version 5.0 Protocol Amendment 3: 16 August 2019: Version 4.0 Protocol Amendment 2: 01 July 2019: Version 3.0 Protocol Amendment 1: 05 March 2019: Version 2.0 Original Protocol: 06 February 2019: Version 1.0

PROTOCOL SIGNATURE PAGE

Sponsor's Approval

Signature: [redacted]	**Date:** January 25, 2021 | 9:07 AM PST
[redacted] **MD, PhD** **Marinus Pharmaceuticals** [redacted], **Clinical Development**	

Investigator's Acknowledgement

I have read this protocol for Marinus Study 1042-PCDH19-3002.

Title: A double-blind, randomized, placebo-controlled trial of adjunctive ganaxolone treatment in female children with protocadherin 19 (PCDH19)-related epilepsy 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.

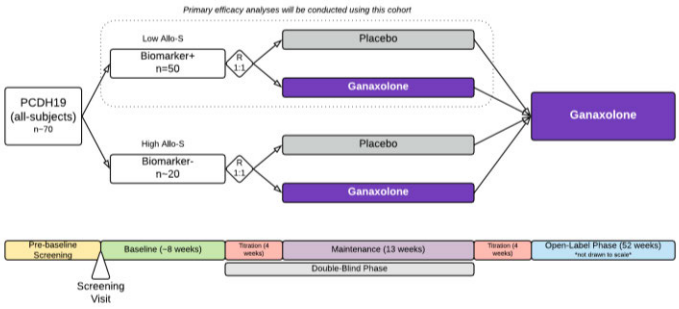
Investigator Name and Institution Name and Address: (please hand print or type)	

Signature: _____ **Date:** _____

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **05 March 2019**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
Updated to redefine the primary seizure types used to determine patient eligibility and conduct the primary/secondary endpoint analyses		Synopsis, Sections 4.1, 7.3.6, 7.4.1, 9.13.1.2, and 9.13.1.4
Added watermark to BRIEF scale		Section 12.5 (Appendix 5)
Amendment Number **2**	**Amendment Date** **01 July 2019**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
Removed CRO Contacts section.		CRO Contacts and Section 6.3
Added Table 5 and Table 6 to the List of Tables.		List of Tables
Revised: Updated from 30 to **50** total biomarker-positive subjects		Synopsis (Number of subjects, Methodology), Section 3.1
Revised: Updated total enrollment from *50-70* to **approximately 70 subjects**		Synopsis (Number of subjects, Methodology), Section 3.1
Updated total number of sites up to **45** sites		Study Synopsis (Sites and Regions) Section 3.3
Revised: **12**-week historical		Synopsis (Methodology), Section 3.1, 3.2, 4.1, 7.2.1.1, 7.3, 7.3.4, 9.7, Table 1 Footnote c
Revised: **Acceptable historical seizure data must include at least 12 consecutive weeks prior to the Screening visit of documenting seizure type and frequency (also noting seizure-free days).** *Removed: Acceptable historical seizure data must include seizure type, frequency, and denote seizure free days, with the historical seizure calendar starting at Week-16 (8-week historical [pre-baseline screen] + 8-week prospective [baseline] = 16 weeks).*		Synopsis (Methodology) and Section 3.1
Added: treatment of **primary** seizure **types**		Study Synopsis (Objectives)

Added: treatment of **primary** seizure	Study Synopsis (Objectives) & Section 2.2.1
Revised: To assess changes in other types of seizures **(non-primary)** in PCDH19	Synopsis (Objectives), Section 2.2.3
Revised: • was a decrease of **25**% (n = 11). • had a **50**% reduction in seizure • had a **84**% increase • there were **4** SAEs (**3** related to seizures and 1 related to rash)	Synopsis (Rationale), Section 2.1
Replaced "patient(s)" with "**subject(s)"** for consistency	Throughout entire document
Revised: Based on the **completed** 11-subject *(Removed: OL study)* **1042-0900 Phase 2a study**, it is estimated that approximately 65% of all subjects will be biomarker-positive.	Synopsis (Methodology), Section 3.1
Revised: *(Removed "If available")*, **A** 12-week daily historical	Synopsis (Methodology, Rationale), Section 3.1,
Revised: seizure calendar **or genetic testing has not been performed** **Revised:** historical seizure calendar **and/or genetic testing has been completed**	Synopsis (Methodology)
Revised: To assess the long-term efficacy *(Removed: safety, and tolerability)* of GNX when administered as adjunctive therapy throughout the open-label phase**s**. **Added: To assess the long-term safety and tolerability of GNX when administered as adjunctive therapy throughout the open-label phases.**	Synopsis (Objectives) and Section 2.2.2
Revised: To assess behavioral/neuropsychiatric changes in subjects receiving GNX compared with subjects receiving PBO as adjunctive therapy at the end of the 17-week DB phase *(Removed: using objective scales such as Behavior Rating Inventory of Executive Function (BRIEF), Aberrant Behavior Checklist–Community (ABC-C), and Children's Sleep Habit Questionnaire (CSHQ)).*	Synopsis (Objectives) and Section 2.2.2
Revised: A minimum dose of 33 mg/kg/day or 900 mg/day is **generally** required **following the escalation period** during the double-blind phase **unless a lower dose is agreed to with the sponsor due to tolerability issues such as somnolence.** 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. **However, the final decision to adjust drug dosages lies with the PI.**	Synopsis (Methodology and Investigational product, dose, and mode of administration), Section 3.1, 3.4 and 6.2.3
Revised: **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.** *(Remove: Any subject who is unable to be maintained at the minimum dose should contact the sponsor to discuss continued IP dosing.)*	Synopsis (Investigational product, dose, and mode of administration) and Section 3.4
Revised: Subjects who discontinue investigational product should undergo a 2-week taper period**, unless otherwise medically indicated**	Synopsis (Methodology, Duration of Treatment) Section 3.1, 3.2, 3.4, and 4.5

Revised: Subjects who discontinue investigational product treatment before the completion of the DB phase will continue to be followed per protocol and, at a minimum, **subjects will be encouraged to maintain daily seizure eDiary entries until the DB phase is completed.**	Synopsis (Methodology, Investigational product, dose, and mode of administration, and Duration of Treatment) Section 3.1, 3.2, 3.4, 4.5, and 4.5.1
 Figure was revised to remove enrollment numbers.	Synopsis (Methodology) and Section 3.1
Revised: Participants will be required to complete an eDiary to determine GNX's effect on *(removed "drug resistant")* seizures.	Synopsis (Methodology)
Revised Inclusion Criteria # 5 – Have at least **12** *(Removed: 4)* countable/witnessed primary seizures **over an 84 day (12 week)** *(Removed: per 28 days (average) over an 8 week)* period prior to the screening visit (pre-baseline screening).	Synopsis (Inclusion Criteria), Section 4.1
Revised Inclusion Criteria # 10 – Parent/caregiver is able and willing to maintain an accurate and complete daily *(remove "electronic")* seizure diary	Synopsis (Inclusion Criteria), Section 3.1, 4.1, 10.2.3.2,
Revised Inclusion Criteria # 11 - or adequate barrier methods (eg, diaphragm or **condom** and foam)	Synopsis (Inclusion Criteria), Section 4.1
Removed Exclusion Criteria #3 - Known historical seizure frequency pattern that is highly variable with long remission periods per PI's medical judgment.	Synopsis (Exclusion Criteria), Section 4.2
Revised: Exclusion Criteria #4 (now #3) - Subjects with >6 consecutive weeks (42 consecutive days) of primary seizure freedom during the 12-week pre-baseline screening period	Synopsis (Exclusion Criteria), Section 4.2, 5.4
Revised Exclusion Criteria #5 - Subjects with a positive result on tetrahydrocannabinol (THC) or non-**approved** cannabidiol (CBD) test (*(Removed: urine or)* via plasma drug screen) *(Removed: at the screening visit). (Removed: or a positive result on THC or non-regulated CBD test (via urine or plasma) at the baseline visit will be excluded from the study)*	Synopsis (Exclusion Criteria), Section 4.2
There will be no urine drug screens, all drug tests will be plasma. **Revised**: (*(Removed: via urine or)* plasma drug screen)	Synopsis (Exclusion Criteria), Section 4.2, Table 1 footnote,
Updated non-regulated **to non-approved**	Synopsis (Exclusion Criteria), Section 4.2, 5.4
Revised Exclusion Criteria #14- Unwillingness to withhold grapefruit, Seville oranges, star fruit, **or grapefruit containing products from diet at least 14 days prior to 1st dose and for the duration of the study.**	Synopsis (Exclusion Criteria), Section 4.2, 4.3, 6.4

Added table for Oral Suspension (50 mg/ml) Dosing for Subjects Weighing ≤ 28 kg and Oral Suspension (50 mg/ml) Dosing for Subjects Weighing > 28 kg	Synopsis (Investigational product, dose, and mode of administration)
Revised table title: **Oral Suspension** Dosing[a] for Subjects Weighing ≤ 28 kg (62 pounds) [b] and **Oral Suspension** Dosing[a] for Subjects Weighing > 28 kg (62 pounds)[c]	Synopsis (Investigational product, dose, and mode of administration)
Revised: while subjects randomized to GNX will stay on 63 mg/kg/day suspension **(1800 mg/day maximum),**	Synopsis (Duration of treatment), 6.2.3.1
Revised: Placebo is to be administered as an oral suspension **TID** with food during the 4-week, titration period of the DB phase of the study. *Removed: as follows: PBO TID suspension Days 1-7/ PBO TID suspension Days 8-14/ PBO TID suspension Days 15-21/ PBO TID suspension Days 22-28.*	Synopsis (Reference Therapy, Dose, and Mode of Administration)
Removed: Post-baseline 28-day seizure frequency will be calculated as the total number of seizures in the 17-week DB treatment phase divided by the number of days with seizure data, observed or imputed, in the phase, multiplied by 28. Baseline 28-day seizure frequency will be calculated as the total number of seizures in the baseline phase divided by the number of days with seizure data in the phase, multiplied by 28. **Replaced with: Post-baseline 28-day seizure frequency will be calculated as the total number of seizures in the 17-week DB treatment phase divided by the number of days with seizure data in the phase, multiplied by 28. Baseline 28-day seizure frequency will be calculated as the total number of seizures in the baseline phase divided by the number of days with seizure data in the phase, multiplied by 28. If a subject experiences no primary seizures during the baseline phase then the 28-day seizure frequency in the baseline phase will be set to 0.5, equivalent to having 1 seizure during the phase, and 0.5 will be added to the 28-day seizure frequency in the post-baseline phase.**	Synopsis (Primary Endpoint, Statistical Methods), Section 9.13.1.2
Revised: The difference between the *(removed "ganaxolone")* GNX and placebo groups in the percent changes within each stratum will be tested using the Wilcoxon Rank-Sum statistic.	Synopsis (Primary Endpoint), Section 9.13.1.2,
Revised Secondary endpoints: • Moved: "Arithmetic change in percentage of seizure-free days, based on all countable focal seizures that include progressive hypotonia and impaired awareness, or any countable focal or generalized seizure with a clear motor component." **from a secondary endpoint to an exploratory endpoint** • **Added: Percentage of subjects experiencing a ≥ 50% reduction in 28-day primary seizure frequency compared to the 8-week baseline**	Synopsis (Secondary endpoints), Section 9.13.1.3.1.1
Removed: Additional time points will be analyzed including but not limited to Week 34 and the end of the OL phase.	Synopsis (Exploratory Endpoints, Statistical Methods), Section 9.13.1.4

Revised Exploratory Endpoints: [redacted]	Synopsis (Exploratory Endpoints, Statistical Methods), Section 9.13.1.4
Revised: With few exceptions, all of the analyses for the DB phase *(Removed: except for seizure frequencies during the titration and maintenance phases)* will be repeated for the OL phase **with the following differences**.	Synopsis (Statistical Methods) and Section 9.13.1.4
Revised: For all other PK draws, there is no specified time to draw the PK sample and can be drawn when convenient during the study visits **for Visit 5 (Week 17), Visit 7 (Week 36), Visit 9 (Week 68), and every 16 weeks for the duration of the open-label phase.** **Added** to 7.7.: **Exact time of sample withdrawal and drug intake will be recorded in the electronic case report form (eCRF).**	Synopsis (Pharmacokinetic Assessments), Section 7.7
Removed: sufficiently complete concentration-time data. The following GNX plasma PK parameters will be calculated as data allows and as appropriate using noncompartmental approaches. • *Maximum plasma concentration (C_{max})* • *Time of maximum concentration (t_{max})* • *Area under the concentration versus time curve from time 0 to t hours (AUC_t)* • *Area under the concentration versus time curve from time 0 to infinity (AUC_∞)* • *Clearance (CL). Calculated as dose/AUC_∞* • *Additional parameters may be calculated at the discretion of the pharmacokineticist, pending review of the data.* **Added**: The PK population will include all subjects who have received at least 1 dose of IP and who **have had at least 1 sample collected and a valid bioanalytical result obtained. The samples will be drawn between 1 and 5 hours or between 4 and 8 hours after the last dose during the double-blind and open label periods. Pharmacokinetic analyses will be limited to listing of concentrations because sufficient concentration-time data will not be available**	Synopsis (Pharmacokinetic Assessments), Section 9.15

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.	
Removed: Except for the exploratory endpoints of seizure frequency within the titration and maintenance phases of the DB phase, derived seizure exploratory endpoints will be based on data through the end of the 17-week DB phase relative to the 8-week prospective baseline period.	Synopsis (Statistical Methods)
Revised: Visit 3 (Week 5): between **1** and **5** hours since the last investigational product dosing **Added**: Visit 6 (Week 21): **between 1 and 5 hours since the last investigational product dosing** Visit 8 (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 visits.**	Synopsis (Pharmacokinetic Analysis), Section 7.7
Added: 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.**	Synopsis (Interim Analysis)
Table 1, Schedule of Assessments for the 17-Week, Double Blind has been updated: Changed the Table header to state Double-blind **Treatment** Phase of the study *Removed (Pre-baseline Screening Visit) week range to -20 to -9* **Added** the visit window of + 6 days for Day 0 (Baseline -Randomization) **Added** an additional Phone Follow – up Visit on Day 3 with visit window of +/- 1 days. The assessments include Adverse Event and Seizure and Medication eDiary Review, **Added** additional Phone Follow – up Visits on Week 11 with visit window of +/- 3 days. The assessments include Adverse Event, Seizure and Medication eDiary Review. **Revised** per content in protocol to add X for Physical/Neurological/Developmental Exam for Visit 4 (Week 9) **Added** X to Genetic testing for Pre-Screening Visit. **Added** footnote **g** for Vital Signs to Visit 2, Visit 3, and Visit 4 **Added** footnote **r** to Visit 2	Table 1, Section 3.1, 7.2.1.1, 7.2.1.3, Section 7.2.2. Section 7.2.2.1, Section 7.2.2.4

Updated the footnotes as follows: e. **Added**: Genetic testing to be performed to confirm pathogenic or likely pathogenic PCDH19 variant only. **If genetic testing is not performed as Standard of Care, a pre-baseline screening visit will be scheduled to obtain informed consent/assent and complete the genetic testing. If genetic testing results are available per SOC, the genetic testing will be done at screening to confirm the results by the Sponsors designated lab. Genetic testing is to be performed to confirm pathogenic or likely pathogenic PCDH19 variant only.** g. **Added: At each visit, dosing will be reviewed and adjusted as needed based on a subject's current weight.** j. A drug screen (*(Removed: urine or)* plasma) will be performed to test for THC and CBD at screening. *(Removed: A negative drug test at screening meets the protocol eligibility criteria.)* If the screening drug test is positive, *(Removed: a plasma drug screen will be performed to test for THC and CBD at baseline.)* **the subject can be rescreened after 2 weeks.** l. **Revised**: Visit 3: between **1-5** hours since last IP dosing, r. **The 8 weeks between Screening and Randomization can be no less than 56 days and no more than 62 days.**	
Table 2, Schedule of Assessments for the Open-Label has been updated: **Added** additional Phone Follow – up Visits on Day 3 after Visit 5 (+/- 1 day). The assessments include Adverse Event and Seizure and Medication eDiary Review. Updated the footnotes as follows: c. **Revised**: In addition, height will be measured annually after Visit **8** (Week 52), except the safety follow-up visit. **i. Added: Population PK will be conducted at these visits (Visit 6: between 1-5 hours since the last IP dosing and Visit 8: between 1-5 hours since last IP dosing)**	Table 2, Section 7.2.4.1
Revised: however, the seizure frequency **decreases**,	Section 1.1 and 2.1
Removed: As of 10 October 2017, approximately 1,587 unique subjects have received treatment with GNX in ongoing and 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, 9 subjects are enrolled in the ongoing post-partum depression study, which remains blinded (GNX Investigator Brochure [IB] version 08 Feb 2018). *In 20 completed Phase 1 studies, 319 healthy subjects received GNX oral doses of 50 to 2,000 mg/day for periods of up to 2 weeks or IV bolus doses ranging from 10 to 30 mg over durations of 2 minutes to 1 hour or a bolus dose of 6 mg over 5 minutes followed with a continuous infusion of 20 mg per hour for 4 hours.* *In the 20 completed Phase 2/3 clinical studies, 1238 unique subjects have received GNX in studies of adult subjects with epilepsy, pediatric subjects with seizure disorders, pediatric subjects with Fragile X Syndrome (FXS), adult subjects with post-traumatic stress disorder (PTSD), and adult subjects with migraine.* *Two company-sponsored clinical studies of GNX are ongoing and have enrolled approximately 39 unique subjects: one study in subjects with rare*	Section 1.2

genetic epilepsies including female pediatric subjects with protocadherin 19 (PCDH19) and other genetic epilepsies (Study 1042-0900), including CDD, continuous spikes and waves during sleep (CSWS), and LGS, and one in females with post-partum depression (Study 1042-PPD-2002). Enrollment is complete for Study 1042-0900; however, the study is still ongoing. Enrollment is ongoing for Study 1042-PPD-2002 and results remain blinded. *In addition to the company-sponsored studies, 18 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. In addition, 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 and one pediatric subject received intravenous GNX up to a dose of 2880 mg/day in an emergency Investigational New Drug (IND) Application to treat super refractory status epilepticus.* **Added: As of 10 Oct 2018, 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 double-blind study)** • **Study 1042-PPD-2003 in women with PPD (GNX oral capsule multi-dose escalation open label study)** **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**	
Removed: Most rashes improved either while the drug was continued or following discontinuation. Two subjects participating in the Phase 2 study investigating GNX in treatment of epilepsy developed a serious adverse event (SAE) of rash. Both events resolved after discontinuation of the investigational product. **Added: 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.**	Section 1.2
Added: condition aggravated (10/59 subjects; 16.9%), and upper respiratory tract infection (9/59 subjects; 15.3%) Removed: vomiting (8/59 subjects; 13.6%), decreased appetite (8/59 subjects; 13.6%), aggression (6/59 subjects; 10.2%) and rash (5/59 subjects; 8.5%).	Section 1.2
Revised: assess the effect of GNX on **primary** seizure rate	Synopsis (Objectives) and Section 2.2.2
Added: At each visit, dosing will be reviewed and adjusted as needed based on subject's current weight.	Section 3.1 and Section 6.2.3.1
Added: An electronic eDiary is the standard, in rare cases when an eDiary completion is not feasible, a paper seizure calendar will be used to log daily seizure type and frequency. These cases will need approval by the sponsor.	Section 3.1
Added: Additionally, if genetic testing is not completed as standard of care, a pre-baseline screening visit can be conducted to do so.	Section 3.2

Added: Abstinence is an acceptable method of birth control only if this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.	Section 4.4.1
Revised: in the informed consent/ **(and/or subject assent)** form **Revised:** informed consent/**assent** form	Section 4.5.1, 7.2.1.1, 7.2.1.2, 7.3.1, 7.3.4, 8.1, 8.1.6, 8.2.4, 8.2.5, 9.1, 9.7, 10.3.1
Added: If a subject must be abruptly discontinued from investigational product, (e.g., severe rash), careful attention should be paid for 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.	Section 4.5.1
Revised reasons for early termination: **Added:** Adverse event **in which the character, severity or frequency is new in comparison to the subject's existing risk profile with the exception of somnolence and seizures.** **Added: 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)** **Added: A laboratory abnormality or vital sign change that is irreversible and considered medically significant, associated with use of the investigational product** **Added: Pregnancy**	Section 4.5.2
Added: During the screening visit **and after consent is obtained,**	Section 4.6
Revised: assigned by the **IWRS** ***(removed "study staff")***.	Section 4.6
Added: Concomitant medications may be reduced or discontinued at the discretion of the investigator if medically warranted.	Section 5.2, 5.2.1

<table>
<tr><td>Excluded medications include oral (removed: “all”) steroid medications, other IPs, and ketoconazole. Use of St. John’s Wort and concurrent use of strong inducers or inhibitors of CYP3A4/5/7 is not permitted. A list of CYP3A4/5/7 inhibitors and inducers is included in Section 12.1. Any strong inhibitor or inducer of CYP3A4/5/7 must be discontinued at least 28 days before Randomization Visit; note that this does not apply to (removed: “included”) approved AED medications.

Products containing tetrahydrocannabinol (THC) or non-approved CBD are excluded in the DB phase of the study but allowed in the OL phase. THC or non-approved CBD should be washed out for at least 2 weeks before screening. Subjects with a positive result on THC or non-approved cannabidiol CBD test (plasma drug screen) (Removed: at the screening) visit can be re-screened after 2 weeks. (Removed: or a positive result on THC or non-regulated CBD test (via urine or plasma at the baseline will be excluded from the study.)

Added: Use of any herbal product or nutritional supplement must be reviewed and approved by Marinus Medical Monitor.</td><td>Section 5.4</td></tr>
<tr><td>Revised: Interactive Web Response System for Investigational</td><td>Section 6.2.1</td></tr>
<tr><td>Revised: Dose de-escalation (taper) will occur in decreasing increments of 15 mg/kg/day or 450 mg every 3 days over 2 weeks whenever feasible</td><td>Section 6.2.3.1</td></tr>
<tr><td>Removed: Dosing Instructions in Sections 12.3.2 and 12.3.3.
Revised: Examples of dosing for subjects of different weights are provided in Section 12.3. Dosing instructions for the DB dose titration, DB and OL maintenance and taper are provided in the Pharmacy Manual. Dosing instructions for DB to OL transition are provided in the Pharmacy Manual.</td><td>Section 6.2.3.2, 12.3.2, and 12.3.3</td></tr>
<tr><td>Revised: Typically, doses will be reduced by 15 mg/kg/day or 450 mg/day every (removed “at least”) 3 days until the subject is completely off IP. Subjects should then return for a Safety Follow-up Post-Taper visit.</td><td>Section 6.2.3.3</td></tr>
<tr><td>Added Table 5

Table 5: De-Escalation of Investigational Product
<table>
<tr><th>Formulation</th><th>Dose</th><th>Frequency</th></tr>
<tr><td>Suspension (weighing ≤ 28 kg)</td><td>Reduce 15mg/kg/day</td><td>Every 3 days</td></tr>
<tr><td>Suspension (weighing > 28 kg)</td><td>Reduce 450 mg/day</td><td>Every 3 days</td></tr>
</table></td><td>Section 6.2.3.3</td></tr>
<tr><td>Revised: 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, star fruit, and grapefruit containing products are prohibited 14 days prior to 1st dose and for the duration of the study.

<u>Ganaxolone oral suspension</u> will be administered through an oral dosing syringe administered by parents/caregivers 3 times daily (TID), following the morning,</td><td>Section 6.2.4</td></tr>
</table>

<table>
<tr><td>noon, and evening meal or snack. Each dose should be separated by a minimum of 4 hours and a maximum of 12 hours.</td><td></td></tr>
<tr><td>Added: <u>Ganaxolone oral suspension:</u> A missed dose of IP may be taken up to 4 hours before the next scheduled dose; otherwise, the missed dose should not be given.
Added: The site will confer with the medical monitor to devise a dosing plan.</td><td>Section 6.2.5</td></tr>
<tr><td>Added Table 6
Table 6: Missed Dose of Investigational Product
<table>
<tr><th>Formulation</th><th>Proceed to Dose</th><th>DO NOT DOSE</th></tr>
<tr><td>Suspension</td><td>≥ 4 hours before next scheduled dose</td><td>< 4 hours before next scheduled dose</td></tr>
</table></td><td>Section 6.2.5</td></tr>
<tr><td>Added: Prior to unblinding or immediately following, the sponsor’s Medical Monitor must be contacted. Removed: The sponsor’s Medical Monitor must be contacted to initiate unblinding in the IWRS system. If unavailable, the Sponsor’s Back-up Medical Monitor or Sponsor Project Managers should be contacted.
Added: The Sponsor’s Medical Monitor does not have to be contacted to initiate unblinding in the IWRS system.</td><td>Section 6.3</td></tr>
<tr><td>Revised: Compliance with IP treatment will be monitored by inspecting the electronic diary (Removed: seizure and medication) entries and returned supplies with queries as necessary.</td><td>Section 6.6</td></tr>
<tr><td>Revised: Historical Seizure Type and Frequency and/or Genetic Testing</td><td>Section 7.2.1.1</td></tr>
<tr><td>Revised: maintain a daily seizure calendar or have genetic testing results with a confirmed PCDH19 diagnosis per standard of care, written informed consent/assent will be obtained. and the subject will be asked to return to the clinic for the Screening (Visit 1) after she has maintained a 3-month (12-week) daily historical seizure calendar and/or complete genetic testing.</td><td>Section 3.1 and 7.2.1.1</td></tr>
<tr><td>Revised: 3-month (12-week) daily</td><td>Section 7.2.1.1</td></tr>
<tr><td>Added: Genetic testing to confirm pathogenic or likely pathogenic PCDH19 variant by Sponsor identified lab, if not done at prescreening.</td><td>Section 7.2.1.2</td></tr>
<tr><td>Added: Baseline Visit – Randomization (Visit 2, Week 0 + 6 days)
The following study procedures/assessments to be completed, the results received, and the investigator must ensure the subject meets all inclusion and exclusion criteria prior to IP administration. The 8 weeks between Screening and Randomization can be no less than 56 days and no more than 62 days.</td><td>Section 7.2.1.3</td></tr>
<tr><td>Added weight to every visit with the exception of the safety follow-up.
Revised: Vital signs (to include BP, HR, RR, body temperature, and weight)</td><td>Section 7.2.1.3, 7.2.2.2, 7.2.2.3, 7.2.4.2</td></tr>
</table>

Corrected error by adding CGI-C and CGI-I to assessments under Baseline Visit.	Section 7.2.1.3
Added: population PK **1-5 hours post dose** or population PK **4-8 hours post dose**	Section 7.2.2.2, 7.2.2.3, 7.2.4.2, 7.2.5.2, 7.7
Revised: Telephone Follow-Up (**3 days after Visit 5 ± 1 day**, Weeks 18, 19 and 20 ± 3 Days) A telephone follow-up visit will be conducted **3 days after** Visit 5 **and at Weeks, 18, 19, and 20** of the OL phase to assess the following:	Section 7.2.4.1
Revised to correspond with Table 2. Follow-Up (Weeks 28, **44, and 60** ± 7 Days)	Section 7.2.5.1
Revised: Vital Signs (All Visits: to include BP, HR, RR, body temperature, and weight; Visit 7 and 8: to include height)	Section 7.2.5.2
Added: ECG (annually after Visit 8, Week 52) and Neurosteroid level sample draw (annually)	Section 7.2.5.3
Revised: Procedures specific to this protocol and not otherwise considered standard of care, will not be performed until written informed consent /**Assent** from the **subject**/parent/caregiver/LAR has been appropriately obtained.	Section 7.3.1
Revised: A drug screen (*(Removed: urine or)* plasma) will be performed to test for THC and **non-approved** *(removed non-regulated)* CBD at Visit 1 (screening). If the screening drug test is positive, a **confirmatory** plasma drug screen will be performed **after 2 weeks**. A positive drug test at Visit 2 will exclude the subject from the study. *(Removed: to test for THC and CBD at Visit 2 (baseline).)*	Section 7.3.2
Revised: The **33**-question test is filled out by the parent/caregiver/LAR.	Section 7.4.3
Added: The EEGs will be compared for changes in overall background features of paired sets of EEGs from each subject (in blinded order) and determined which EEG has the better overall organization and complexity of background or identify them as equivalent overall. Quantitative EEG parameters will also be conducted and will include: total power, relative alpha, beta, theta, and delta, theta/delta ratio, and alpha/delta ratio.	Section 7.5.1
Revised: Blood samples will be drawn *(removed at)* during the DB phase at Visit 1 (screening) and Visit 5 (Week 17;	Section 7.5.2
Revised text to correspond with Table 1. The CGI-C – target behavior will be assessed as follows: in the DB phase at Visit 2 (baseline), **Visit 3, Visit 4,** and Visit 5	Section 7.5.5 and 7.5.6

Added: 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.	Section 7.6
, **and weight** will be collected at every clinic visit starting with Visit 1 **other than the Safety Follow-Up Visit**. Height will be collected at Visit 1 (screening) (during DB phase) and during the OL phase at Visit 7 (Week 36), at Visit 8 (Week 52), annually thereafter (except for the Safety Follow-up Visit), and at the Final OL Visit. *Removed: Weight will be collected as follows: during the DB phase at Visit 1 (screening) and Visit 5 (Week 17; also Final DB Visit/First OL Visit in OL phase); during the OL phase at Visit 7 (Week 36) and every clinic visit thereafter; and at the Final OL Visit.*	Section 7.6.2
Replaced *OLE* with **OL**	Synopsis (Safety Analysis) Section 9.7, 9.8, 9.14
Removed: A third party will provide central ECG services for this study including provision of equipment to clinical sites, project management, site training and education, and data analysis as well as delivery of clean quality data. Complete details regarding the third party's ECG services will be provided in the PI Site File.	Section 7.6.4
Revised language to correspond with Table 1 visits. Due to the difficulty in obtaining urine samples, urinalysis will be conducted as follows: during the DB phase at Visit 1 (screening) or baseline (Visit 2), **Visit 3**, and at Week 17 (Visit 5;	Section 7.6.5
Removed Clinical Pharmacokinetic Blood Sample Collection and Handling Procedures *Pharmacokinetic blood collection must not deviate from the nominal collection time set forth in the protocol by more than ± 30 minutes from samples drawn within 4 hours post-dose or by more than ± 60 minutes for samples drawn beyond 4 hours post-dose. Samples drawn outside these parameters will be considered a protocol deviation.* *Please refer to the central laboratory manual for processing instructions.*	Section 7.7.1
Added: 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." *Removed: Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, the AE should be considered "related."*	Section 8.1.2
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**	Section 8.3

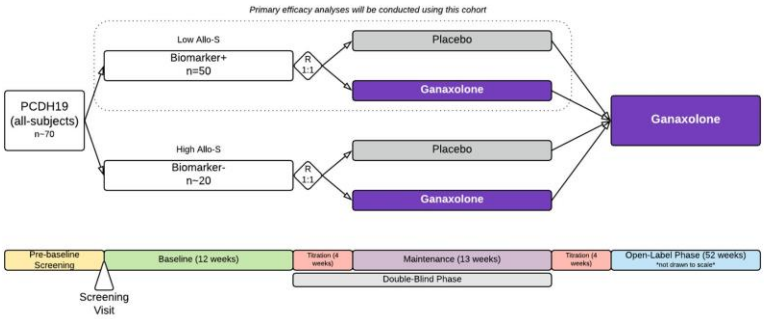
Removed: the standard deviation for the percent change in 28-day seizure frequency for all seizures is estimated to be 28.4, although other relevant data suggest the actual standard deviation could be meaningfully higher. If we assume the percent change in 28-day seizure frequency on GNX minus that on PBO truly to be approximately 40%, then a trial with 30 (respectively, 50) biomarker-positive PCDH19-related epilepsy patients randomized in a 1:1 manner will have about 96% (respectively, 99%) power to detect this effect when using a test statistic that preserves a (1-sided) 2.5% blinded positive error rate. But if we assume the standard deviation to be 40, then a trial with 30 (respectively, 50) biomarker-positive PCDH19 patients randomized in a 1:1 manner will have about 77% (respectively, 94%) power to detect this effect. *The threshold for achieving statistical significance in the biomarker-positive cohort at the final analysis when 30 (respectively, 50) subjects have completed their 17-week DB phase would be an estimate of the difference that is 72% (respectively, 55.5%) of the standard deviation. (If the standard deviation is 28.4, then the threshold for statistical significance is approximately 20.5%, (respectively, approximately 16%). If the standard deviation is 40, then the threshold for statistical significance is approximately 29%, (respectively, approximately 23%).* **Added: the standard deviation for the percent change in 28-day seizure frequency is estimated to be 28.4, although other relevant data suggest the actual standard deviation could be meaningfully higher. If we assume the standard deviation to be 40 and the percent change in 28-day seizure frequency on GNX minus that on placebo truly to be −40%, then a trial with 50 biomarker positive PCDH19 patients randomized in a 1:1 manner will have about 94% power to detect this effect when using a test statistic that preserves a (one-sided) 2.5% false positive error rate. The threshold for achieving statistical significance in the biomarker positive cohort at the final analysis when 50 subjects have completed their 17-week double-blind phase would be an estimate of the difference that is 55.5% of the standard deviation. (If the standard deviation is 40, then the threshold for statistical significance is approximately −23%).**	Section 9.5
Revised: The Safety and ITT populations comprise all randomized subjects who received at least one dose of study drug. In addition to being the population for the safety analyses, the biomarker-positive subjects in it is the primary population for the efficacy analyses. ***Removed:*** *The Per-Protocol (PP) population consists of subjects who receive IP for at least 6 weeks, who provided at least 5 weeks of post-baseline seizure data, and who have no major protocol violations.* **Added: The Per-Protocol (PP) population includes all ITT subjects without major protocol violations (defined prior to database lock).**	Section 9.6
Revised: in subject**s** daily seizure *(Removed: "calendars")* **eDiary**,	Section 9.7

Removed: For the primary outcome measure, if a subject stops recording measurements permanently (anticipated to be zero or minimal in occurrence) prior to the end of the 17-week DB phase, the corresponding median PBO data for the missing days will be imputed (irrespective of treatment arm) within each stratum, as follows: • *Compute the median 28-day seizure frequency in the PBO arm based on all available PBO measurements during the 17-week DB treatment phase. Label that 'X' and define 'A' to be 'X'/28, (ie, the daily average on PBO during the 17-week during the DB phase).* • *For any days (whether they be on the PBO or GNX arm) that occur AFTER a subject has become lost to follow up, impute 'A' on that day.* *A conceptually similar imputation approach will be used will be used for the secondary outcome measures when a subject stops recording measurements permanently prior to the end of the 17-week DB phase.* **Added: The primary analysis will use all available data. Careful educating and monitoring of the study sites will attempt to limit the amount of missing data to nearly zero, but despite these efforts, some missing data may still arise. Thus, a sensitivity analysis, in which the missing data will be replaced/imputed, will be performed on the primary efficacy endpoint.**	Section 9.13.1.1
Removed: In order to explore the possibility that subjects who stop recording their seizure counts tend to have higher seizure counts than the other subjects, the imputation method described in the SAP will be modified to use the median of the 5 highest counts, rather than the median count, among the PBO subjects with data. **Added: Two sensitivity analyses of the primary efficacy endpoint of change in 28-day frequency of the primary seizure types will be performed:** **Intermittent (random/sporadic) missing data during the 17-week DB phase and any missing data during the baseline phase will be assumed missing completely at random and the collected data will be used to calculate the 28-day seizure frequencies. For early drug termination prior to the end of the 17-week DB phase, caregivers will be instructed to continue to provide daily seizure records until the end of the 17-week DB phase (hence further preventing missingness).** **In the first sensitivity analysis, the following imputation approach will be used for the primary outcome measure when a subject stops recording measurements permanently (anticipated to be zero or minimal in occurrence) prior to the end of the 17-week DB phase: for the missing days, the corresponding median PBO data will be imputed (irrespective of treatment arm), within each stratum, as follows:** • **Compute the median 28-day seizure frequency in the PBO arm based on all available PBO measurements during the 17-week DB treatment phase. Label that 'X', and define 'A' to be 'X'/28, (i.e., the daily average on placebo during the 17-week during the DB phase).** • **For any days (whether they be on the PBO or GNX arm) that occur AFTER a subject has become lost to follow up, impute 'A' on that day.** • **The second sensitivity analysis will explore the possibility that subjects who stop recording their seizure counts tend to have higher seizure counts than the other subjects. The imputation method described above will be modified to use the median of the 5 highest counts, rather than the median count, among the PBO subjects with data.**	Section 9.13.3

Revised: All of the analyses for the DB phase, *(removed: except for seizure frequencies during the titration and maintenance phases,)* will be repeated for the OL phase with the following differences: • **The r**esults will be presented overall and also classified according to the DB *(removed phase)* **treatment received by subjects.** • Post-baseline seizure endpoints will be derived based on the first day *(Removed "following the start") of OL treatment.* • *(Removed: "No data will be imputed, and thus")* No sensitivity analyses **will be performed.** **Added: The complete list of differences will be outlined in the SAP.**	Section 9.13.5
Removed: The number of days that subjects received study drug, the total amount of study drug received, and the number and percent of subjects for whom dose reduction was required will be summarized, and a subject data listing will be provided with full details of the study drug dispensation. **Added: 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.** **Added: Detailed analysis and complete listings will be outlined in the SAP.**	Section 9.14
Revised: It will be conducted when **33** subjects in the biomarker-positive stratum	Section 9.16
Added: In rare cases when an eDiary completion is not feasible, a paper diary will be used to log daily seizure type and frequency. The Sponsor will provide the paper diary template which should not be modified.	Section 10.2.3.2
Removed: 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.	Section 10.3.1
Revised: Appendix 3: **Examples of** Dosing **Titration** for Oral Suspension Removed: *12.3.1 Examples of Dosing Transition*	Section 12.3

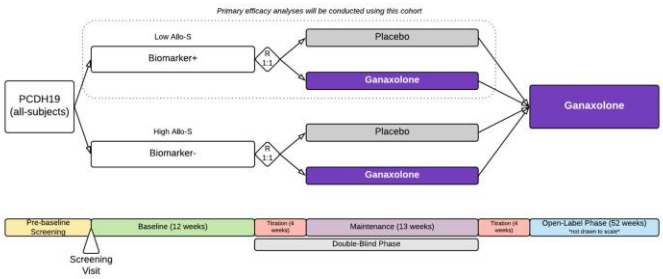
Removed: Appendices for Dosing Instructions and Scales.	Section 12.3.2, 12.3.3, 12.4, 12.5, 12.6, 12.7, 12.8, 12.9, 12.10, 12.11, 12.12
Administrative changes: Minor changes involving grammar, rephrasing for clarity, punctuation, and other editorial changes have been made throughout the document.	Entire document

Amendment Number	**Amendment Date**	**Global/Country/Site Specific**
3	16 August 2019	**Global**

Description of Change	**Section(s) Affected by Change**
Added: Exclusion Criteria **- Subjects with ≤ 3 primary seizures during the 12-week baseline period.**	Synopsis (Exclusion Criteria) and Section 4.2
Revised: Subjects with >**8** (*Removed: 6*) consecutive weeks (**56** (*Removed: 42*) consecutive days) of primary seizure freedom during the 12-week pre-baseline screening period.	Synopsis (Exclusion Criteria) and Section 4.2
Updated: 8-week baseline period to **12-week** baseline period	Synopsis (Methodology, Duration of Treatment, Secondary Endpoint, Exploratory Endpoint, and Statistical Methods), Table 1, Sections 3.1, 3.2, 5.2, 7.2.1.2, 7.2.1.3, 9.7, 9.13.1, 9.13.1.3, 9.13.1.3.1.1 , 9.13.1.4, and 9.13.5
 Figure was revised to update Baseline.	Synopsis (Methodology) and Section 3.1
Removed: If a subject experiences no primary seizures during the baseline phase then the 28-day seizure frequency in the baseline phase will be set to 0.5, equivalent to having 1 seizure during the phase, and 0.5 will be added to the 28-day seizure frequency in the post-baseline phase.	Synopsis (Primary Endpoint and Statistical Methods) and Section 9.13.1.2
Added: **N/A** to Visit Windows in Table 1 for Pre-baseline Screening Visit and Screening Visit.	Table 1

Revised: The **12** (*removed: 8*) weeks between Screening and Randomization can be no less than **84** (*removed:* 56) days and no more than **90** (*removed:* 62) days.	Table 1, footnote r and Section 7.2.1.3
Updated: Serum pregnancy tests were added to Visit 3, Visit 4, Visit 6, Visit 7, Visit 8, Visit 9, Visit X (every 16 weeks in OL), Final OL, and Safety Follow-Up Visit.	Table 1 and Table 2, Sections 7.2.2.2, 7.2.2.3, 7.2.3, 7.2.4.2, 7.2.5.2, 7.2.5.3, 7.2.7
Revised: Week 17 +3 Days (*Removed Post Visit 5)*	Table 2 and Section 7.2.4.1
Added: Line for Drug Screen in Table 2 to be consistent with Table 1 for Week 17 Final DB Visit/First OL Visit	Table 2
Added: However, the final decision to adjust drug dosages lies with the PI.	Section 3.1
Added: If a subject fails to qualify because of Exclusion Criteria #4 (≤ 3 primary seizures during the 12-week baseline period), she will not be randomized. However, she can be rescreened after collecting another 12 or more weeks of seizure history that satisfies all eligibility criteria including Inclusion Criteria #5 and Exclusion Criteria #3. Each subject is allowed a maximum of 1 rescreening visit.	Section 3.1 and 7.2.1.2
Updated: A minimum oral suspension dose of 33 mg/kg/day or 900 mg/day is **generally required following the escalation period, during the DB phase unless a lower dose is agreed to with the sponsor due to tolerability issues such as somnolence** *(Removed: must be maintained)***.**	Section 3.4
Updated: Subjects with a positive result on THC or non-approved cannabidiol CBD test (via plasma drug screen) can be **retested,** *(Removed: re-screened)* **via plasma,** after 2 weeks.	Section 5.4, 7.3.2, and Table 1, footnote J
Revised: A positive drug test **during the DB phase will result in early termination.** *(Removed: at Visit 2 will exclude the subject from the study)* Table 1 Footnote j j. **Revised**: A positive drug test **during the DB phase will result in early termination.** *(Removed: at Visit 2 will exclude the subject from the study)*	Section 7.3.2 and Table 1, footnote J
Revised: Note that if a subject is taking marketed Epidiolex **(may go by another name in countries outside the United States)** then the parent/caregiver will have to provide evidence of an active prescription or confirmation from prescriber.	Section 5.4
Revised: 450 mg/**day**	Section 6.2.3.1
Revised: Instructions for genetic testing sample collection and processing can be found in the central *(Removed: genetic testing)* laboratory manual	Section 7.3.5
Updated: The preschool version (BRIEF-P) is a 63-item modified form and is **typically** utilized in individuals 2-5 years of age. **For this study, the BRIEF-P will be used for any subject less than 5 years of age.**	Section 7.4.4
Updated: Quantitative EEG parameters will also be conducted and will include **the following**	Section 7.5.1
Updated: (*Removed: Laboratory safety assessments will be collected at every clinic visit throughout the study to monitor subject safety.)* Clinical laboratory tests are listed in Section 12.1**2** and will be collected per the schedules listed in Table 1 and Table 2. *(Removed: These clinical laboratory assessments will include CBC with automated differential, creatinine, blood urea nitrogen, and eGFR calculation, comprehensive metabolic panel, and serum pregnancy test for all females of childbearing potential.)*	Section 7.6.5 and Appendix 2
Updated: Appendix 2. Drug Screen removed from urinalysis column. All drug tests are serum.	Appendix 2

Administrative changes: Minor changes involving grammar, rephrasing for clarity, punctuation, and other editorial changes have been made throughout the document.	Entire document
Amendment Number 4 / **Amendment Date 30 June 2020**	**Global/Country/Site Specific Global**
Description of Change	**Section(s) Affected by Change**
Violet Study changed from a Phase 3 to a Phase 2 Study.	Synopsis
[redacted]	Protocol Signature Page
Updated primary and back-up Medical Monitor contacts. **Added:** [redacted] **added as the** [redacted] **Revised:** [redacted] **moved from** [redacted] **Revised:** [redacted] **from** [redacted] **Added:** [redacted] *Removed:* [redacted] *Removed:* [redacted]	Emergency Contact Information and Section 6.3
Updated CHSQ to **CSHQ**	Abbreviations, Synopsis (Methodology and Secondary Endpoints), Sections 3.1 and 9.13.1.3.2.3
Updated: A sufficient number of eligible PCDH19 subjects will be screened and enrolled, with a 1:1 randomization to either ganaxolone (GNX) or placebo (PBO). As study enrollment was discontinued early (as of 01July2020) due to administrative reasons, the total number of the randomized patients is expected to be approximately **25** subjects resulting in approximately 15 randomized biomarker-positive subjects. Previously: A sufficient number of eligible PCDH19 subjects will be screened and enrolled *to include at least 50 total biomarker-positive subjects*, with a 1:1 randomization to either ganaxolone (GNX) or placebo (PBO). *The number of biomarker-negative subjects will be based on the distribution of biomarker status in the enrolled population with a minimum of 10 biomarker-negative subjects required.* Total enrollment is planned to be approximately *70* subjects.	Synopsis (Number of Subjects and Methodology), and Section 3.1
Updated: Global, multicenter study to be conducted at approximately **11** sites Previously: *45 sites*	Synopsis (Sites and Regions), Section 3.3
Removed: from the subject's parent or legally authorized representative (LAR) and *(Removed: /or)* subject assent has been appropriately obtained.	Synopsis (Methodology and Inclusion), Table 1 – footnote c, Sections 3.1, 3.2, 4, 7.2.1.1, 8.1, 8.1.6, 8.2.5 and 9.1
Updated figure.	Synopsis (Methodology) and Section 3.1

	
Revised: during the DB phase unless a lower dose is agreed to with the sponsor due to tolerability issues *(removed: such as somnolence).*	Synopsis (Methodology and Investigational product, dose, and mode of administration), Sections 3.4, and 6.2.3.1
Revised Inclusion #1: Molecular confirmation of a pathogenic or likely pathogenic PCDH19 variant. Genetic mutations will be confirmed by the sponsor's chosen central laboratory. *Removed: The principal investigator (PI) must review the results of the genetic analysis and confirm that the causal relationship to the epilepsy syndrome is likely. If the subject has a de novo variant of unknown significance (VUS) then the central assessor, PI, and Sponsor will review study inclusion.*	Synopsis (Inclusion Criteria) and Section 4.1
Revised Inclusion #7: *(removed: Subjects should be on a stable regimen of anti-seizure medications, if any, for ≥ 1 month prior to the screening visit, without a foreseeable change in dosing for the duration of baseline and the DB phase.)* **Concomitant AED regimens must have been stable for at least 1 month prior to the screening visit and must remain stable from screening to the end of the DB phase.** *(removed: Vagus nerve stimulator (VNS))* Ketogenic diets and modified Atkins diet**s** should be unchanged for 3 months prior to screening **and must remain stable throughout baseline and the DB phase.**	Synopsis (Inclusion), Sections 4.1 and 5.2.1
Update: All references to baseline visit or randomization visit updated to **baseline/randomization** visit	Throughout Protocol
Revised Exclusion #7: Chronic use of oral steroid medications, ketoconazole (except for topical formulations), St. John's Wort, or other investigational products is not permitted. **Intermittent (<5 consecutive days/month or 10 cumulative days per month) use of corticosteroids as a rescue medication for breakthrough seizures may be allowed after sponsor approval.**	Synopsis (Exclusion) and Section 4.2
Revised Exclusion #8: Changes in any chronic **AED** medication **(i.e., changes in dose or starting a new chronic AED)** within the last month prior to the screening visit (Visit 1) **and during the 12 week baseline period (i.e., between Visit 1 and Visit 2). Changes in rescue AED medications to treat acute breakthrough seizures may be permitted with Sponsor's approval. Changes in other (i.e., non-AED) chronic medications may be permitted with Sponsor's approval.**	Synopsis (Exclusion) and Section 4.2
Revised Exclusion #11: An aspartate aminotransferase (AST/serum glutamic oxaloacetic transaminase [SGOT]) or alanine aminotransferase (ALT/serum glutamic pyruvic transaminase [SGPT]) > 3 × the upper limit of normal (ULN) at screening *(removed: or baseline visit)* and **if applicable,** confirmed by a repeat test. **If the subject has another reason to be excluded, repeated liver enzymes are not required.**	Synopsis (Exclusion) and Section 4.2
Revised Exclusion #12: Total bilirubin levels > 1.5 × ULN at screening *(removed: or baseline visit)* and **if applicable,** confirmed by a repeat test. In cases of	Synopsis (Exclusion) and Section 4.2

documented, stable medical condition (i.e., Gilbert's Syndrome) resulting in levels of total bilirubin > ULN, the medical monitor can determine if a protocol exception can be made.	
Revised: The analyses of the primary endpoint will be performed on the sum of the individual countable seizures and **each series of continuous** uncountable *(removed: series of)* seizures (each contributes 1 to the sum).	Synopsis (Primary Endpoint and Statistical Method), Sections 7.4.1 and 9.13.1.2
Added: As enrollment in the study was discontinued early due to administrative reasons, and only 15 biomarker-positive subjects are expected to be randomized, the study is not considered to have adequate power for formal testing of the statistical hypotheses. Since the reason for stopping enrollment is external to the study, the statistical analysis will be performed as planned. All p-values produced as part of the pre-specified analysis would therefore be considered as nominal. *Previously: Formal interim analyses are planned, in addition to the final analysis, of treatment effect on the primary endpoint, in accordance with the SAP.*	Synopsis (Interim Analysis) and Section 9.16
Added: A drug screen (plasma) will be performed to test for THC and CBD at screening. If the screening drug test is positive, the subject can be retested, via plasma, after two weeks. **A drug screen may be performed at any time at Investigator's discretion.** A positive drug test during the DB phase will result in early termination.	Table 1 – footnote j and Section 7.3.2
Revised: Concomitant AEDs *(removed: or their dose)* must be stable for 1 month prior	Table 1 – footnote m
Revised: Changed windows for open label visits from ± 7 to ± **14** days	Table 2, Table 2 (footnote a), Sections 7.2.5, 7.2.5.1, 7.2.5.2, 7.5.2.3, and 7.2.6
Added: Urinalysis to Visit 7	Table 2, Sections 7.2.5.2, and 7.6.5
Added footnote j to Table 2: **Subjects who discontinue IP treatment before the completion of the DB phase will continue to be followed per protocol and, at a minimum, subjects will be encouraged to maintain daily seizure eDiary entries until the DB phase is completed. These subjects will also return to the site 2 to 4 weeks after the taper for safety follow-up post-taper assessments.**	Table 2 – footnote j
Revised: Any subject who completes the study or discontinues IP treatment **at any time during the study** should undergo a 2-week drug de-escalation (taper) period.	Sections 3.1 and 6.2.3.3
Revised: Concomitant medications, **other than AEDs**, may be reduced or discontinued at the discretion of the investigator if medically warranted.	Section 5.2
Revised: The use of rescue medication is allowed on an occasional basis **and as medically needed**.	Section 5.3
Revised: Excluded medications include oral steroid medications, *(removed: other IPs)* ketoconazole and other **investigational drugs or devices** *(removed: investigational treatments).*	Section 5.4
Revised: 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 *(removed for safety reasons)*. Dose de-escalation (taper) will occur in decreasing increments of 15 mg/kg/day or 450 mg/day **approximately** every 3 days over 2 weeks whenever feasible (See	Sections 6.2.3.1 and 6.2.3.3

Section 6.2.3.3 for more details). **Taper is not required if the subject is receiving the dose of 18 mg/kg/day or 450 mg/day (or lower).**	
Revised: Any subject who completes the study or discontinues IP treatment **at any time during the study** should undergo a 2-week drug de-escalation (taper) period.	Section 6.2.3.3
Revised: As a generally accepted guideline, subjects should remain 80% compliant with diary entries. Parents/caregivers **who fall short of this standard** will be re-educated on the importance of adhering to daily seizure, IP and non-study AED recording **and a deviation recorded**.	Section 6.6 and 7.4.1
Added: In the event of unforeseen circumstances, in-person study visit assessments may not be able to be performed. To conduct the study according to protocol while preserving patient safety, operational alternatives such as those listed below can be employed as long as the site's actions are in compliance with the institution's IRB/EC policies and regulations. • **Telemedicine visits (video and/or audio communication methods)** • **In-home visits** • **Local physician visits** • **Use of local and/or off-site laboratories** • **Site-to-patient IP distribution**	Section 7.1
Revised: A drug screen (plasma) will be performed to test for THC and non-approved CBD **during the DB phase** at Visit 1 (screening), **Visit 2 (baseline/randomization), and Visit 5 (final DB/first OL visit).** If the screening drug test is positive at **Visit 1 (screening)**, a confirmatory retest, via plasma, will be performed after 2 weeks. **A drug screen may be performed at any time at Investigator's discretion.**	Sections 7.3.2
Revised: If the subject has a de novo **PCDH19** VUS then the central assessor, PI, and Sponsor will review study inclusion. **Some subjects may have multiple PCDH19 mutations that include both VUS and pathogenic variants. In these cases, the subject is known to have a pathogenic variant and is eligible (does not require discussion with expert).**	Section 7.3.5
Added: If any test result is unexpectedly out of range, a repeat test can be performed at any time as decided by the PI to confirm the initial result.	Section 7.6.5
Revised: Medication errors are reportable to the sponsor only as defined below. • Cases of subjects missing doses of the IP are not considered reportable *(removed: as medication errors)*. • *(Removed: Medication errors should be collected and reported)***Applicable only** for the IP under investigation. • All IP provided to pediatric subjects should be supervised by the parent/caregiver/LAR. **Lapses in supervision should be reported.**	Section 8.1.7
Revised: Once the subject's parent/caregiver/LAR signs informed consent (and subject assent), it is expected that all eDiary entries will be made daily *(removed: and no longer than 72 hours after each day)*. **Added: Retrospective entry of diary events (seizure and medication) can be completed by the caregiver up to 5 days later and proxy entry by the site is also available to the site staff (greater than 5 days), but neither method is encouraged.**	Section 9.1
Revised: If **nominal** statistical significance is achieved in the biomarker-positive stratum, then efficacy will be assessed in the biomarker-negative stratum. GNX efficacy in the biomarker-positive stratum will be established if that stratum's ITT analysis results are **nominally** statistically significant.	Section 9.13.1.2

Removed: *There is a single primary endpoint, and formal hypothesis testing will not be performed for the other endpoints. Hence, no protections for multiplicity are needed.* **Added: No formal hypothesis testing is planned in this study due to enrollment discontinuation for administrative reasons.**	Section 9.13.4
Added: As enrollment in the study was discontinued early due to administrative reasons, and only 15 biomarker-positive subjects are expected to be randomized, the study is not considered to have adequate power for formal testing of the statistical hypotheses. Since the reason for stopping enrollment is external to the study, the statistical analysis will be performed as planned. All p-values produced as part of the pre-specified analysis would therefore be considered as nominal. **Removed:** *One formal interim analysis of the primary efficacy endpoint is planned in addition to the final analysis. It will be conducted when 33 subjects in the biomarker-positive stratum have completed their 17-week DB phase and will be based on use of O'Brien-Fleming monitoring boundaries. The interim analysis will be conducted in both the biomarker-positive stratum and the biomarker-negative stratum. Early termination can occur due to either reliable evidence of lack of benefit or definitive evidence of benefit.*	Section 9.16
Administrative changes: Minor changes involving grammar, rephrasing for clarity, punctuation, and other editorial changes have been made throughout the document.	Entire document

Amendment Number **5**	**Amendment Date** **20 January 2021**	**Global/Country/Site Specific** **Global**
Description of Change		**Section(s) Affected by Change**
Signatory updated from [redacted] **to** [redacted]		**Protocol Signature Page**
Added: [redacted] MD, PhD added as [redacted] **Removed:** [redacted], MD, PhD removed as [redacted]		**Emergency Contact Information and Section 6.3**
Revised Primary Objective: To assess the efficacy of GNX compared with PBO *(Removed: in all biomarker positive subjects,)*, as adjunctive therapy for the treatment of primary seizure types in children with genetically confirmed PCDH19-related epilepsy **during** (*Removed: at the end of)* the 17-week double-blind (DB) phase.		**Synopsis (Objectives) and Section 2.2.1**
Revised Secondary Objectives: • To assess the effect of GNX on primary seizure rate in biomarker-**positive** *(Removed: negative)* subjects		**Synopsis (Objectives) and Section 2.2.2**
Added Exploratory Efficacy Objective: [redacted]		**Synopsis (Objectives) and Section 2.2.3**

Revised wording for clarification. No change to the content. **Revised:** Subjects who are not able to tolerate 63 mg/kg/day (or 1800 mg/day maximum) may be maintained on a lower dose. *(Removed: after discussion with the sponsor).* A minimum dose of 33 mg/kg/day or 900 mg/day is generally required following the **DB** escalation period, (*Removed: during the DB phase*) unless a lower dose is agreed to with the sponsor due to tolerability issues **such as somnolence**. **Revised: Of note** *(Removed: However, the final decision to adjust drug)*, **the sponsor defers the final decision to adjust IP to the treating study clinician** *(Removed: dosage lies with the PI)*; **dose changes may not exceed the maximum total daily dose defined by the protocol.**	**Synopsis (Methodology and Investigational product, dose, and mode of administration), Sections 3.1, 3.4, and 6.2.3.1**
Added throughout to be consistent with other sections of the protocol. No change to content. **Added:** Taper is not required if the subject is receiving the dose of 18 mg/kg/day or 450 mg/day (or lower).	**Synopsis (Methodology), Table 2, and Section 3.1**
Revised: Focal and generalized nonmotor seizures and myoclonic seizures do not count as the primary seizure types **for the primary efficacy endpoint**.	**Synopsis (Primary Endpoint) and Section 9.13.1.2**
Revised: The difference between the GNX and placebo groups in the percent changes *(Removed: within each stratum)* will be tested using the Wilcoxon Rank-Sum statistic. **Revised:** • The primary analysis will be conducted in the **ITT population** *(Removed: biomarker-positive stratum).* • If nominal statistical significance is achieved in the **ITT population** *(Removed: biomarker-positive stratum),* **the primary analysis will be conducted** in the biomarker-**positive** stratum **of the ITT population as a secondary endpoint** *(Removed: then efficacy will be assessed in the biomarker-negative stratum).*	**Synopsis (Primary Endpoint and Statistical Methods) and Section 9.13.1.2**
Added Secondary Endpoint: The percent change in 28-day primary seizure frequency during the 17-week DB Phase relative to baseline in biomarker-positive subjects.	**Synopsis (Secondary endpoints (seizure control)), Section 9.13.1.3.1.1**
Added Exploratory Endpoint: [redacted]	**Synopsis (Exploratory Endpoints and Statistical Methods) and Section 9.13.1.4**

Added: No formal interim analysis is planned for this study. After all active subjects complete the17-week double-blind phase, the double-blind data in the database will be locked and used to perform endpoint analysis. Data collected during the open label phase will be analyzed separately. *Removed: As enrollment in the study was discontinued early due to administrative reasons, and only 15 biomarker-positive subjects are expected to be randomized, the study is not considered to have adequate power for formal testing of the statistical hypotheses. Since the reason for stopping enrollment is external to the study, the statistical analysis will be performed as planned. All p-values produced as part of the pre-specified analysis would therefore be considered as nominal.*	**Synopsis (Interim Analysis) and Section 9.16**
Added: A total of 50 subjects (25 in each treatment group) was planned to be enrolled in the study. ***Note: Protocol versions 5 and 6 were implemented after enrollment was stopped early due to administrative reasons. The final sample size is not based on statistical considerations. Formal hypothesis testing will be performed based on all available sample size at the time of the study discontinuation.*** *Removed: Based on data from the 7 biomarker-positive PCDH19-related epilepsy in Study 1042-0900 evaluating GNX, the standard deviation for the percent change in 28-day seizure frequency is estimated to be 28.4, although other relevant data suggest the actual standard deviation could be meaningfully higher. If we assume the standard deviation to be 40 and the percent change in 28-day seizure frequency on GNX minus that on placebo truly to be −40%, then a trial with 50 biomarker-positive PCDH19 patients randomized in a 1:1 manner will have about 94% power to detect this effect when using a test statistic that preserves a (one-sided) 2.5% false positive error rate. The threshold for achieving statistical significance in the biomarker positive cohort at the final analysis when 50 subjects have completed their 17-week double-blind phase would be an estimate of the difference that is 55.5% of the standard deviation. (If the standard deviation is 40, then the threshold for statistical significance is approximately −23%). The actual analysis will use a Wilcoxon rank-sum test, which has approximately the same power as the analysis of variance (ANOVA).* *As enrollment in the study was discontinued early due to administrative reasons and only 15 biomarker-positive subjects are expected to be randomized, the study is not considered to have adequate power for formal testing of the statistical hypotheses. Since the reason for stopping enrollment is external to the study and a purely administrative decision, the statistical analysis of this study will be performed as planned. All p-values produced as part of the planned pre-specified analysis would be considered as nominal.*	**Section 9.5**
Added: The Randomized population comprises all subjects who are randomized to one of GNX or PBO treatment group. **Revised:** The Safety *(Removed: and ITT)* population comprises all randomized subjects who received at least one dose of study drug. *(Removed: In addition to being the population for the safety analyses, the biomarker-positive subjects in it is the primary population for the efficacy analyses.)*	**Section 9.6**

Added: The ITT population comprises all randomized subjects who received at least one dose of study drug and have at least one post-baseline efficacy assessment.	
Revised wording for clarification. No change to the content. Baseline seizure activity will be determined by prospective recording in subject**'s** daily seizure eDiar**ies**, which are provided after signing informed consent/assent. Within the DB phase of the study, **determination of** post-baseline seizure activity **will begin on the day** following the first day of DB treatment. **Determination of** post-baseline seizure activity assigned to the OL phase **will begin on the day** following the first OL treatment.	**Section 9.7**
Revised: Tables will be provided **using the ITT subject population as well as** within each of the biomarker-positive and biomarker-negative strata *(Removed: and the primary endpoint table as well as the subject background and safety tables will also be provided as pooling over the strata.)*	**Section 9.7**
Revised: Medical history will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) Terminology **version 22.0** *(Removed: version 16.0)*.	**Section 9.11**
Revised: For the analyses of seizures, the baseline phase consists of **the 8- or** -12 week **period** before the first day of treatment**,** and the DB phase starts the day following the first day of DB treatment **and continues until the final visit for subjects who do not enter the OL, and up to the day before the first dose of OL treatment for those who do.** *(Removed: The first day of treatment is not in either phase since the times of seizures are not collected.)* *Removed: The estimand that is most clinically relevant as well as estimable in a manner that protects the integrity of randomization is the outcome measure (eg, the percent change in 28-day seizure frequency), where ALL randomized subjects would be included in this analysis throughout the study period. Hence, all available data will be used, even if they were collected after the subject stopped taking study medication, regardless of whether the subject took rescue medication.*	**Section 9.13.1**
Revised: Careful educating and monitoring of the study sites will attempt to limit the amount of missing data. *(Removed: to nearly zero, but despite these efforts, some missing data may still arise)* Sensitivity analyses is, **with replacement** of missing data *(Removed: will be replaced/imputed),* will be performed **for** the primary efficacy endpoint.	**Section 9.13.1.1**
Added: Testing will be conducted in the following order: **Added: In addition, as an exploratory analysis,** [redacted] *Removed: The primary analysis will be conducted in the biomarker-positive stratum (defined as a baseline Allo-S level of less than or equal to 2500 pg/mL).*	**Section 9.13.1.2**

GNX efficacy in the biomarker-positive stratum will be established if that stratum's ITT analysis results are nominally statistically significant. Hierarchically, if GNX efficacy is established in the biomarker-positive stratum, its efficacy will then be assessed in the biomarker-negative stratum. To be positive, the difference between the GNX and PBO groups in that stratum must be both clinically relevant and at least as large as would be required for statistical significance in an analysis of the pooled strata ITT population (Rothmann 2012).	
Added: **9.13.1.3.1.1. Percent Change in Primary Seizure Frequency** **The percent change in 28-day primary seizure frequency during the 17-week DB Phase relative to baseline in biomarker-positive subjects.** **The same analysis methods for the primary endpoint will also be applied to this secondary endpoint. Please also refer to Section 9.13.1.2 for the hypothesis testing order.**	**Section 9.13.1.3.1.1**
Revised: Except where indicated otherwise, all the seizure exploratory endpoints will be based on the primary seizure types **defined for inclusion in the primary efficacy endpoint.**	**Synopsis (Statistical Methods) and Section 9.13.1.4.**
Added: To control the family-wise Type I error rate, hypothesis testing of the primary efficacy endpoint will be conducted sequentially in the order specified in Section 9.13.1.2. *Removed: No formal hypothesis testing is planned in this study due to enrollment discontinuation for administrative reasons.*	**Section 9.13.4**
Revised throughout the protocol for clarification. No change to the content. **Revised:** ***(removed: at the end of*** *the 17-week DB phase****) and replaced with****:* **during** the 17-week DB phase **Revised***: (****Removed: 12-week****) when referencing statistical language to read as just baseline or prospective baseline* **Revised**: PCDH19-**related epilepsy**	Entire document
Administrative changes: Minor changes involving grammar, rephrasing for clarity, punctuation, and other editorial changes have been made throughout the document.	Entire document

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 Clinical Study Serious Adverse Event Form within 24 hours to Marinus Safety Department at:

Email: safetyPCDH3002@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]

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

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

Sponsor Project Managers:

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

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

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ABBREVIATIONS

Term	Definition
AE	adverse event
ABC-C	Aberrant Behavior Checklist-Community
AED	antiepileptic drug
Allo-S	allopregnanolone sulfate
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-HCG	β-human chorionic growth hormone
BP	blood pressure
BRIEF	Behavior Rating Inventory of Executive Function
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
CNS	central nervous system
CRA	clinical research associate
CRO	clinical research organization
CSHQ	Children's Sleep Habit Questionnaire
CSWS	continuous spike and wave during slow wave sleep
CYP3A4	cytochrome P450 3A4
DB	double-blind
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic seizure diary
EEG	electroencephalogram
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
FXS	Fragile X Syndrome
GABA	γ-Aminobutyric acid
$GABA_A$	γ-Aminobutyric acid type A
GCP	Good Clinical Practice
GNX	ganaxolone
HR	heart rate
IB	Investigator Brochure
IND	Investigational New Drug
IRB	institutional review board
ITT	Intent-to-Treat Population
IWRS	interactive web response system
LAR	legally authorized representative
LGS	Lennox Gastaut syndrome

Term	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	Maximum Tolerated Dose
OL	open-label
PBO	Placebo
PCDH19	protocadherin 19
PedsQL-FIM	Pediatric Quality of Life Inventory – Family Impact Module
PI	principal investigator
PK	Pharmacokinetic
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	3 times daily
ULN	upper limit of normal
UK	United Kingdom
US	United States
VNS	Vagus nerve stimulator
VUS	variant of unknown significance

STUDY SYNOPSIS

Protocol number: 1042-PCDH19-3002	**Drug:** ganaxolone
Title of the study: A double-blind, randomized, placebo-controlled trial of adjunctive ganaxolone treatment in female children with protocadherin 19 (PCDH19)-related epilepsy followed by long-term open-label treatment	
Number of subjects (total and for each treatment arm): A sufficient number of eligible PCDH19 subjects will be screened and enrolled, with a 1:1 randomization to either ganaxolone (GNX) or placebo (PBO). As study enrollment was discontinued early (as of 01July2020) due to administrative reasons, the total number of the randomized patients is expected to be approximately **25** subjects resulting in approximately 15 randomized biomarker-positive subjects.	
Investigators: Multicenter study	
Sites and Regions: Global, multicenter study to be conducted at approximately 11 sites	
Study period (planned): March 2019 to June 2022	**Clinical phase:** 2

Objectives:

Primary: To assess the efficacy of GNX compared with PBO as adjunctive therapy for the treatment of primary seizure types in children with genetically confirmed PCDH19-related epilepsy during the17-week double-blind (DB) phase.

Secondary:

- To assess the effect of GNX on primary seizure rate in biomarker-positive subjects
- To assess behavioral/neuropsychiatric changes in subjects receiving GNX compared with subjects receiving PBO as adjunctive therapy during the17-week DB phase
- To assess the safety and tolerability of GNX compared with PBO as adjunctive therapy during the 17-week DB phase
- To assess pharmacokinetic (PK) parameters in subjects receiving GNX doses up to 63 mg/kg/day (or 1800 mg/day maximum) throughout the study
- To assess the long-term efficacy of GNX when administered as adjunctive therapy throughout the open-label (OL) phase
- To assess the long-term safety and tolerability of GNX when administered as adjunctive therapy throughout the open-label phase

Exploratory Efficacy:

- [redacted]

Rationale:

Protocadherin19 (PCDH19)-related epilepsy is a serious epileptic condition characterized by early-onset cluster seizures, cognitive and sensory impairment of varying degrees, and psychiatric and behavioral disturbances affecting primarily females (Camacho 2012). The condition is caused by an inherited mutation of the PCDH19 gene located on the X chromosome. This gene encodes for a calcium-dependent cell-cell adhesion molecule that is expressed in the central nervous system (CNS; eg, hippocampus, cerebral cortex, thalamus, amygdala) and which appears to be related to synaptic transmission and formation of synaptic connections during brain development (Depienne 2009).

The mean age of seizure onset in this condition is approximately 10 months (range of 3-38 months) (Scheffer 2008, Specchio 2011, Dipienne 2011, Cappelletti 2015, van Harssel 2013). The mean age of offset of epileptic seizures is approximately 12.5 years (1-35 years). PCDH19-related epilepsy has been described as a "semiprogressive" condition, meaning that seizure frequency increases during the first few years of life (Specchio 2011). However, over time the seizure frequency lessens, and seizures become less frequent with increased age.

There is also evidence supporting an allopregnanolone deficiency as a proposed contributor to the onset of seizures in individuals with PCDH19-related epilepsy (Tan 2015). It was found that individuals with this genetic mutation demonstrated a downregulation of steroid hormone-metabolizing enzymes resulting in reduced allopregnanolone levels compared to non-affected, age-matched controls. Since this neurosteroid is known to have strong anti-convulsant properties, it is hypothesized that treatment with neurosteroids with similar action, or analogs such as GNX, may have therapeutic benefit to seizure control.

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 1997) in activating synaptic and extrasynaptic $GABA_A$ receptors at a site distinct from benzodiazepines and barbiturates. Ganaxolone has protective activity in diverse rodent seizure models (Reddy 2012, Bialer 2010). Clinical studies have demonstrated that 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 2017, Laxer 2000, Kerrigan 2000, Pieribone 2007). Further, GNX reduces seizures in children with IS and refractory pediatric epilepsy. In an OL 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 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 PCDH19-related epilepsy has emerged from an ongoing OL flexible-dose exploratory study (Study 1042-0900) of GNX in children (age range 2-15 years) with rare genetic epilepsies (including PCDH19) with uncontrolled seizures despite multiple antiepileptic drug (AED) regimens (ClinicalTrials.gov Identifier: NCT02358538). Following the screening and baseline evaluations, consenting subjects enrolled into a 26-week study during which investigators could dose GNX starting with a titration 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 dose could also be reduced for tolerability reasons. 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 25% (n = 11).

The median change from baseline in seizure-free days in the ITT population (key secondary endpoint) was an increase of 14% (n = 11). Baseline levels of allopregnanolone sulfate (Allo-S, an endogenous neurosteroid) and 28-day seizure rates were also assessed. A ganaxolone-responder was specified by post-hoc definition, as having at least a 25% reduction in 28-day seizure rate. In the PCDH19 cohort, responders (n = 6) and non-responders (n = 5) had plasma Allo-S concentrations (mean ± SD) of 501 ± 430 pg mL^{-1} and 9,829 ± 6,638 pg mL^{-1}, respectively. When performing a retrospective separation of the PCDH19 cohort according to their Allo-S level, the 7 subjects with Allo-S levels below 2,500 pg mL^{-1} (biomarker-positive) had a 50% reduction in seizure rates while the 4 subjects with Allo-S levels above 2,500 pg mL^{-1} (biomarker-negative) had a 84% increase (performed in the research lab of Dr. Graziano Pinna at the University of Illinois, Chicago, the only laboratory during the conduct of the study that could reliably produce results for sulphated neurosteroids). The Clinical Global Impression Scale rated by Investigators (CGI-I) and Caregivers (CGI-P) has been consistent with seizure control. In the OL study (1042-0900), there were 4 SAEs (3 related to seizures and 1 related to rash) possibly related to the study drug in the PCDH19 subjects.

In addition to anticonvulsant activity, GNX has shown positive effects on anxiety, hyperactivity, and attention in children with fragile X syndrome (Ligsay 2016). Similar behavior problems occur in individuals with PCDH19 mutations (Smith 2018). 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 individuals with the PCDH19 mutation.

Methodology: This is a global, biomarker-stratified, DB, randomized, PBO-controlled trial of adjunctive GNX treatment in children with a confirmed pathogenic or likely pathogenic *PCDH19* mutation. The trial consists of a 12-week prospective baseline period to collect seizure data, followed by a 17-week DB phase, which is then followed by a long-term OL phase. 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.

A 12-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 at least 12 consecutive weeks prior to the Screening visit of documenting seizure type and frequency (also noting seizure-free days). 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 subject assent has been appropriately obtained. In the event that parent/caregiver/LAR do not routinely maintain a daily seizure calendar or genetic testing has not been performed per standard of care, written informed consent will be obtained from the parent/LAR and subject assent, and the subject will be asked to return to the clinic for the screening visit after they have maintained a 12 week daily historical seizure calendar and/or genetic testing has been completed.

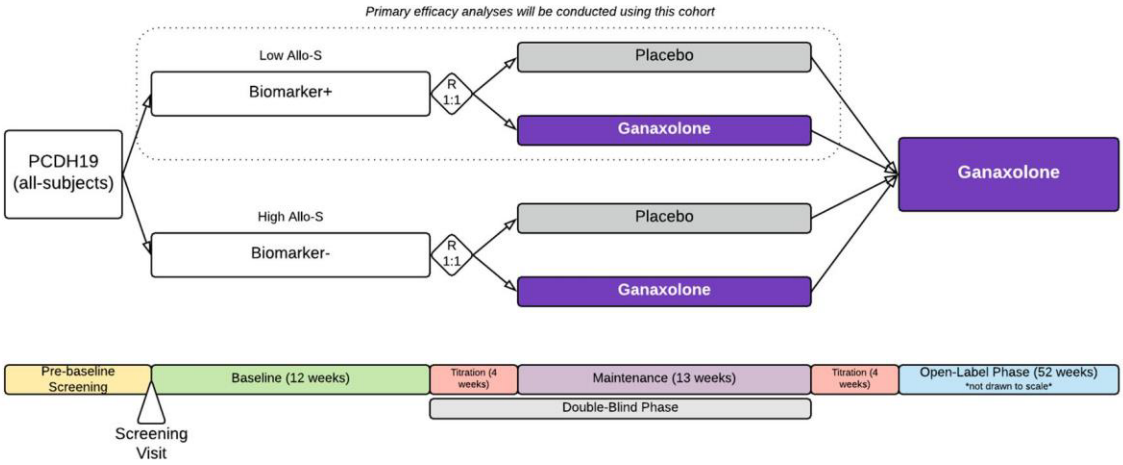
During the screening visit, each subject's biomarker level will be assessed via a blood draw and subsequent analytical quantification. Each subject will then be assigned to 1 of 2 groups: biomarker-positive or biomarker-negative. A subject will be considered biomarker-positive if her baseline Allo-S level is less than or equal to 2500 pg/mL (Pinna Lab method or similar). The biomarker group assignment will remain blinded until database unblinding after the study has completed. Based on the completed 11-subject 1042-0900 Phase 2a study, it is estimated that approximately 65% of all subjects will be biomarker-positive.

Subject rescreening is allowed as agreed by Sponsor and Investigator unless there is a general concern for subject safety or an inability for the subject to become eligible (eg, GNX allergy, sensitivity or exposure, non-PCDH19 and/or other ineligible epilepsy, chronic prohibited medical condition or treatment). Subsequent screening should take place at least 30 days from the subject's last visit.

The DB phase includes 4 weeks of investigational product titration followed by 13 weeks of dose maintenance. After meeting the eligibility criteria, approximately 25 children aged 1-17 years (inclusive) with PCDH19-related epilepsy will be randomly assigned to receive GNX or PBO (1:1 ratio within each biomarker stratum) 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. A minimum dose of 33 mg/kg/day or 900 mg/day is generally required following the DB escalation period, unless a lower dose is agreed to with the sponsor due to tolerability issues such as somnolence.

Dose changes including alternative dosing paradigms (e.g., lower dose during the daytime and higher dose in the evening) should be discussed with the clinical research organization (CRO)/sponsor medical monitor prior to making the change or within 48 hours of making the change. Of note, the sponsor defers the final decision to adjust IP to the treating study clinician; dose changes may not exceed the maximum total daily dose defined by the protocol. 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 such as drug-induced rash. Subjects who discontinue investigational product treatment before the completion of the DB phase will continue to be followed per protocol and, at a minimum, subjects will be encouraged to maintain daily seizure eDiary entries until the DB phase is completed. These subjects will also return to the site 2 to 4 weeks after the taper for safety follow-up assessments.

After completing the initial 17-week, DB, PBO-controlled treatment phase, all subjects will be treated with GNX in the OL 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 blinded 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. Any subject who completes the study or discontinues investigational product treatment should undergo a 2-week drug de-escalation (taper) period and return to the site 2 weeks later for safety follow-up assessments. Taper is not required if the subject is receiving the dose of 18 mg/kg/day or 450 mg/day (or lower).



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 PCDH19-related epilepsy, and include:

- Behavior Rating Inventory of Executive Function (BRIEF)
- Aberrant Behavior Checklist – Community (ABC-C)
- Children's Sleep Habit Questionnaire (CSHQ)
- Pediatric Quality of Life Inventory – Family Impact Module (PedsQL-FIM)
- Quality of Life Inventory – Disability (QI-Disability)
- Caregiver Global Impression of Change (CGI-C) – Target Behavior, Clinical Global Impression-Improvement (caregiver), and Clinical Global Impression-Improvement (clinician)

Inclusion and Exclusion criteria:

Inclusion Criteria:

1. Molecular confirmation of a pathogenic or likely pathogenic PCDH19 variant. Genetic mutations will be confirmed by the sponsor's chosen central laboratory.
2. Female subjects aged 1 through 17 years, inclusive.
3. Subject/parent or LAR willing to give written informed consent and subject 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 12 countable/witnessed primary seizures over an 84-day (12 week) period prior to the screening visit (pre-baseline screening). The primary seizure types are defined as countable focal seizures that include progressive hypotonia and impaired awareness, or any countable focal or generalized seizure with a clear motor component. Focal and generalized nonmotor seizures and myoclonic seizures do not count as the primary seizure types.
6. Subject must be approved to participate by sponsor or its designee (eg, Epilepsy Consortium) after review of medical history, genetic testing, seizure classification video (if available), and historical seizure calendars.
7. Concomitant AED regimens must have been stable for at least 1 month prior to the screening visit and must remain stable from screening to the end of the DB phase. Ketogenic diets and modified Atkins diet should be unchanged for 3 months prior to screening and must remain stable throughout the baseline and the DB phase.
8. 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 baseline and the DB phase.
- The battery is expected to last for the duration of baseline and the DB phase.

9. Parent/caregiver is able and willing to maintain an accurate and complete daily seizure diary for the duration of the study.
10. Able and willing to take investigational product (suspension) with food 3 times daily. Ganaxolone must be administered with food.
11. 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 the screening visit, surgical sterilization, or adequate barrier methods (eg, diaphragm or condom and foam). An oral contraceptive alone is not considered adequate for the purpose of this study. Use of oral contraceptives in combination with another method (eg, a spermicidal cream) is acceptable. In subjects who are not sexually active, abstinence is an acceptable form.

Exclusion Criteria:

1. Previous exposure to GNX.
2. Pregnant or breastfeeding.
3. Subjects with >8 consecutive weeks (56 consecutive days) of primary seizure freedom during the 12-week pre-baseline screening period.
4. Subjects with ≤ 3 primary seizures during the 12-week baseline period.
5. Concurrent use of strong inducers or inhibitors of CYP3A4/5/7 is not permitted. Any strong inhibitor or inducer of CYP3A4/5/7 must be discontinued at least 28 days before Baseline/Randomization Visit. This does not include approved AEDs.
6. Subjects with a positive result on tetrahydrocannabinol (THC) or non-approved cannabidiol (CBD) test (via plasma drug screen). Tetrahydrocannabinol and/or non-approved CBD will be allowed in the OL phase.
7. Chronic use of oral steroid medications, ketoconazole (except for topical formulations), St. John's Wort, or other investigational products is not permitted. Intermittent (<5 consecutive days/month or 10 cumulative days per month) use of corticosteroids as a rescue medication for breakthrough seizures may be allowed after sponsor approval.
8. Changes in any chronic AED medication (i.e., changes in dose or starting a new chronic AED) within the last month prior to the screening visit (Visit 1) and during the 12 week baseline period (i.e., between Visit 1 and Visit 2). Changes in rescue AED medications to treat acute breakthrough seizures may be permitted with Sponsor's approval. Changes in other (i.e., non-AED) chronic medications may be permitted with Sponsor's approval.
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 PCDH19-related epilepsy) at the screening visit 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 aspartate aminotransferase (AST/serum glutamic oxaloacetic transaminase [SGOT]) or alanine aminotransferase (ALT/serum glutamic pyruvic transaminase [SGPT]) > 3 × the upper limit of normal (ULN) at screening and if applicable confirmed by a repeat test. If the subject has another reason to be excluded, repeated liver enzymes are not required.
12. Total bilirubin levels > 1.5 × ULN at screening and if applicable confirmed by a repeat test. In cases of documented, stable medical condition (i.e., Gilbert's Syndrome) resulting in levels of total bilirubin > ULN, the medical monitor can determine if a protocol exception can be made.
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 fewer than 5 half-lives prior to the screening visit.
15. Unwillingness to withhold grapefruit, Seville oranges, star fruit, or grapefruit-containing products from diet 14 days prior to 1st dose and for the duration of the study
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.

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 given as an oral suspension with food. Subjects ≤ 28 kg will be dosed on an mg/kg basis. Subjects > 28 kg will be dosed on a fixed regimen in increments of 450 mg/day up to 1800 mg/day. Ganaxolone is to be administered during the 4-week titration period of the DB phase of the study as follows:

Oral Suspension Dosing[a] for Subjects Weighing ≤ 28 kg (62 pounds)[b]			
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
Oral Suspension Dosing[a] for Subjects Weighing > 28 kg (62 pounds)[c]			
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 = 3 times daily.

[a] To be administered in 3 divided doses following a meal or snack.

[b] Subjects weighing ≤ 28 kg will be dosed according to the subject's weight in kilograms.

[c] Subjects > 28 kg will be dosed on a fixed regimen in increments of 450 mg/day up to 1800 mg/day.

Any subject not tolerating the next dose level can be maintained at the lower dose for additional days before advancing to the next dose. If the next dose level is still not tolerated, the subject can drop back to the last tolerated dose . A minimum dose of 33 mg/kg/day or 900 mg/day is generally required following the DB escalation period, unless a lower dose is agreed to with the sponsor due to tolerability issues such as somnolence.

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 /CRO medical monitor prior to making the change or within 48 hours of making the change. Of note, the sponsor defers the final decision to adjust IP to the treating study clinician; dose changes may not exceed the maximum total daily dose defined by the protocol. 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 treatment before the completion of the DB phase will continue to be followed per protocol and, at a minimum, subjects will be encouraged to maintain daily seizure eDiary entries until the DB phase is completed. These subjects will also return to the site 2 to 4 weeks after the taper for safety follow-up assessments.

During the OL phase, all subjects will be treated with GNX. Those subjects who received GNX oral suspension in the 17-week DB phase will receive the same GNX dose in the OL phase of the study. However, to maintain the study blind, GNX subjects will enter into a 4-week blinded titration phase by increasing PBO doses in addition to maintaining GNX. Subjects who received PBO oral suspension in the 17-week DB phase will enter a 4-week, GNX titration period in the OL phase of the study.

Reference Therapy, Dose and Mode of Administration: Placebo is to be administered as an oral suspension TID with food during the 4-week, titration period of the DB phase of the study.

Placebo will only be used in the OL phase of the study during the 4-week blinded titration phase for those subjects who were originally randomized to GNX in the 17-week DB phase.

Duration of treatment: Eligible subjects will collect 12 weeks of prospective baseline seizure data. Subjects will be randomized (1:1 within each biomarker stratum) to a 17-week DB phase with GNX or PBO (4 weeks titration and 13 weeks dose maintenance), followed by a long-term OL treatment phase with GNX. Following the completion of the 17-week DB phase, subjects randomized to PBO will transition to GNX (using blinded titration), while subjects randomized to GNX will stay on 63 mg/kg/day suspension (1800 mg/day maximum), or their maximum tolerated dose (MTD) and also receive a blinded titration of PBO. Subjects will begin the 4-week blinded dose titration to 63 mg/kg/day (1800 mg/day or MTD) after completing the final DB visit. The OL phase will continue until the sponsor terminates the development of the investigational product in PCDH19-related epilepsy 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 she will return to the study site for a safety follow up visit. Subjects who discontinue investigational product treatment before the completion of the DB phase will continue to be followed per protocol and, at a minimum, subjects will be encouraged to maintain daily seizure eDiary entries until the DB 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 Endpoint (seizure control)

The primary efficacy endpoint is the percent change in 28-day primary seizure frequency during the 17-week DB phase relative to the baseline. The primary seizure types are defined as countable focal seizures that include progressive hypotonia and impaired awareness, or any countable focal or generalized seizure with a clear motor component. Focal and generalized nonmotor seizures and myoclonic seizures do not count as the primary seizure types for the primary efficacy endpoint. The analyses of the primary endpoint will be performed on the sum of the individual countable seizures and each series of continuous uncountable seizures (each contributes 1 to the sum).

Post-baseline 28-day seizure frequency will be calculated as the total number of seizures in the 17-week DB treatment phase divided by the number of days with seizure data in the phase, multiplied by 28. Baseline 28-day seizure frequency will be calculated as the total number of seizures in the baseline phase divided by the number of days with seizure data in the phase, multiplied by 28. The difference between the GNX and placebo groups in the percent changes will be tested using the Wilcoxon Rank-Sum statistic. The primary analysis will be conducted in the ITT population. If nominal statistical significance is achieved in the ITT population, the primary analysis will be conducted in the biomarker-positive stratum of the ITT population as a secondary endpoint.

Secondary endpoints (seizure control):

- The percent change in 28-day primary seizure frequency during the 17-week DB Phase relative to baseline in biomarker-positive subjects.
- Percentage of subjects experiencing a $\geq$ 50% reduction in 28-day primary seizure frequency compared to the baseline

Secondary endpoints (behavioral/neuropsychiatric):

- Behavior Rating Inventory of Executive Function (BRIEF, preschool version BRIEF-P)
- Aberrant Behavior Check – Community (ABC-C)
- Children's Sleep Habit Questionnaire (CSHQ)

Exploratory Endpoints: [redacted]

Pharmacokinetic Assessments:

The PK population will include all subjects who have received at least 1 dose of IP and who have had at least 1 sample collected and a valid bioanalytical result obtained. The samples will be drawn between 1 and 5 hours or between 4 and 8 hours after the last dose during the double-blind and open label periods. 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. Further details will be provided in the SAP.

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, 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, DB phase and the OL phase. Height and weight will also be measured.

Statistical Methods:

The primary efficacy endpoint (seizure control) is the percent change in 28-day primary seizure frequency during the 17-week DB phase relative to the baseline, based on all countable focal seizures that include progressive hypotonia and impaired awareness, or any countable focal or generalized seizure with a clear motor component.

The analyses of the primary endpoint will be performed on the sum of the individual countable seizures and each series of continuous uncountable seizures (each contributes 1 to the sum). Post-baseline 28-day seizure frequency will be calculated as the total number of seizures in the 17-week DB treatment phase divided by the number of days with seizure data in the phase, multiplied by 28. Baseline 28-day seizure frequency will be calculated as the total number of seizures in the baseline phase divided by the number of days with seizure data in the phase, multiplied by 28.

The primary analysis will be conducted in the ITT Population.

All secondary efficacy endpoints will compare GNX and PBO during the 17-week DB treatment phase relative to the prospective baseline phase.

The percentages of seizure-free days will be based on the primary seizure types.

BRIEF (BRIEF-P where appropriate) will be assessed as follows: in the DB phase at Visit 2 (baseline/randomization) and Visit 5 (Week 17; also Final DB Visit/First OL Visit in open label phase); in the OL phase at Visit 7 (Week 36) and Visit 9 (Week 68) and thereafter every 16 weeks for the duration of this phase; and at the Final OL Visit.

The ABC-C will be assessed as follows: in the DB phase at Visit 2 (baseline/randomization) and Visit 5 (Week 17; also Final DB Visit/First OL Visit in open label phase); in the OL phase at Visit 7 (Week 36) and Visit 9 (Week 68) and thereafter every 16 weeks for the duration of this phase; and at the Final OL Visit.

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With few exceptions, all of the analyses for the DB phase will be repeated for the OL phase with the following differences.

Safety Analysis:

All safety analyses will be performed in the Safety Population. The results in the DB and OL phases will be summarized separately. Adverse events will be tabulated by overall, system organ class, and Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA) coding system. Incidence and percentage of AEs will be presented. Additional tables, with AEs classified by severity and by only those related to drug as assessed by the PI will be presented. Subset listings will be produced for AEs that cause withdrawal and for SAEs. Clinical laboratory tests (hematology, chemistry and urinalysis), vital signs and ECGs will be summarized using descriptive statistics including changes from baseline. Physical, neurological and developmental examinations will be summarized using number and percentage of subjects with abnormalities.

Pharmacokinetic Analysis: A population PK approach addressing the relationship between GNX PK parameters and individual characteristics will be implemented during the study. One blood sample will be obtained at the following visits for PK analyses:

- During the DB Phase:
  - 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
- During the OL Phase:
  - Visit 6 (Week 21): between 1 and 5 hours since the last investigational product dosing
  - Visit 8 (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 visits for Visit 5 (Week 17), Visit 7 (Week 36), Visit 9 (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: Blood samples will be drawn at screening visit, Week 17, and the final OL 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: No formal interim analysis is planned for this study. After all active subjects complete the17-week double-blind phase, the double-blind data in the database will be locked and used to perform endpoint analysis. Data collected during the open label phase will be analyzed separately.

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 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 Assessments for the 17-Week, Double-Blind Treatment Phase of the Study

	Pre-screen/Screen/Baseline			DB Titration + Maintenance					Final DB Visit
WEEK	**- (Pre-baseline Screening Visit)**	**-12 (Screening Visit – Start of Baseline)**	**0 (Baseline Visit – Randomization)**	**3 days**	**1, 2, 3, 4**	**5**	**9**	**11, 13**	**17**
Visit Windows	**N/A**	**N/A**	**+ 6 days**	**± 1 day**	**± 3 days**	**± 3 days**	**± 3 day**	**± 3 days**	**± 3 days**
VISIT	**Visit 0**	**Visit 1[a]**	**Visit 2[r]**	**Phone Follow-up**	**Phone Follow-up**	**Visit 3**	**Visit 4**	**Phone Follow-up**	**Visit 5**
Screening and Diagnosis									
Informed Consent[b]	X[c]	X							
Demographics & Medical History		X	X[d]						
Historical Seizure Calendar Review[c]	X	X							
Inclusion/Exclusion Criteria	X	X	X						
Genetic testing[e]	X	X							
Seizure Identification and Diagnostic Review Form (Epilepsy Study Consortium)		X	X						
Safety Assessments									
Vital signs (BP, HR, RR, and body temperature)		X[f]	X[g]			X[g]	X[g]		X[g]
Physical/Neurological/ Developmental Exam		X	X			X	X		X
ECG			X			X			X
Clinical Laboratory Tests[h]		X	X			X	X		X
Urinalysis		X[i]	X[i]			X			X
Drug screen[j]		X	X						X
Pregnancy Test (WCBP)[k]		X	X			X	X		X
Tanner Staging		X							
Investigational Product PK						X[l]	X[l]		X

Table 1: Schedule of Assessments for the 17-Week, Double-Blind Treatment Phase of the Study

	Pre-screen/Screen/Baseline			DB Titration + Maintenance					Final DB Visit
WEEK	**- (Pre-baseline Screening Visit)**	**-12 (Screening Visit – Start of Baseline)**	**0 (Baseline Visit – Randomization)**	**3 days**	**1, 2, 3, 4**	**5**	**9**	**11, 13**	**17**
Visit Windows	**N/A**	**N/A**	**+ 6 days**	**± 1 day**	**± 3 days**	**± 3 days**	**± 3 day**	**± 3 days**	**± 3 days**
VISIT	**Visit 0**	**Visit 1[a]**	**Visit 2[r]**	**Phone Follow-up**	**Phone Follow-up**	**Visit 3**	**Visit 4**	**Phone Follow-up**	**Visit 5**
Concomitant AED Review and levels if per standard of care[m]		X	X			X	X		X
Neurosteroid levels		X							X
Adverse Event		X	X	X	X	X	X	X	X
Efficacy Assessments									
Seizure and Medication eDiary review[n]		X[o]	X	X	X	X	X	X	X
Children's Sleep Habit Questionnaire (CSHQ)			X						X
Behavior Rating Inventory of Executive Function (BRIEF)			X						X
Aberrant Behavior Checklist – Community (ABC-C)			X						X
Exploratory Assessments									
[redacted]			[redacted]						[redacted]
[redacted]			[redacted]						[redacted]
[redacted]			[redacted]						[redacted]
[redacted]			[redacted]			[redacted]	[redacted]		[redacted]

Table 1: Schedule of Assessments for the 17-Week, Double-Blind Treatment Phase of the Study

	Pre-screen/Screen/Baseline			DB Titration + Maintenance					Final DB Visit
WEEK	**- (Pre-baseline Screening Visit)**	**-12 (Screening Visit – Start of Baseline)**	**0 (Baseline Visit – Randomization)**	**3 days**	**1, 2, 3, 4**	**5**	**9**	**11, 13**	**17**
Visit Windows	**N/A**	**N/A**	**+ 6 days**	**± 1 day**	**± 3 days**	**± 3 days**	**± 3 day**	**± 3 days**	**± 3 days**
VISIT	**Visit 0**	**Visit 1[a]**	**Visit 2[r]**	**Phone Follow-up**	**Phone Follow-up**	**Visit 3**	**Visit 4**	**Phone Follow-up**	**Visit 5**
[redacted]									
[redacted]			[redacted]			[redacted]	[redacted]		[redacted]
[redacted]			[redacted]			[redacted]	[redacted]		[redacted]
Dispense Investigational Product[q]			X			X	X		X

Table 1. Schedule of Assessments for the 17-Week, Double-Blind Phase of the Study: Footnotes

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. Subject rescreening is allowed as agreed by Sponsor and Investigator unless there is a general concern for subject safety or an inability for the subject to become eligible (eg, GNX allergy, sensitivity or exposure, non-PCDH19 and/or other ineligible epilepsy, chronic prohibited medical condition or treatment). Subsequent screening should take place at least 30 days from the subject's last visit.

b. Written informed consent/assent must be obtained from subject, parent or LAR before any study assessments are performed.

c. In the event that the parent/caregiver/LAR does not routinely maintain a daily seizure calendar per standard of care, written informed consent will be obtained from the parent/LAR and subject assent, and the subject will be asked to return to the clinic for the screening visit after she has maintained a 12-week daily historical seizure calendar.

d. Review of medical history only.

e. Genetic testing to be performed to confirm pathogenic or likely pathogenic *PCDH19* variant. If genetic testing is not performed as Standard of Care, a pre-baseline screening visit will be scheduled to obtain informed consent/assent and complete the genetic testing. If genetic testing results are available per SOC, the genetic testing will be done at screening to confirm the results by the Sponsors designated lab.

f. In addition, height and weight will be measured.

g. In addition, weight will be measured. At each visit, dosing will be reviewed and adjusted as needed based on a subject's current weight.

h. Chemistry & Hematology.

i. 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.

j. A drug screen (plasma) will be performed to test for THC and CBD at screening. If the screening drug test is positive, the subject can be retested, via plasma, after two weeks. A drug screen may be performed at any time at Investigator's discretion. A positive drug test during the DB phase will result in early termination.

k. Serum pregnancy test is required for all girls/women of childbearing potential.

l. 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 investigational product dosing).

m. Concomitant AEDs 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.

n. For recording of seizures in the eDiary, seizure events will be recorded either as a countable seizure or a series of continuous uncountable seizures. Both of these events will be counted as 1 seizure (equally weighted) in the efficacy analysis. A seizure cluster will be defined as 3 or more seizure events (either a countable or a series of continuous uncountable seizures), occurring within a period of time, followed by a period of at least 24 hours of seizure-freedom.

   Examples: (Figure 2):

   - If a child experiences 3 seizure events at 5:00, 5:30, and 6:00 PM on Monday, and the next seizure event occurs before 6:00 PM on Tuesday, the Monday and Tuesday seizure events are considered part of the same seizure cluster (Figure 2, Scenario 1).
   - If a child experiences 3 seizure events at 5:00, 5:30, and 6:00 PM on Monday, and the next seizure event occurs at 6:00 PM or later on Tuesday, the Tuesday seizure event is <u>not</u> considered part of the same cluster (Figure 2, Scenario 2).

o. Caregiver given eDiary and instructions for use.

p. During the screening visit, the principal investigator and parent/caregiver/LAR will decide on a domain and identify the specific behavior that the subject exhibits that denotes the domain. This behavior will be used at subsequent visits to assess change after the initiation of investigational product.

q. Subjects who discontinue investigational product early will be encouraged to continue with all procedures and scheduled visits.

r. The 12 weeks between Screening and Randomization can be no less than 84 days and no more than 90 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, this schedule continues after 68 weeks)						Final OL Visit or Taper Visit[J]	Safety Follow-up post taper[J]
WEEK	**17**	**Week 17 +3 Days**	**18, 19, 20**	**21**	**28**	**36**	**44**	**52**	**60**	**68[a] and X visit**	**X/ or early D/C[J]**	**2 weeks post last dose**
Visit Windows		**± 1 day(s)**	**± 3 days**	**± 3 days**	**± 14 days**	**± 14 days**	**± 14 days**	**± 14 days**	**± 14 days**	**± 14 days**	**± 14 days**	**± 3 days**
VISIT	**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 and Visit X**	**Visit X**	**Visit X**
Safety Assessments												
Vital signs (BP, HR, RR, and body temperature)[b]	X[b]			X[b]		X[b,c]		X[b,c]		X[b, c]	X[b,c]	X
Physical/Neurological/ Developmental Exam	X			X		X		X		X	X	X
ECG	X			X				X[d]			X	
Clinical Laboratory Tests[e]	X			X		X		X		X	X	X
Urinalysis	X					X		X		X[g]	X	X
Drug Screen	X											
Pregnancy Test (WCBP)[f]	X			X		X		X		X	X	X
Tanner Staging								X		X[g]	X	
Investigational Product PK	X			X[i]		X		X[i]		X	X	X
Concomitant AED Review and levels if per standard of care	X			X		X		X		X	X	X
Neurosteroid Levels	X							X		X[g]	X	
Adverse Event	X	X	X	X	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, this schedule continues after 68 weeks)						Final OL Visit or Taper Visit[J]	Safety Follow-up post taper[J]
WEEK	**17**	**Week 17 +3 Days**	**18, 19, 20**	**21**	**28**	**36**	**44**	**52**	**60**	**68[a] and X visit**	**X/ or early D/C[J]**	**2 weeks post last dose**
Visit Windows		**± 1 day(s)**	**± 3 days**	**± 3 days**	**± 14 days**	**± 14 days**	**± 14 days**	**± 14 days**	**± 14 days**	**± 14 days**	**± 14 days**	**± 3 days**
VISIT	**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 and Visit X**	**Visit X**	**Visit X**
Efficacy Assessments												
Seizure eDiary review[h]	X	X	X	X	X	X	X	X	X	X	X	X
Children's Sleep Habit Questionnaire (CSHQ)	X					X				X	X	
Behavior Rating Inventory of Executive Function (BRIEF)	X					X				X	X	
Aberrant Behavior Checklist – Community (ABC-C)	X					X				X	X	
Exploratory Assessments												
[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, this schedule continues after 68 weeks)						Final OL Visit or Taper Visit[J]	Safety Follow-up post taper[J]
WEEK	17	Week 17 +3 Days	18, 19, 20	21	28	36	44	52	60	68[a] and X visit	X/ or early D/C[J]	2 weeks post last dose
Visit Windows		± 1 day(s)	± 3 days	± 3 days	± 14 days	± 14 days	± 14 days	± 14 days	± 14 days	± 14 days	± 14 days	± 3 days
VISIT	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 and Visit X	Visit X	Visit X
[redacted]	▮					▮				▮	▮	
[redacted]	▮					▮				▮	▮	
[redacted]	▮					▮				▮	▮	
Dispense Investigational Product	X			X		X		X		X	X	

Table 2. Schedule of Assessments for Open-Label Phase: Footnotes

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.

Note: The timing of the final OL 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 PCDH19-related epilepsy (approximately an additional 3 years).

a. If the subject continues in the OL phase beyond Week 68, a telephone follow-up visit will occur in between clinic visits (8 weeks ± 14 days after each clinic visit) to assess the following adverse events and seizure and medication diary review.

b. In addition, weight will be measured at every visit, except the safety follow-up visit.

c. In addition, height will be measured annually after Visit 8 (Week 52), except the safety follow-up visit.

d. After Visit 8 (Week 52), ECGs to be performed annually (and at last OL visit).

e. Chemistry & Hematology.

f. Serum pregnancy test is required for all girls/women of childbearing potential.

g. Conduct annually and at the final OL visit.

h. For recording of seizures in the eDiary, seizure events will be recorded either as a countable seizure or a series of continuous uncountable seizures. Both of these events will be counted as 1 seizure (equally weighted) in the efficacy analysis. For recording of seizures in the eDiary, seizure events will be recorded either as a countable seizure or a series of continuous uncountable seizures. Both of these events will be counted as 1 seizure (equally weighted) in the efficacy analysis. A seizure cluster will be defined as 3 or more seizure events (either a countable or a series of continuous uncountable seizures), occurring within a period of time, followed by a period of at least 24 hours of seizure-freedom.

   Examples: (Figure 2):

   - If a child experiences 3 seizure events at 5:00, 5:30, and 6:00 PM on Monday, and the next seizure event occurs before 6:00 PM on Tuesday, the Monday and Tuesday seizure events are considered part of the same seizure cluster (Figure 2, Scenario 1).
   - If a child experiences 3 seizure events at 5:00, 5:30, and 6:00 PM on Monday, and the next seizure event occurs at 6:00 PM or later on Tuesday, the Tuesday seizure event is <u>not</u> considered part of the same cluster (Figure 2, Scenario 2).

i. Population PK will be conducted at these visits (Visit 6: between 1-5 hours since the last IP dosing and Visit 8: between 1-5 hours since last IP dosing)

j. Subjects who discontinue IP treatment before the completion of the DB phase will continue to be followed per protocol and, at a minimum, subjects will be encouraged to maintain daily seizure eDiary entries until the DB phase is completed. These subjects will also return to the site 2 to 4 weeks after the taper for safety follow-up post-taper assessments. Taper is not required if the subject is receiving the dose of 18 mg/kg/day or 450 mg/day (or lower).

1. BACKGROUND INFORMATION

1.1. Indication and Current Treatment Options

Pediatric patients with rare epilepsy conditions, such as protocadherin 19 (PCDH19)-related epilepsy, cyclin-dependent kinase-like 5 (CDKL5) Disorder (CDD), Dravet Syndrome, as well as many other refractory genetic epilepsy conditions that may share common seizure types and often their seizures, become treatment-resistant. These seizure disorders may overlap idiopathic Lennox-Gastaut syndrome (LGS) or other genetically-based conditions with intractable epilepsy clinically resembling LGS. This population has been at times, treated with, and responsive to, classes of corticosteroids like prednisone or adrenocorticotropic hormone. Other epileptic diagnostic conditions, such as continuous spike and wave during slow wave sleep (CSWS) or electrical status epilepticus in sleep, may also respond to corticosteroid medications, and be refractive to standard antiepileptic agents. The mechanism by which any of these mutations contributes to the development of epilepsy is not well understood. No single anticonvulsant has been found to be uniformly effective, and often multiple anticonvulsants are needed; even then, patients still become treatment-resistant.

The need for novel treatments to address seizure control is critical for pediatric patients living with these conditions. This study will assess the efficacy and safety of ganaxolone as an experimental drug with a new and distinct mechanism of action.

Ganaxolone (GNX) is the 3β -methylated synthetic analog of allopregnanolone, an endogenous allosteric modulator of γ-aminobutyric acid type A ($GABA_A$) receptors in the central nervous system (CNS). Ganaxolone has potency and efficacy comparable to allopregnanolone in activating synaptic and extrasynaptic $GABA_A$ receptors at a site distinct from the benzodiazepine site. Ganaxolone has protective activity in diverse rodent seizure models (Bialer 2010, Reddy 2012).

Clinical studies have demonstrated that GNX has anticonvulsant efficacy with an acceptable safety and tolerability profile in the dose range of 900 to 1800 mg in adults and children (Sperling 2017, Laxer 2000, Kerrigan 2000, Pieribone 2007). The present study will investigate whether GNX provides efficacy for children with uncontrolled seizures and PCDH19-related epilepsy and other genetic epilepsies.

Protocadherin 19- female-pediatric epilepsy, also known as PCDH19 female-limited epilepsy, or epilepsy in females with mental retardation (hereon referred to as PCDH19-related epilepsy), is a serious epileptic syndrome characterized by early-onset cluster seizures, cognitive and sensory impairment of varying degrees, and psychiatric and behavioral disturbances in some individuals (Camacho 2012, Depienne 2014).

PCDH19-related epilepsy is associated with a mutation of the PCDH19 gene, the gene that encodes for protocadherin19 on the X chromosome (Depienne 2014a, Dibbens 2008). The mechanism by which this mutation contributes to the development of epilepsy and intellectual impairment is not fully understood. Protocadherin is, however, a transmembrane protein of calcium-dependent cell-cell adhesion molecules that is strongly expressed in neural tissue (eg, hippocampus, cerebral cortex, thalamus, and amygdale) and which appears to be related to synaptic transmission and formation of synaptic connections during brain development

(Depienne 2009). Research suggests that impairment of γ-Aminobutyric acid (GABA)-ergic signaling both at the agonist and receptor levels is present in girls with PCDH19 mutations and pediatric-onset epilepsy (Tan 2015).

The hallmark characteristics of PCDH19-related epilepsy are clusters of seizures which start in infancy or early childhood that are often associated with fever or immunization (Depienne 2012, Higurashi 2013, Marini 2010). Patients with PCDH19-related epilepsy may experience individual seizures in addition to clusters and multiple seizure types. In some patients, seizures improve as patients reach puberty, possibly due to increased endogenous levels of progesterone and allopregnanolone (Camacho 2012, Specchio 2011, Scheffer 2008).

The mean age of onset of PCDH19-related epilepsy is approximately 10 months (range of 3-38 months) (Scheffer 2008, Specchio 2011, Dipienne 2011, Cappelletti 2015, van Harssel 2013). The mean age of offset of epileptic seizures is approximately 12.5 years (1-35 years). PCDH19-related epilepsy has been described as a "semiprogressive" condition, meaning that seizure frequency increases during the first few years of life (Specchio 2011); however, the seizure frequency decreases, and seizures become less frequent with increased age.

There is also evidence supporting an allopregnanolone deficiency as a proposed contributor to the onset of seizures in individuals with PCDH19-related epilepsy (Tan 2015). It was found that individuals with this genetic mutation demonstrated a downregulation of steroid hormone-metabolizing enzymes, resulting in reduced allopregnanolone levels compared to non-affected, age-matched controls. Since this neurosteroid is known to have strong anti-convulsant properties, it is hypothesized that treatment with neurosteroids with similar action, or analogs such as GNX, may have therapeutic benefit to seizure control.

1.2. Product Background and Clinical Information

Ganaxolone is the 3β-methylated synthetic analogue of the neuroactive steroid allopregnanolone, but it is designed to not activate nuclear (classical) progesterone receptors. Ganaxolone differs from other GABA agents by interacting with both synaptic and extra-synaptic $GABA_A$ 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, 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 pentylenetetrazol 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 1997, Kaminski 2004, Reddy 2004).

As of 10 Oct 2018, 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 double-blind study)
- Study 1042-PPD-2003 in women with PPD (GNX oral capsule multi-dose escalation open label study)

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 placebo (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-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. These events 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 have been noted for electrocardiogram (ECG) intervals, vital signs, physical or neurologic examinations, or mean changes from baseline in clinical laboratory results. Overall, there have been 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 × 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 (DB), randomized trials and 5 open-label (OL), uncontrolled clinical trials of GNX in the pediatric population. One additional pediatric trial, OL 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 October 10, 2017) have received at least 1 dose of GNX. The largest cohorts received 12 to 54 mg/kg/day, although some subjects received doses as high as 63 mg/kg/day or 1800 mg/day for adolescents. As of October 10, 2017, 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 subjects received GNX during the trial), 39 subjects with infantile spasms (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, DB, 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-treated subjects, respectively.

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

Protocadherin19 (PCDH19)-related epilepsy is a serious epileptic condition characterized by early-onset cluster seizures, cognitive and sensory impairment of varying degrees, and psychiatric and behavioral disturbances affecting primarily females (Camacho 2012). The condition is caused by an inherited mutation of the PCDH19 gene located on the X chromosome. This gene encodes for a calcium-dependent cell-cell adhesion molecule that is expressed in the CNS (hippocampus, cerebral cortex, thalamus, amygdala) and which appears to be related to synaptic transmission and formation of synaptic connections during brain development (Depienne 2009).

The mean age of seizure onset in this condition is approximately 10 months (range of 3-38 months) (Scheffer IE 2008, Specchio N 2011, Dipienne 2011, Cappelletti 2015, van Harssel 2013). The mean age of offset of epileptic seizures is approximately 12.5 years (1-35 years). PCDH19-related epilepsy has been described as a "semiprogressive" condition, meaning that seizure frequency increases during the first few years of life (Specchio 2011). However, over time the seizure frequency decreases, and seizures become less frequent with increased age.

There is also evidence supporting an allopregnanolone deficiency as a proposed contributor to the onset of seizures in individuals with PCDH19-related epilepsy (Tan 2015). It was found that individuals with this genetic mutation demonstrated a downregulation of steroid hormone-metabolizing enzymes resulting in reduced allopregnanolone levels compared to non-affected, age-matched controls. Since this neurosteroid is known to have strong anti-convulsant properties, it is hypothesized that treatment with neurosteroids with similar action, or analogs such as GNX, may have therapeutic benefit to seizure control.

Ganaxolone is the 3β-methylated synthetic analog of allopregnanolone, an endogenous allosteric modulator of CNS $GABA_A$ receptors. Ganaxolone has potency and efficacy comparable to allopregnanolone (Carter 1997) in activating synaptic and extrasynaptic $GABA_A$ receptors at a site distinct from benzodiazepines and barbiturates. Ganaxolone has protective activity in diverse rodent seizure models (Reddy 2012, Bialer 2010). Clinical studies have demonstrated that 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 2017, Laxer 2000, Kerrigan 2000, Pieribone 2007). Further, GNX reduces seizures in children with IS and refractory pediatric epilepsy. In an OL 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 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 PCDH19-related epilepsy has emerged from an ongoing OL flexible-dose exploratory study (Study 1042-0900) of GNX in children (age range 2-15 years) with rare genetic epilepsies (including PCDH19) 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 could dose GNX starting with a titration 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 dose could also be reduced for tolerability reasons. 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 25% (n = 11).

The median change from baseline in seizure-free days in the ITT population (key secondary endpoint) was an increase of 14% (n = 11). Baseline levels of allopregnanolone sulfate (Allo-S, an endogenous neurosteroid) and 28-day seizure rates were also assessed. A ganaxolone-responder was specified by post-hoc definition, as having at least a 25% reduction in 28-day seizure rate. In the PCDH19 cohort, responders (n = 6) and non-responders (n = 5) had plasma Allo-S concentrations (mean ± SD) of 501 ± 430 pg mL^{-1} and 9,829 ± 6,638 pg mL^{-1}, respectively. When performing a retrospective separation of the PCDH19 cohort according to their Allo-S level, the 7 subjects with Allo-S levels below 2,500 pg mL^{-1} (biomarker-positive) had a 50% reduction in seizure rates while the 4 subjects with Allo-S levels above 2,500 pg mL^{-1} (biomarker-negative) had a 84% increase (performed in the research lab of Dr. Graziano Pinna at the University of Illinois, Chicago, the only laboratory during the conduct of the study that could reliably produce results for sulphated neurosteroids). The Clinical Global Impression Scale rated by Investigators (CGI-I) and Caregivers (CGI-P) has been consistent with seizure control. In the OL study (1042-0900), there were 4 SAEs (3 related to seizures and 1 related to rash) possibly related to the study drug in the PCDH19 subjects.

In addition to anticonvulsant activity, GNX has shown positive effects on anxiety, hyperactivity, and attention in children with fragile X syndrome (Ligsay 2016). Similar behavior problems occur in individuals with PCDH19 mutations (Smith 2018).

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 individuals with the PCDH19 mutation.

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 the treatment of primary seizures in children with genetically-confirmed PCDH19-related epilepsy during the17-week DB phase.

2.2.2. Secondary Objectives

The secondary objectives of this study are the following:

- To assess the effect of GNX on primary seizure rate in biomarker-positive subjects.
- To assess behavioral/neuropsychiatric changes in subjects receiving GNX compared with subjects receiving PBO as adjunctive therapy during the17-week DB phase.
- To assess the safety and tolerability of GNX compared with PBO as adjunctive therapy during the17-week DB 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 OL phase.
- To assess the long-term safety and tolerability of GNX when administered as adjunctive therapy throughout the OL phase.

2.2.3. Exploratory Objectives

[redacted]

3. STUDY DESIGN

3.1. Study Design and Flow Chart

This is a global, biomarker-stratified, DB, randomized, PBO-controlled trial of adjunctive GNX treatment in female children with a confirmed pathogenic or likely pathogenic PCDH19 mutation. The trial consists of a 12-week prospective baseline period to collect seizure data, followed by a 17-week DB treatment phase, which is then followed by a long-term OL phase (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 (Section 6.2.1).

A 12-week daily historical seizure calendar will be reviewed at the screening visit to determine eligibility per inclusion/exclusion criteria (Section 4). Acceptable historical seizure data must include at least 12 consecutive weeks prior to the Screening visit of documenting seizure type and frequency (also noting seizure-free days). If genetic testing is not performed as Standard of Care, a pre-baseline screening visit will be scheduled to obtain informed consent/assent and complete the genetic testing. If genetic testing results are available from SOC, the genetic testing will be done at screening to confirm the results by the Sponsors designated lab. Genetic testing is to be performed to confirm pathogenic or likely pathogenic *PCDH19* variant. 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 subject assent has been appropriately obtained. In the event that parent/caregiver/LAR does not routinely maintain a daily seizure calendar or have genetic testing results per standard of care, written informed consent will be obtained from the parent/LAR and subject assent. The subject will be asked to return to the clinic for the screening visit after she has maintained a 12-week daily historical seizure calendar.

During the screening visit, each subject's biomarker level will be assessed via a blood draw and subsequent analytical quantification. Each subject will then be assigned to 1 of 2 groups: biomarker-positive or biomarker-negative. A subject will be considered biomarker-positive if her baseline Allo-S level is less than or equal to 2500 pg/mL (Pinna Lab method or similar). The biomarker group assignment will remain blinded until database unblinding after the study has completed. Based on the 11-subject OL study, it is estimated that approximately 65% of all-comers will be biomarker-positive.

Subject rescreening is allowed as agreed by Sponsor and Investigator unless there is a general concern for subject safety or an inability for the subject to become eligible (eg, GNX allergy, sensitivity or exposure, non-PCDH19 and/or other ineligible epilepsy, or chronic prohibited medical condition or treatment). Subsequent screening should take place at least 30 days from the subject's last visit. If a subject fails to qualify because of Exclusion Criteria #4 (≤ 3 primary seizures during the 12-week baseline period), she will not be randomized. However, she can be rescreened after collecting another 12 or more weeks of seizure history that satisfies all eligibility criteria including Inclusion Criteria #5 and Exclusion Criteria #3. Each subject is allowed a maximum of 1 rescreening visit.

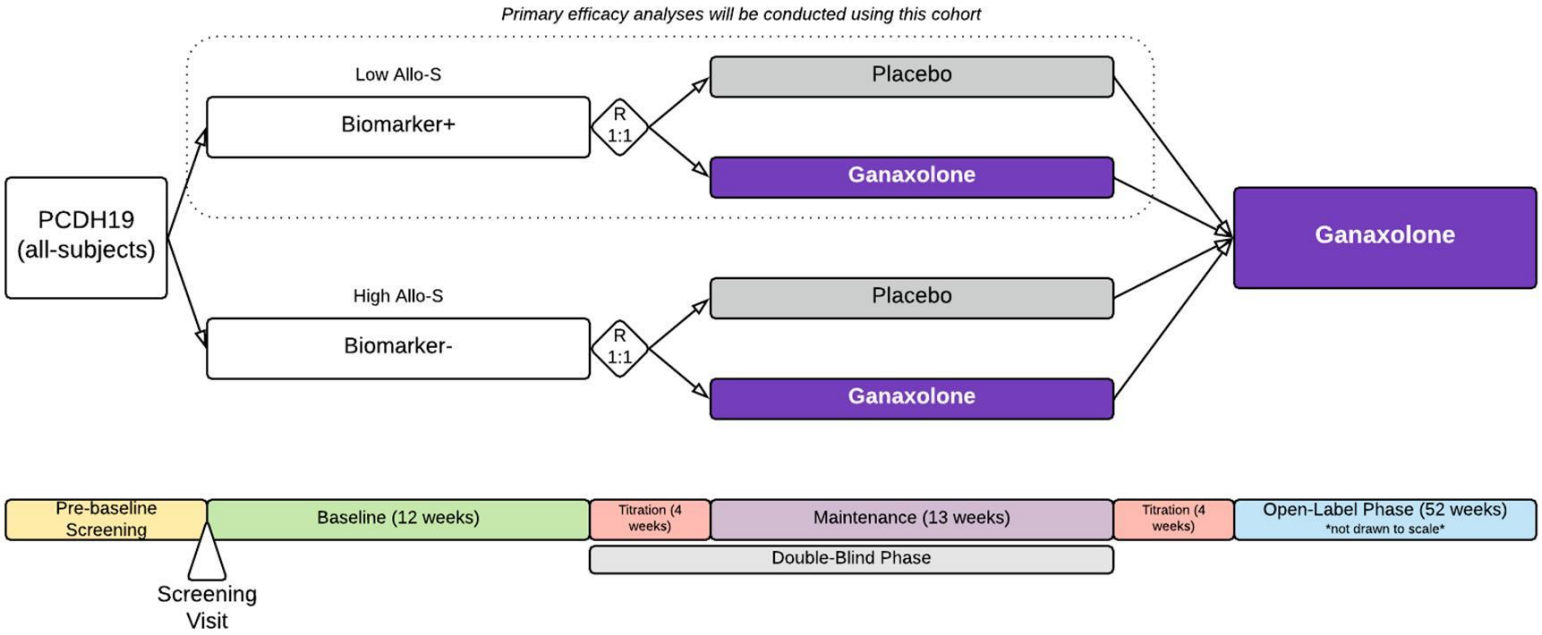
The DB phase includes 4 weeks of IP titration (Section 6.2.3.1) followed by 13 weeks of dose maintenance. After meeting the eligibility criteria, approximately 25 children aged 1 to 17 years

(inclusive) with PCDH19-related epilepsy will be randomly assigned to receive GNX or PBO (1:1 ratio within each biomarker stratum) for 17 weeks in addition to their standard anti-seizure treatment. Subjects 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. A minimum dose of 33 mg/kg/day or 900 mg/day is generally required following the DB escalation period, unless a lower dose is agreed to with the sponsor due to the tolerability such as somnolence. At each visit, dosing will be reviewed and adjusted as needed based on subject's current weight.

Dose changes, including alternative dosing paradigm (e.g. lower dose during the daytime and higher dose in the evening), should be discussed with the clinical research organization (CRO)/sponsor medical monitor prior to making the change or within 48 hours of making the change. Of note, the sponsor defers the final decision to adjust IP to the treating study clinician; dose changes may not exceed the maximum total daily do defined by the protocol. For any subject who is unable to be maintained at the minimum dose, the investigator should contact the sponsor to discuss continued IP dosing. Subjects who discontinue IP should undergo a 2-week taper period, unless otherwise medically indicated (Section 6.2.3.3). Subjects who discontinue IP treatment before the completion of the DB phase will continue to be followed per protocol and, at a minimum, subjects will be encouraged to maintain daily seizure eDiary entries until the DB phase is completed. These subjects will also return to the site 2 to 4 weeks after the taper for safety follow-up post-taper assessments.

After completing the initial 17-week, DB, PBO-controlled phase, all subjects will be treated with GNX in the OL 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 blinded titration (increasing PBO doses) for 4 weeks, whereas PBO subjects will titrate up to 63 mg/kg/day GNX (1800 mg/day maximum) during the same time period (Section 6.2.3.2). Any subject who completes the study or discontinues IP treatment should undergo a 2-week drug de-escalation (taper) period (Section 6.2.3.3) and return to the site 2 weeks later for safety follow-up post-taper assessments. Taper is not required if the subject is receiving the dose of 18 mg/kg/day or 450 mg/day (or lower).

Figure 1: Study Design



Subjects will be required to complete an eDiary to determine the effect of GNX on drug-resistant seizures. An electronic eDiary is the standard, in rare cases when an eDiary completion is not feasible, a paper diary will be used. These cases will need approval by the sponsor. A variety of clinician- and caregiver- administered instruments will be used to assess the efficacy of adjunctive GNX in PCDH19, and will include the following:

- Behavior Rating Inventory of Executive Function (BRIEF)
- Aberrant Behavior Checklist – Community (ABC-C)
- Children's Sleep Habit Questionnaire (CSHQ)
- Pediatric Quality of Life Inventory – Family Impact Module (PedsQL-FIM)
- Quality of Life Inventory – Disability (QI-Disability)
- Caregiver Global Impression of Change (CGI-C) – Target Behavior, Clinical Global Impression – Improvement [caregiver], and Clinical Global Impression – Improvement [clinician].

Safety and tolerability will be assessed by monitoring vital signs (blood pressure [BP], heart rate [HR], respiratory rate [RR], body temperature, weight, and height); 12-lead ECGs, clinical laboratory tests (hematology, chemistry, and urinalysis); physical, neurological, and developmental examinations; and frequency, type, and severity of AEs during the 17-week, DB phase and the OL phase.

3.2. Duration and Study Completion Definition

In the event that the parent/caregiver/LAR does not routinely maintain a daily seizure calendar per standard of care, written informed consent will be obtained from the parent/LAR and subject assent, and the subject will be asked to return to the clinic for the screening visit after she has maintained a 12-week daily historical seizure calendar. Additionally, if genetic testing is not completed as standard of care, a pre-baseline screening visit can be conducted to do so.

Eligible subjects will collect 12 weeks of prospective baseline seizure data. During the screening visit, each subject's biomarker level will be assessed via a blood draw and subsequent analytical quantification. Each subject will then be assigned to 1 of 2 groups: biomarker-positive or biomarker-negative. A subject will be considered biomarker-positive if her baseline Allo-S level is less than or equal to 2500 pg/mL (Pinna Lab method or similar). Subjects will then be randomized (1:1 GNX: PBO within each biomarker stratum) to a 17-week DB treatment phase (4 weeks titration and 13 weeks dose maintenance), followed by a long-term OL treatment phase with GNX. The biomarker group assignment will remain blinded until database unblinding after the study has completed.

Following completion of the 17-week DB phase, subjects randomized to PBO will transition to GNX (using blinded titration, Section 6.2.3.2), while subjects randomized to GNX will stay on 63 mg/kg/day (1800 mg/day or MTD) suspension or their maximum tolerated dose (MTD) and also receive a blinded titration of PBO. Subjects will begin the 4-week blinded dose titration to 63 mg/kg/day (1800 mg/day or MTD) after completing the final DB visit. The OL phase will continue until the sponsor terminates the development of the IP in PCDH19-related epilepsy or GNX has been approved and marketed in the subjects' respective country.

Subjects who complete the study or discontinue IP treatment before the end of the study will undergo a 2-week taper period (Section 6.2.3.3), unless otherwise medically indicated, after which they will return to the study site for a safety follow up visit. Subjects who discontinue IP treatment before completion of the DB phase will continue to be followed per protocol and, at a minimum, subjects will be encouraged to maintain daily seizure eDiary entries until the DB phase is completed.

3.3. Sites and Regions

This multicenter study is to be conducted globally, with approximately 11 sites planned to participate.

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

Treatment will be based on doses that have been shown to be safe in multiple studies with normal volunteers and children with epilepsy. In this study, subjects will be randomized to receive either oral suspension GNX or PBO (1:1 ratio within each biomarker stratum), prescribed in increments of 15 mg/kg/day up to 63 mg/kg/day (maximum 1800 mg/day). Full details of GNX dosing is provided in Section 6.2.3.

The DB phase will be followed by an OL 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. Ganaxolone subjects will continue GNX treatment and PBO subjects will titrate onto GNX. To maintain the study blind, GNX subjects will enter into a 4-week blinded titration phase by increasing PBO doses in addition to maintaining GNX. Subjects who received PBO oral suspension in the 17-week DB phase will enter a 4-week, GNX titration period in the OL phase of the study. Administration of GNX adjunctive therapy to background AEDs provides standard-of-care therapy in addition to any benefit that IP might provide.

Any subject not tolerating the next dose level can be maintained at the lower dose for additional days before advancing to next dose. If the next dose level is still not tolerated, the subject can drop back to the last tolerated dose. A minimum oral suspension dose of 33 mg/kg/day or 900 mg/day is generally required following the DB escalation period, unless a lower dose is agreed to with the sponsor due to tolerability issues such as somnolence.

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/CRO medical monitor prior to making the change or within 48 hours of making the change. Of note, the sponsor defers the final decision to adjust IP to the treating clinician; dose changes may not exceed the maximum daily dose defined by the protocol. 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 IP should undergo a 2-week taper period, unless otherwise medically indicated. Subjects who discontinue IP treatment before the completion of the DB phase will continue to be followed per protocol and, at a minimum, subjects will be encouraged to maintain daily seizure eDiary entries until the DB phase is completed. These subjects should also return to the site after the taper for safety follow-up post-taper assessments.

4. STUDY POPULATION

Each subject's parent/LAR must participate in the informed consent process and provide written informed consent (and 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. Molecular confirmation of a pathogenic or likely pathogenic PCDH19 variant. Genetic mutations will be confirmed by the sponsor's chosen central laboratory.
2. Female subjects aged 1 through 17 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 12 countable/witnessed primary seizures over an 84-day (12 week) period prior to the screening visit (pre-baseline screening). The primary seizure types are defined as countable focal seizures that include progressive hypotonia and impaired awareness or any countable focal or generalized seizure with a clear motor component. Focal and generalized nonmotor seizures and myoclonic seizures do not count as the primary seizure types.
6. Subject must be approved to participate by sponsor or its designee (eg, Epilepsy Consortium) after review of medical history, genetic testing, seizure classification video (if available), and historical seizure calendars.
7. Ketogenic diets and modified Atkins diets should be unchanged for 3 months prior to screening and must remain stable throughout baseline and the DB phase.
8. 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 baseline and the DB phase.
   - The battery is expected to last for the duration of baseline and the DB phase.
9. Parent/caregiver is able and willing to maintain an accurate and complete daily electronic seizure diary for the duration of the study.
10. Able and willing to take IP (suspension) with food 3 × daily. Ganaxolone must be administered with food.
11. 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 the screening visit, surgical sterilization, or adequate barrier methods (eg, diaphragm or condom and foam). An oral contraceptive alone is not considered adequate for the purpose of this study. Use of oral contraceptives in combination with another method (eg, a spermicidal cream) is acceptable. 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. Subjects with >8 consecutive weeks (56 consecutive days) of primary seizure freedom during the 12-week pre-baseline screening period.
4. Subjects with Subjects with ≤ 3 primary seizures during the 12-week baseline period.
5. Concurrent use of strong inducers or inhibitors of CYP3A4/5/7 is not permitted. A list of CYP3A4/5/7 inhibitors and inducers is included in Section 12.1. Any strong inhibitor or inducer of CYP3A4/5/7 must be discontinued at least 28 days before Baseline/Randomization Visit. This does not include approved AEDs.
6. Subjects with a positive result on tetrahydrocannabinol (THC) or non-approved cannabidiol (CBD) test (via plasma drug screen). Tetrahydrocannabinol and/or non-approved CBD will be allowed in the OL phase.
7. Chronic use of oral steroid medications, ketoconazole (except for topical formulations), St. John's Wort, or other IPs is not permitted (Section 12.1). Intermittent (<5 consecutive days/month or 10 cumulative days per month) use of corticosteroids as a rescue medication for breakthrough seizures may be allowed after sponsor approval.
8. Changes in any chronic AED medications (i.e., changes in dose or starting a new chronic AED) within the last month prior to the screening visit (Visit 1) and during the 12 week baseline period (i.e., between Visit 1 and Visit 2). Changes in rescue AED medications to treat acute breakthrough seizures may be permitted with Sponsor's approval. Changes in other (i.e., non-AED) chronic medications may be permitted with Sponsor's approval.
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 PCDH19-related epilepsy) at the screening visit 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 IP, or would place the subject at increased risk.
11. An aspartate aminotransferase (AST/serum glutamic oxaloacetic transaminase [SGOT]) or alanine aminotransferase (ALT/serum glutamic pyruvic transaminase [SGPT]) > 3 × the upper limit of normal (ULN) at screening and if applicable, confirmed by a repeat test. If the subject has another reason to be excluded, repeated liver enzymes are not required.

12. Total bilirubin levels > 1.5 × ULN at screening and if applicable, confirmed by a repeat test. In cases of documented, stable medical condition (i.e., Gilbert's Syndrome) resulting in levels of total bilirubin > ULN, the medical monitor can determine if a protocol exception can be made.
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 fewer than 5 half-lives prior to the screening visit.
15. Unwillingness to withhold grapefruit, Seville oranges, star fruit, or grapefruit containing products from diet 14 days prior to 1st dose and for the duration of the study
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 IP(s), progesterone or other related steroid compounds.

4.3. Restrictions

Subjects must abstain from the use of alcohol and from consuming grapefruit, Seville oranges, star fruit, or grapefruit containing products from diet at least 14 days prior to the 1st dose and for the duration of the study. Excluded medications are described in Section 5.4.

4.4. Reproductive Potential

4.4.1. Contraception

Sexually active females of childbearing potential should be using a medically acceptable form of birth control. Females 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 IP. If hormonal contraceptives are used, they should be administered per the package insert.

Females of childbearing potential who are not currently sexually active, but who become sexually active during the period of the study and 30 days after the last dose of IP must agree to use acceptable contraception, as defined below:

- Premenarchal and either Tanner stage 1 or < 9 years or age, *or*
- Surgically sterile (having undergone 1 of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy, or bilateral salpingectomy) and at least 8 weeks' post-sterilization, *or*
- Females of childbearing potential must have a negative serum pregnancy test prior to taking the first dose of IP 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 subject. 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 (eg, 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 subject becomes sexually active during the study, she should use 1 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.

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 PI or sponsor may withdraw the subject at any time (eg, in the interest of subject safety). The PI is encouraged to discuss withdrawal of a subject from IP with the medical monitor when possible.

Subjects who discontinue IP treatment before the completion of the DB phase will continue to be followed per protocol and, at a minimum, subjects will be encouraged to maintain daily seizure eDiary entries until the DB phase is completed. These subjects should also return to the site after the taper for safety follow-up post taper assessments (Section 7.2.7).

If the IP is discontinued at any time, subjects should follow the 2-week taper schedule, unless otherwise medically indicated (Section 7.2.6). If the subject discontinues during the OL phase, evaluations listed for the 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 (Section 7.2.7). Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for termination, date of stopping IP, and total amount of IP taken must be recorded in the electronic case report form (eCRF) and source documents. Discontinuation of IP due to AEs must also be reflected on the AE eCRF page.

4.5.1. Subject Withdrawal Criteria

All subjects or her parent/LAR reserve the right to withdraw from the clinical study at any time, as stated in the informed consent/assent form. The PI 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;
- It is the PI's opinion that it is not in the subject's best interest to continue in the study;
- Subject has an AST or ALT increase > 3 × upper limit of normal (ULN) during the study. **NOTE**: If this occurs, the subject should be followed with weekly laboratory repeat testing and continue in the study if levels are trending down. Discontinuation of treatment should be considered if levels do not decline to under 3 x ULN and if presented with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) and if there are no initial findings of cholestasis (elevated serum ALP) or other reason can be found to explain the combination of increased ALT or AST and total bilirubin, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury; or
- Subject has a total bilirubin increase to 1.5 x ULN or more during study. **NOTE**: if this occurs, the subject should be followed with weekly laboratory repeat testing and continue in the study if levels are trending down. Discontinuation of treatment should be considered if levels do not decline to under 1.5 x ULN within the time period that is considered reasonably safe per PIs' judgment. Laboratory, medical, or clinical finding for which clinical intervention should take precedence over study participation.

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 IP during the DB phase will continue to record daily seizure frequency at minimum until the completion of the DB 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 $GABA_A$ receptor modulator medication for 1-2 weeks such as clobazam to mitigate the potential risk of withdrawal from a positive modulator of $GABA_A$ receptors.

4.5.2. Reasons for Early Discontinuation

The reason for early discontinuation must be determined by the PI 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 subject's existing risk profile with the exception of somnolence and 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
- Other (must be specified in the subject source document and eCRF)
- Pregnancy

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 she return to the site for final safety evaluations and return any unused IP. If contact is made but the subject refuses or is unable to return to the site for the final Safety Follow-up Post-Taper visit (Section 7.2.7), it should be documented in the eCRF.

4.6. Subject Numbering

During the screening visit and after consent is obtained, each subject will be assigned a unique 6-digit subject number by the 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 (eg, 001) assigned by the IWRS. 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 number and be used to track the subject throughout the study. Each randomized subject's 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 IP 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

Prior medications include all treatment, including but not limited to herbal treatments, vitamins, surgical implants (such as VNS), and prescribed medications received within 30 days (or PK equivalent of 5 half-lives, whichever is longer) of the date prior to screening. Prior treatment information, if available, must be recorded on the appropriate eCRF page.

5.2. Concomitant Medications

Concomitant medications refer to all treatment taken between the date of the first dose of IP and the date of the last dose of IP. 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 12-week baseline period.

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

5.2.1. Concomitant Antiepileptic (AED) Medications

Concomitant AED regimens must have been stable for at least 1 month prior to the screening visit and must remain stable from screening to the end of the DB phase. Ketogenic diets and modified Atkins diets should be unchanged for 3 months prior to the screening visit and must remain stable throughout baseline and the DB phase.

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 baseline and the DB phase.
- The battery is expected to last for the duration of baseline and the DB phase.

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

5.3. Rescue Medications

The use of rescue medication is allowed on an occasional basis and as medically needed. The type, dose, date, and frequency will be recorded.

5.4. Excluded Medications

Excluded medications include oral steroid medications, other IPs, ketoconazole and other investigational drugs or devices. Use of St. John's Wort and concurrent use of strong inducers or inhibitors of CYP3A4/5/7 is not permitted. A list of CYP3A4/5/7 inhibitors and inducers is included in Section 12.1. Any strong inhibitor or inducer of CYP3A4/5/7 must be discontinued at least 28 days before Baseline/Randomization Visit; note that this does not apply to approved AED medications.

Products containing tetrahydrocannabinol (THC) or non-approved CBD are excluded in the DB phase of the study but allowed in the OL phase. THC or non-approved CBD should be washed out for at least 2 weeks before screening. Subjects with a positive result on THC or non-approved cannabidiol CBD test (via plasma drug screen) can be retested, via plasma, after 2 weeks.

Note that if a subject is taking marketed Epidiolex (may go by another name in countries outside the United States) then the parent/caregiver will have to provide evidence of an active prescription or confirmation from prescriber.

Use of any herbal product or nutritional supplement must be reviewed and approved by Marinus Medical Monitor.

6. INVESTIGATIONAL PRODUCT

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 120 mL bottles, containing 110 mL GNX. A PBO suspension, which is identical in taste and appearance, will be supplied at an equal volume.

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

All IP will be stored at the research pharmacy prior to dispensing, or in a locked cabinet accessible only to members of the investigative research team after the completion of each study visit. Study medication should be stored at room temperature 15°C to 25°C (59°F to 77°F).

6.1. Identity of Investigational Product

6.1.1. Ganaxolone

Manufacturer: Catalent Pharma Solutions, Somerset, NJ 08873 USA

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 120 mL high-density polyethylene bottles

6.1.2. Placebo

Manufacturer: Catalent Pharma Solutions, Somerset, NJ 08873 USA

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.

6.1.3. Blinding the Treatment Assignment

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

6.2. Administration of Investigational Products

6.2.1. Interactive Web Response System for Investigational Product Management

For the DB phase and the titration period of the OL phase and thereafter an IWRS will be utilized for the following IP 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 stratified into 2 groups during the Screening period as either Allo-S biomarker-positive or Allo-S biomarker-negative. A subject will be considered biomarker-positive if her baseline Allo-S level is less than or equal to 2500 pg/mL. Eligible subjects will then be randomly assigned at a 1:1 ratio (GNX:PBO) based on a randomization schedule at Visit 2 (Week 0). Only the IP supplier and the sponsor's IP manager will be unblinded as to the contents of each bottle of IP. Study staff as well as subject and caregiver will be blinded to treatment assignments. In addition, the biomarker group assignment will remain blinded until database unblinding after the study has completed.

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

The contents of each bottle will be blinded using labels. The IWRS will use the randomization schedule to match a subject number to a bottle number. Upon completion of baseline evaluations for each subject, the PI or appropriate designee will log into the IWRS to receive assigned bottle(s). 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 IP and distribute the bottle to the PI or designee.

6.2.3. Dosing

6.2.3.1. Double-Blind Period

Ganaxolone is to be administered in increments of 15 mg/kg/day up to 63 mg/kg/day (maximum 1800 mg/day) given as an oral suspension with food. Any subject not tolerating the next dose level can be maintained at the lower dose for additional days before advancing to next dose. If the next dose level is still not tolerated, the subject can drop back to the last tolerated dose. A minimum dose of 33 mg/kg/day or 900 mg/day is generally required following the DB escalation

period, unless a lower dose is agreed to with the Sponsor due to tolerability issues such as somnolence. Dose changes, including alternative dosing paradigm (e.g., lower dose during the daytime and higher dose in the evening) should be discussed with the CRO/sponsor medical monitor prior to making the change or within 48 hours of making the change. Of note, the sponsor defers the final decision to adjust IP to the treating study clinician; dose changes may not excess the maximum total daily dose defined by the protocol. At each visit, dosing will be reviewed and adjusted as needed based on subject's current weight. Dosing for subjects weighing ≤ 28 kg and > 28 kg is described in Table 3.

Table 3: Oral Suspension (50 mg/ml) Dosing for Subjects Weighing ≤ 28 kg and > 28 kg

Dosing[a] for Subjects Weighing ≤ 28 kg (62 pounds)[b]			
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
Dosing[a] for Subjects Weighing > 28 kg (62 pounds)[c]			
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 = 3 times daily.

[a] To be administered in 3 divided doses following a meal or snack.

[b] Subjects weighing ≤ 28 kg (62 pounds) will be dosed according to the subject's weight in kilograms.

[c] Subjects > 28 kg will be dosed on a fixed regimen in increments of 150 mg/day up to 1800 mg/day.

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 (taper) will occur in decreasing increments of 15 mg/kg/day or 450 mg/day approximately every 3 days over 2 weeks whenever feasible (See Section 6.2.3.3 for more details). Taper is not required if the subject is receiving the dose of 18 mg/kg/day or 450 mg/day (or lower).

6.2.3.2. Open-Label Period

Following the completion of the 17-week, DB phase, subjects randomized to PBO will transition to GNX, whereas subjects randomized to GNX will stay on their MTD (minimum of 33 mg/kg/day [900 mg/day]; maximum of 63 mg/kg/day [1800 mg/day]) in a blinded fashion.

Subjects will begin the 4-week blinded dose titration up to 63 mg/kg/day or 1800 mg/day (or MTD) after completing Visit 5. To maintain the blind of the DB phase, subjects initially randomized to GNX will undergo a blinded titration (increasing PBO doses) for 4 weeks, while

PBO subjects will titrate up to 63 mg/kg/day GNX (1800 mg/day maximum or MTD) during the same time period.

Dosing transition from DB to OL for subjects weighing ≤ 28 kg and > 28 kg is described in Table 4. All subjects will be dispensed 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:

- Subjects initially randomized to GNX: Bottle Group A will contain GNX; Bottle Group B will contain PBO.
- Subjects initially randomized to PBO: Bottle Group A will contain PBO; 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 DB phase, and continue until the end of the OL 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 OL phase, in which they will receive a new set of medication bottles.

Table 4: Transition from Double-Blind to Open-Label: Dosing for Subjects ≤ 28 kg and Subjects > 28 kg

Dosing for Subjects ≤ 28 kg (62 pounds)		
Titration Day	**Bottle Group A Dose**[a]	**Bottle Group B Dose**[b]
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)
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 6, Week 21	One set of GNX bottles dispensed, return to dosing from a single bottle (not 2 different ones): 63 mg/kg/day (21 mg/kg TID)	
Dosing for Subjects > 28 kg (62 pounds)		
Titration Day	**Bottle Group A Dose**[a]	**Bottle Group B Dose**[b]
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
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 6, Week 21	One set of GNX bottles dispensed, return to dosing from a single bottle at a time (not 2 different ones): 1800 mg/day; 12 mL per dose TID	

DB = double-blind, GNX = ganaxolone, TID = 3 times daily.

[a] For subjects initially randomized to GNX, Bottle Group A will contain GNX; for subjects initially randomized to placebo, Bottle Group A will contain placebo.

[b] For subjects initially randomized to GNX, Bottle Group B will contain placebo; for subjects initially randomized to placebo, Bottle Group B will contain GNX.

Examples of dosing for subjects of different weights are provided in Section 12.3. Dosing instructions for the DB dose titration, DB and OL maintenance and taper are provided in the Pharmacy Manual. Dosing instructions for DB to OL transition are provided in the Pharmacy Manual.

6.2.3.3. De-escalation (Taper) Period

Any subject who completes the study or discontinues IP treatment at any time during the study 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 approximately every 3 days until the subject is completely off IP. Subjects should then return for a Safety Follow-up Post-Taper visit. Taper is not required if the subject is receiving the dose of 18 mg/kg/day or 450 mg/day (or lower).

Table 5: 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, star fruit, and grapefruit containing products are prohibited 14 days prior to 1st dose and for the duration of the study

Ganaxolone oral suspension will be administered through an oral dosing syringe administered by parents/caregivers 3 times daily (TID), following the morning, noon, and evening meal or snack. Each dose should be separated by a minimum of 4 hours and a maximum of 12 hours. A missed dose of IP may be taken up to 4 hours before the next scheduled dose; otherwise, the missed dose should not be given. Subjects and their parent or legal guardian will be informed about possible side effects from the IP and cautioned to avoid quick postural changes, at least until they know how the IP affects them. Subjects will be advised that the IP might affect mental alertness. They will also be cautioned that non-adherence to the dosing instructions (eg, increasing the dose or taking the IP doses too close together) could produce side effects.

6.2.5. Missing a Dose

Ganaxolone oral suspension: A missed dose of IP 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 IP 2 days in a row or more, the site should be contacted to determine whether any adjustment in IP 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 6: 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. The sponsor's Medical Monitor does not have to be contacted to initiate unblinding in the IWRS system. Prior to unblinding or immediately following, the sponsor's Medical Monitor must be contacted. Subjects who are unblinded during the DB phase will be discontinued from investigational drug treatment but asked to continue seizure charting until the completion of the DB phase. To initiate unblinding procedures anytime, please contact:

SPONSOR CONTACTS:

[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, PhD
Clinical Development
Mobile Telephone: [redacted](primary contact method/send text message if no immediate response)
Email: [redacted]

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

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

6.4. Labeling, Packaging, Storage, and Handling

6.4.1. Labeling

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

All IP 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 IP 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

Investigational product will be supplied as an oral suspension. The suspension formulation can be used for subjects regardless of weight.

IP will be provided to the site as individual bottles containing 110 mL in 120-mL HDPE bottles 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 PI has overall responsibility for ensuring that IP 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.

Investigational product 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 IP is required at the storage location to ensure that the IP is maintained within an established temperature range. The PI 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 IP 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 IP 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 IP to carry out this protocol for the agreed number of subjects. The PI or designee will acknowledge receipt of the IP, documenting shipment content and condition. Accurate records of all IP dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

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

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

The subject's parent/caregiver must be instructed to save and bring their unused IP and empty/used IP 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 IP that is contained within the original tamper-evident sealed container (eg, bottles) or at the individual count level for opened containers/packaging. The pharmacist/nominated person will record details on the IP accountability form.

No IP 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 IP 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 IPs will be packed in a tamper-evident manner to ensure product integrity. Shipment of all returned IP must comply with local, state, and national laws.

With the written agreement of the sponsor, unused stock, subject-returned, and expired IP 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 IPs 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 IPs delivered with those used and returned. All IPs 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. Compliance with IP treatment will be monitored by inspecting the electronic diary entries and returned supplies with queries as necessary. As a generally accepted guideline, subjects should remain 80% compliant with diary entries. Parents/caregivers who fall short of this standard will be re-educated on the importance of adhering to daily seizure, IP and non-study AED recording and a deviation recorded.

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.

In the event of unforeseen circumstances, in-person study visit assessments may not be able to be performed. To conduct the study according to protocol while preserving patient safety, operational alternatives such as those listed below can be employed as long as the site's actions are in compliance with the institution's IRB/EC policies and regulations.

- Telemedicine visits (video and/or audio communication methods)
- In-home visits
- Local physician visits
- Use of local and/or off-site laboratories
- Site-to-patient IP distribution

7.2. Study Procedures (Double-Blind Phase)

7.2.1. Pre-Screen/Screen/Baseline

7.2.1.1. Historical Seizure Type and Frequency and/or Genetic Testing (Pre-Baseline Screening Visit (Visit 0))

Potential subjects will have already been pre-identified by the site because of confirmed or suspected PCDH19 genetic mutation testing as part of their standard of care epilepsy work-up.

It is also very common that parents/caregivers/LARs of PCDH19-related epilepsy subjects 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 12-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.

If genetic testing is not done as Standard of Care, a pre-screen visit will be scheduled where informed consent/assent is obtained to complete the genetic testing. If genetic testing results are available per SOC, the genetic testing will be done at screening to confirm the results by the Sponsors designated lab.

Procedures specific to this protocol and not otherwise considered standard of care, will not be performed until written informed consent (and subject 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 or in a situation where the child's PCDH19-related epilepsy diagnosis has not been confirmed with genetic testing per standard of care, written informed consent/assent will be obtained and the subject will be asked to return to the clinic for the Screening (Visit 1) after she has maintained a 12-week daily historical seizure calendar and/or completed genetic testing.

7.2.1.2. Screening Visit – Start to Baseline (Visit 1, Week –12)

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 *PCDH19* variant by Sponsor identified lab, if not done at prescreening.
- 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
- 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 (plasma)
- Serum pregnancy test for females 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 full informed consent/assent 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 IP.

Subject rescreening is allowed as agreed by Sponsor and PI unless there is a general concern for subject safety or an inability for the subject to become eligible (eg, GNX allergy, sensitivity or exposure, non-PCDH19 and/or other ineligible epilepsy, chronic prohibited medical condition or treatment). Subsequent screening should take place at least 30 days from the subject's last visit. If a subject fails to qualify because of Exclusion Criteria #4 (≤ 3 primary seizures during the 12-week baseline period), she will not be randomized. However, she can be rescreened after collecting another 12 or more weeks of seizure history that satisfies all eligibility criteria including Inclusion Criteria #5 and Exclusion Criteria #3. Each subject is allowed a maximum of 1 rescreening visit.

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

The following study procedures/assessments to be completed, the results received, and the investigator must ensure the subject meets all inclusion and exclusion criteria prior to IP administration. The 12 weeks between Screening and Randomization can be no less than 84 days and no more than 90 days.

- Review of inclusion/exclusion criteria
- Demographics and medical history review
- SIF/DRF (Epilepsy Study Consortium) approval
- Vital signs (to include BP, HR, RR, body temperature, and weight)
- 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)
- Drug screen (plasma)
- Serum pregnancy test for females of childbearing potential
- Concomitant AED review and levels if per SOC
- Adverse events
- Seizure and medication diary review
- CSHQ
- BRIEF
- ABC-C
- EEG
- PedsQL-FIM
- QI-Disability
- CGI-C (parent/caregiver/LAR identified behavioral target)
- CGI-I (parent/caregiver/LAR and clinician)
- Dispense IP

7.2.2. Double-Blind Titration + Maintenance (3 Days, Weeks 1 to 4, 5, 9, 11, and 13)

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

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

- Adverse events
- Seizure and medication diary review

7.2.2.2. Visit 3 (Week 5 ± 3 days)

The following study procedures/assessments will be completed at Week 5 DB phase:

- Vital signs (to include BP, HR, RR, body temperature, and weight)
- Physical, neurological, and developmental examination (Visit 3, Week 5 only)
- ECG (Visit 3, Week 5 only)

- Clinical laboratory tests (to include CBC with automated differential, creatinine, blood urea nitrogen, and comprehensive metabolic panel)
- Urinalysis (Visit 3, Week 5 only)
- Serum pregnancy test for females of childbearing potential
- Investigational Product PK (population PK 1-5 hours post dose)
- Concomitant AED review and levels if per SOC
- Adverse events
- Seizure and medication diary review
- CGI-C (parent/caregiver/LAR identified behavioral target)
- CGI-I (parent/caregiver/LAR and clinician)
- Dispense IP

7.2.2.3. Visit 4 (Week 9 ± 3 days)

The following study procedures/assessments will be completed at Week 9 of the DB phase:

- Vital signs (to include BP, HR, RR, body temperature, and weight)
- Physical, neurological, and developmental follow-up examination (Visit 4, Week 9 only)
- Clinical laboratory tests (to include CBC with automated differential, creatinine, blood urea nitrogen, and comprehensive metabolic panel)
- Serum pregnancy test for females of childbearing potential
- Investigational Product PK (population PK 4-8 hours post dose)
- Concomitant AED review and levels if per SOC
- Adverse events
- Seizure and medication diary review
- CGI-C (parent/caregiver/LAR identified behavioral target)
- CGI-I (parent/caregiver/LAR and clinician)
- Dispense IP

7.2.2.4. 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 ± 3 days (Week 17 ± 3 days)

The following study procedures/assessments will be completed during the final DB 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
- Serum pregnancy test for females of childbearing potential
- Drug screen (plasma)
- Investigational Product PK
- Concomitant AED review and levels if per SOC
- Neurosteroid level sample draw
- Adverse events
- Seizure and medication diary review
- CSHQ
- BRIEF
- ABC-C
- EEG
- PedsQL-FIM
- QI-Disability
- CGI-C (parent/caregiver/LAR identified behavioral target)
- CGI-I (parent/caregiver/LAR and clinician)
- Dispense IP (note that this will be the last dose of study medication for the DB phase and the first dose of study medication for the OL phase)

7.2.4. Open-Label Period Blinded Titration

7.2.4.1. Telephone Follow-Up (Week 17 + 3 days ± 1 day, Weeks 18, 19 and 20 ± 3 Days)

A telephone follow-up visit will be conducted 3 days after Visit 5 and at Weeks, 18, 19, and 20 of the OL phase to assess the following:

- Adverse events
- Seizure and medication diary review

7.2.4.2. Open-Label Period Blinded Titration, Visit 6 (Week 21 ± 3 days)

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

- Vital signs (to include BP, HR, RR, body temperature, and weight)
- 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)
- Serum pregnancy test for females of childbearing potential
- 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
- Dispense IP

7.2.5. Open-Label Period Maintenance (Weeks 28-68; ± 14 days window for each visit)

7.2.5.1. Telephone Follow-Up (Weeks 28, 44, and 60 ± 14 Days)

A telephone follow-up visit will be conducted between Visit 6 and Visit 7, Visit 7 and Visit 8, and Visit 8 and Visit 9 of the OL phase to assess the following:

- Adverse events
- Seizure and medication diary review

7.2.5.2. Open-Label Period Maintenance, Visits 7, 8, and 9 (Weeks 36, 52 and 68 ± 14 days)

The following study procedures/assessments will be completed at Weeks 36, 52 and 68 and every 16 weeks thereafter for the duration of the OL phase:

- Vital signs (All Visits: to include BP, HR, RR, body temperature, and weight; Visit 7 and 8: to include height)
- Physical, neurological, and developmental examination
- ECG (Visit 8, Week 52 only)
- Clinical laboratory tests (to include CBC with automated differential, creatinine, blood urea nitrogen and comprehensive metabolic panel)
- Urinalysis (Visit 7 and Visit 8)
- Serum pregnancy test for females of childbearing potential
- Tanner staging (Visit 8, Week 52 only)
- Investigational Product PK (Visit 8 only: population PK draw between 1-5 hours post dose)
- Concomitant AED review and levels if per SOC
- Neurosteroid level sample draw (Visit 8, Week 52 only)
- Adverse events
- Seizure and medication diary review
- CSHQ (Visits 7 and 9; Weeks 36 and 68)
- BRIEF (Visits 7 and 9; Weeks 36 and 68)
- ABC-C (Visits 7 and 9; Weeks 36 and 68)
- PedsQL-FIM (Visits 7 and 9; Weeks 36 and 68)
- QI-Disability (Visits 7 and 9; Weeks 36 and 68)
- CGI-C (parent/caregiver/LAR identified behavioral target) (Visits 7 and 9; Weeks 36 and 68)
- CGI-I (parent/caregiver/LAR and clinician) (Visits 7 and 9; Weeks 36 and 68)
- Dispense IP (Visits 7, 8, and 9; Weeks 36, 52, and 68)

7.2.5.3. Visit X - Additional Maintenance Visits in the Open-Label Period Phase

If the subject continues in the OL phase beyond Week 68, the subject must return for a clinic visit every 16 weeks (± 14 days) 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
- Clinical laboratory tests (to include CBC with automated differential, creatinine, blood urea nitrogen, and comprehensive metabolic panel)
- Urinalysis (annually)
- Serum pregnancy test for females of childbearing potential
- Tanner staging (annually)
- ECG (annually)
- Investigational Product PK
- Concomitant AED review and levels if per SOC
- Neurosteroid level sample draw (annually)
- Adverse events
- Seizure and medication diary review
- CSHQ
- BRIEF
- ABC-C
- PedsQL-FIM
- QI-Disability
- CGI-C (parent/caregiver/LAR identified behavioral target)
- CGI-I (parent/caregiver/LAR and clinician)
- Dispense IP

If the subject continues in the OL phase beyond Week 68, a telephone follow-up visit will occur in between clinic visits (8 weeks ± 7 days after each clinic visit) to assess the following:

- Adverse events
- Seizure and medication diary review

7.2.6. Final Open-Label Period Visit or Taper Visit (or at time of Early Termination ±14 days)

The following study procedures/assessments to be completed during the final OL 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 females 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
- CSHQ
- BRIEF
- ABC-C
- EEG
- PedsQL-FIM
- QI-Disability
- CGI-C (parent/caregiver/LAR identified behavioral target)
- CGI-I (parent/caregiver/LAR and clinician)
- Dispense IP

7.2.7. Safety Follow-up Post Taper (2 Weeks Post Last Dose/Investigational Product Taper ± 3 days)

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 examination
- Clinical laboratory tests (to include CBC with automated differential, creatinine, blood urea nitrogen and comprehensive metabolic panel)
- Urinalysis
- Serum pregnancy test for females 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 PCDH19 genetic mutation testing as part of their standard of care epilepsy work-up. Potential subjects will have historical seizure diary charting 12 weeks prior to screening. Eligible historical seizure diaries 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 / Assent

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

7.3.2. Drug Screen

A drug screen (plasma) will be performed to test for THC and non-approved CBD during the DB phase at Visit 1 (screening), Visit 2 (baseline/randomization), and Visit 5 (final DB/first OL visit). If the screening drug test is positive at Visit 1 (screening), a confirmatory retest, via plasma, will be performed after 2 weeks. A drug screen may be performed at any time at Investigator's discretion. A positive drug test during the DB phase will result in early termination.

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 *PCDH19* variant, relevant medical history, including but not 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. 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/randomization).

7.3.4. Historical Seizure Calendar Review

It is very common for parent/caregivers/LARs to maintain daily seizure calendars for this subject population, which capture both seizure type and frequency. A 12-week 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 subject is not able to provide eligible historical seizure diary (at least 12 weeks prior to screening), the informed consent/assent will need to be obtained and the parent/caregiver will need to chart prospectively.

7.3.5. Genetic Testing

Molecular confirmation of a pathogenic or likely pathogenic *PCDH19* mutation is required. Genetic mutations will be confirmed by the sponsor's chosen central laboratory. The PI must review the results of the genetic analysis and confirm that the causal relationship to the epilepsy syndrome is likely. If the subject has a de novo PCDH19 VUS then the central assessor, PI, and Sponsor will review study inclusion. Some subjects may have multiple PCDH19 mutations that include both VUS and pathogenic variants. In these cases, the subject is known to have a pathogenic variant and is eligible (does not require discussion with expert).

In the event that parents/caregivers/LAR do not have genetic testing results with a confirmed PCDH19-related epilepsy diagnosis per standard of care, written informed consent/assent will be obtained.

Instructions for genetic testing sample collection and processing can be found in the central 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 all countable focal seizures that include progressive hypotonia and impaired awareness, or any countable focal or generalized seizure with a clear motor component.

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 1 example of each of the primary seizure types that their child experiences. Although it is acknowledged that some seizure types (e.g., atonic/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.

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). In rare cases when an eDiary completion is not feasible, a paper diary will be used to log daily seizure type and frequency. These cases will need approval by the sponsor. Primary seizure types of countable focal seizures that include progressive hypotonia and impaired awareness, or any countable focal or generalized seizure with a clear motor component, will be counted towards the primary endpoint.

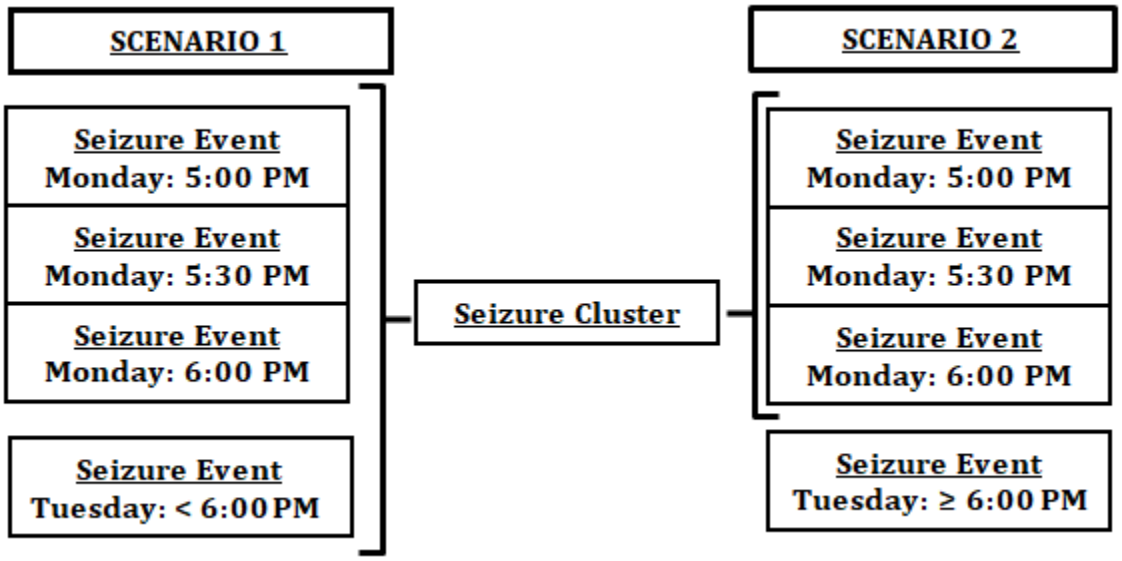
Subjects or parent/caregiver/LAR are to record administration of IP and background AEDs in the eDiary/seizure calendar. Compliance with IP treatment will be assessed by inspecting the subjects' eDiary/seizure calendar and returned supplies with queries as necessary. As a generally accepted guideline, subjects should remain 80% compliant with diary entries. Parents/caregivers who fall short of this standard will be re-educated on the importance of adhering to daily seizure, IP and non-study AED recording and a deviation recorded.

For recording of seizures in the eDiary, seizure events will be recorded either as a countable seizure or a series of continuous uncountable seizures. Both of these events will be counted as 1 seizure (equally weighted) in the efficacy analysis.

A seizure cluster will be defined as 3 or more seizure events (either a countable or a series of continuous uncountable seizures), occurring within a period of time, followed by a period of at least 24 hours of seizure-freedom. For example (Figure 2):

1. If a child experiences 3 seizure events at 5:00, 5:30, and 6:00 PM on Monday, and the next seizure event occurs before 6:00 PM on Tuesday, the Monday and Tuesday seizure events are considered part of the same seizure cluster (Figure 2, Scenario 1).
2. If a child experiences 3 seizure events at 5:00, 5:30, and 6:00 PM on Monday, and the next seizure event occurs at 6:00 PM or later on Tuesday, the Tuesday seizure event is not considered part of the same cluster (Figure 2, Scenario 2).

Figure 2: Seizure Cluster Designation Examples



7.4.2. Rescue Medication

The type, dose, date, and frequency of rescue medication will be recorded in the eDiary and reviewed every visit.

7.4.3. Children's Sleep Habits Questionnaire (CSHQ)

The Children's Sleep Habits Questionnaire (CSHQ) is a psychological questionnaire designed to measure sleep behaviors in children and adolescents. The 33-question test is filled out by the parent/caregiver/LAR.

CSHQ will be assessed as follows: in the DB phase at Visit 2 (baseline/randomization) and Visit 5 (Week 17; also Final DB Visit/First OL Visit in OL phase); in the OL phase at Visit 7 (Week 36) and Visit 9 (Week 68) and thereafter every 16 weeks for the duration of this phase; and at the Final OL Visit.

7.4.4. Behavior Rating Inventory of Executive Function (BRIEF, Preschool Version BRIEF-P)

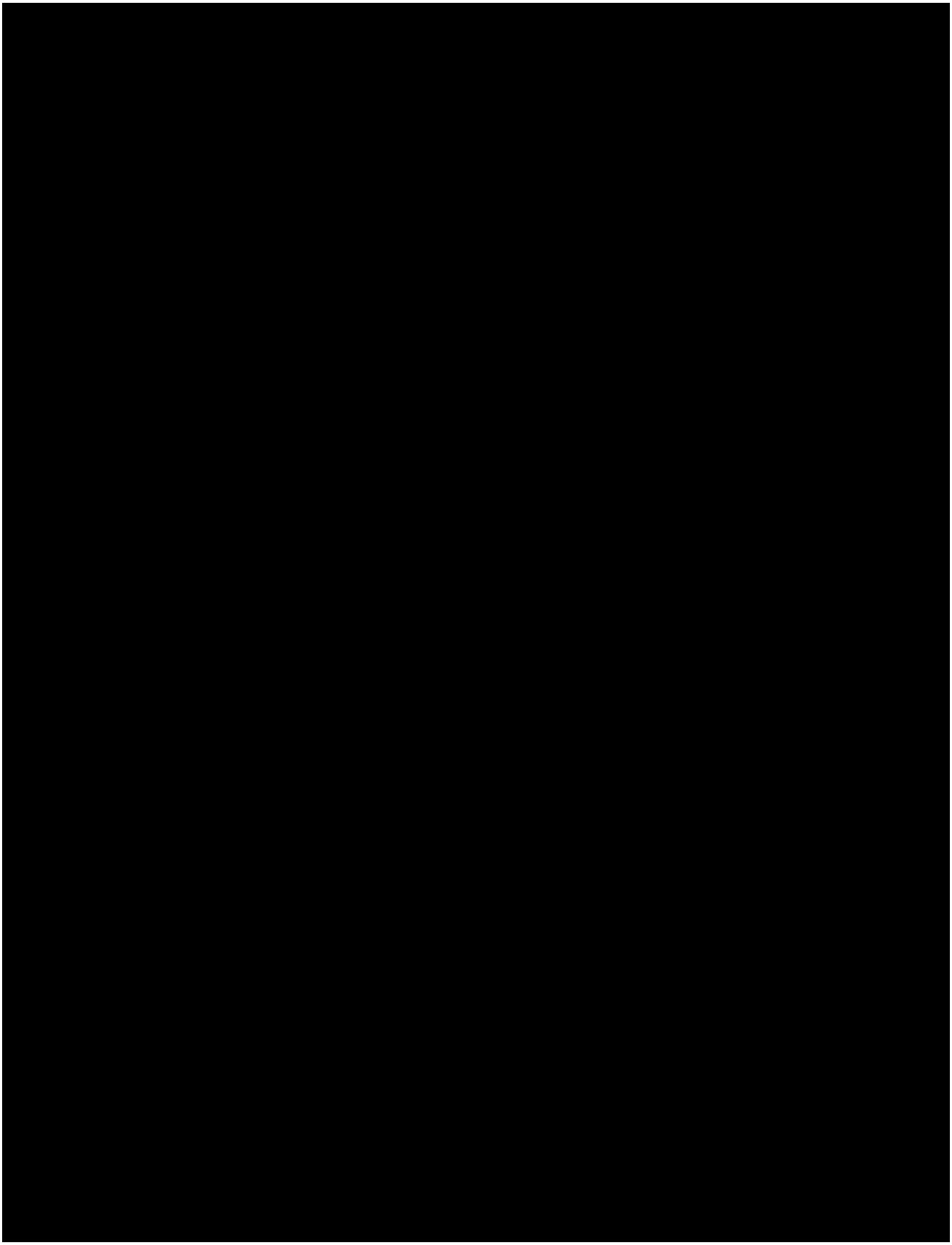
The Behavior Rating Inventory of Executive Function (BRIEF) is an 86-item questionnaire designed to assess executive function behaviors in the school and home environments in individuals 5-18 years of age. The preschool version (BRIEF-P) is a 63-item modified form and is typically utilized in individuals 2-5 years of age. For this study, the BRIEF-P will be used for any subject less than 5 years of age. The questionnaire is completed by the parents/caregiver/LAR.

BRIEF (BRIEF-P where appropriate) will be assessed as follows: in the DB phase at Visit 2 (baseline/randomization) and Visit 5 (Week 17; also Final DB Visit/First OL Visit in OL phase); in the OL phase at Visit 7 (Week 36) and Visit 9 (Week 68) and thereafter every 16 weeks for the duration of this phase; and at the Final OL Visit.

7.4.5. Aberrant Behavior Checklist – Community (ABC-C)

The ABC-C is a questionnaire designed to assess problematic behavior at home, in educational and work setting, and in residential and community-based facilities.

The ABC-C will be assessed as follows: in the DB phase at Visit 2 (baseline/randomization) and Visit 5 (Week 17; also Final DB Visit/First OL Visit in OL phase); in the OL phase at Visit 7 (Week 36) and Visit 9 (Week 68) and thereafter every 16 weeks for the duration of this phase; and at the Final OL Visit.



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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 DB 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), and weight will be collected at every clinic visit starting with Visit 1 other than the Safety Follow-Up Visit. Height will be collected at Visit 1 (screening) (during DB phase) and during the OL phase at Visit 7 (Week 36), at Visit 8 (Week 52), annually thereafter (except for the Safety Follow-up Visit), and at 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 DB phase.

ECGs will be performed as follows:

- DB phase:
  - Visit 2 (baseline/randomization)
  - Visit 3 (Week 5)
  - Visit 5 (Week 17 = Final DB Visit/First OL phase visit)

- OL phase:
  - Visit 6 (Week 21)
  - Visit 8 (Week 52 and then yearly)
  - Final OL Visit

7.6.5. Clinical Laboratory Tests

Clinical laboratory tests are listed in Section 12.2 and will be collected per the schedules listed in Table 1 and Table 2. If any test result is unexpectedly out of range, a repeat test can be performed at any time as decided by the PI to confirm the initial result.

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), will be discontinued if the criterion is met post baseline.

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

Due to the difficulty in obtaining urine samples, urinalysis will be conducted as follows: during the DB phase at Visit 1 (screening) or baseline/randomization (Visit 2), Visit 3, and at Week 17 (Visit 5; also Final DB Visit/First OL Visit in OL phase); in the OL phase at Visit 7 (Week 36), Visit 8 (Week 52) and annually thereafter, or at the Safety Follow-up Post-Taper visit if IP is discontinued; and at the Final OL Visit. An attempt will be made to collect a urine sample at screening 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 during the DB phase at Visit 1 (screening); during the OL phase at Visit 8 (Week 52) and thereafter assessed annually for the duration of the subject's participation in this 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 considered SOC, they will be assessed as follows: during the DB phase at Visit 1 (screening), Visit 2 (baseline/randomization), Visit 3 (Week 5), Visit 4 (Week 9), and Visit 5 (Week 17; also Final DB Visit/First OL Visit in OL phase); in the OL phase of the study at the timepoints noted in Table 1 and Table 2; at the Final OL Visit; and at the Safety Follow-Up Post-Taper Visit. 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. Adverse Events

Details regarding AEs and SAEs are provided in Section 8.

7.7. Pharmacokinetic Assessments

A population PK approach addressing the relationship between GNX PK parameters and individual characteristics will be implemented during the study.

Blood sampling for PK evaluation must be performed at the protocol-scheduled times within the windows specified in Table 1 and Table 2. Exact time of sample withdrawal and drug intake will be recorded in the electronic case report form (eCRF). One blood sample will be obtained at the following visits for PK analyses:

During the DB Phase:

- 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

During the OL Phase:

- Visit 6 (Week 21): between 1 and 5 hours since the last investigational product dosing
- Visit 8 (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 7 (Week 36), Visit 9 (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).

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 (and subject assent) 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 IP has been administered. All AEs reported after the initiation of IP 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 IP 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 PI 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 IP, must be recorded as new AEs (eg, if a subject experiences mild intermittent dyspepsia prior to dosing of the IP, but the dyspepsia becomes severe and more frequent after the first dose of the IP 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 IP and each AE. The PI should decide whether, in their medical judgment, there is a reasonable possibility that the event may have been caused by the IP. 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 IP 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 IP 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 IP, 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 IP), 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 (eg, concomitant disease) is found for the abnormal values.

The PI 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 (and subject assent) is signed until the defined follow-up period.

Any report of pregnancy for any study subject 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 study subject 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 PI 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 PI 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 IP for a nonmedical purpose (eg, 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 IP other than as directed or indicated at any dose. (Note: This includes a situation in which the IP is not used as directed at the dose prescribed by the protocol.)
- **Overdose:** Intentional or unintentional intake of a dose of an IP exceeding a prespecified total daily dose of the product.
- **Medication error:** An error made in prescribing, dispensing, administering, and/or use of an IP. Medication errors are reportable to the sponsor only as defined below.
  - Cases of subjects missing doses of the IP are not considered reportable.
  - Applicable only for the IP under investigation.
  - The administration and/or use of an expired IP should be considered as a reportable medication error.
  - All IP provided to pediatric subjects should be supervised by the parent/caregiver/LAR. Lapses in supervision should be reported.

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 PIs.

8.2.2. Reporting Procedures

All initial and follow-up SAE reports must be reported by the PI 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 PI 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 IP 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/subject signs the informed consent/assent 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 IP and discovered by the PI 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 (and subject assent) 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 IP action was previously taken (eg, the drug was interrupted, reduced, or withdrawn), the action taken with the IP should be recorded as "dose not changed" or "not applicable" (if the subject never received the IP). The IP 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 PI is responsible for notifying the local IRBs, local ethics committee, 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 PI'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 PI'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 (and subject assent), it is expected that all eDiary entries will be made daily. Retrospective entry of diary events (seizure and medication) can be completed by the caregiver up to 5 days later and proxy entry by the site is also available to the site staff (greater than 5 days), but neither method is encouraged.

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; IP 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). A summary of the statistical analyses is provided below; full, updated details are provided in a SAP.

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 subjects and to enhance the integrity and credibility of the trial. To enable the DMC to achieve its mission, the DMC will have ongoing access to 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

A total of 50 subjects (25 in each treatment group) was planned to be enrolled in the study.

Note: Protocol versions 5 and 6 were implemented after enrollment was stopped early due to administrative reasons. The final sample size is not based on statistical considerations. Formal hypothesis testing will be performed based on all available sample size at the time of the study discontinuation.

9.6. Study Populations

The Randomized population comprises all subjects who are randomized to one of GNX or PBO treatment group.

The Safety population comprises all randomized subjects who received at least one dose of study drug.

The ITT population comprises all randomized subjects who received at least one dose of study drug and have at least one post-baseline efficacy assessment.

The Per-Protocol (PP) population includes all ITT subjects without major protocol violations (defined prior to database lock). There will be no PP population for the OL period of the study.

9.7. General Statistical Considerations

Source data for the summary tables and statistical analyses will be presented as subject data listings, which include data collected on the electronic case report forms (eCRFs) as well as any derived efficacy variables for all enrolled subjects.

Except where noted, separate tables and data listings will be prepared for the DB and OL phases of the study. Only events occurring before entry into the OL phase will be included in the DB phase outputs, and except where indicated, only baseline events and events occurring after entry into the OL phase will included in the OL phase outputs.

Baseline seizure activity will be determined by prospective recording in subject's daily seizure eDiaries, which are provided after signing informed consent/assent. Within the DB phase of the study, determination of post-baseline seizure activity will begin on the day following the first day

of DB treatment. Determination of post-baseline seizure activity assigned to the OL phase will begin on the day following the first OL treatment.

Tables will be provided using the ITT subject population as well as within each of the biomarker-positive and biomarker-negative strata. The within-stratum PBO group will consist of only the subjects within the corresponding stratum. The tables for the DB phase will show the results for each DB treatment group and, where noted, combined over the groups as well. The tables for the OL phase will show the results for each DB treatment group (all subjects will be receiving GNX in the OL phase) and combined over them. For the efficacy endpoints, the results will be derived according to the randomized treatment group; for the other endpoints, they will be derived according to the treatment actually received.

Baselines for non-seizure efficacy and safety assessments are defined as the last non-missing value of the assessment before the first dose of treatment.

The OL phase will use the same baseline as the DB phase.

9.8. Subject Disposition

Disposition will be summarized within the DB treatment groups and overall among all subjects within both the DB and extension phases of the study.

Subjects completing the DB phase of the study are those who completed the 17-week DB treatment phase, regardless of whether they entered the OL. A listing of dispositions will be provided for all randomized subjects.

9.9. Eligibility Criteria and Protocol Deviations

The clinical team will identify deviations; these will be provided in a data listing. A data listing of subjects who violate any of the inclusion/exclusion characteristics will also be provided, as well as a data listing of subjects with other protocol violations.

9.10. Demographics and Baseline Characteristics

Demographic data (age, gender, race, height, weight and body mass index (BMI), and ethnicity) and baseline characteristics (Tanner staging) collected prior to the first dose will be summarized using descriptive statistics.

9.11. Medical History and Genetic Testing

Medical history will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) Terminology version 22.0. The number and percent of subjects with clinically significant medical history at screening will be summarized by system organ class and preferred term (PT) by treatment and overall in the safety population.

The results of the genetic testing, historical seizure information, and seizure identification and diagnostic review will be summarized and listed.

9.12. Prior and Concomitant Therapies

Prior medications are defined as medications that started and stopped prior to the first dose of DB study drug. Concomitant medications are defined as medications (other than the study drug) taken on or after the first dose of the DB study drug, regardless of when the medications started.

9.13. Efficacy Analyses

9.13.1. Double-Blind Phase

For the analyses of seizures, the baseline phase consists of the 8- or -12 week period before the first day of treatment, and the DB phase starts the day following the first day of DB treatment and continues until the final visit for subjects who do not enter the OL, and up to the day before the first dose of OL treatment for those who do.

Tests of significance between the 2 treatment groups will be performed for the primary endpoint with a 2-sided significance level of 0.05.

9.13.1.1. Handling of Missing Data

Careful educating and monitoring of the study sites will attempt to limit the amount of missing data to nearly zero, but despite these efforts, some missing data may still arise.

Intermittent (random/sporadic) missing data during the 17-week double blind phase and any missing data during the baseline phase will be assumed missing at random and the collected data will be used to calculate the 28-day seizure frequencies.

For early drug termination prior to the end of the 17-week DB phase, caregivers will be instructed to continue to provide daily seizure records until the end of the 17-week DB phase (hence further preventing missingness).

The primary analysis will use all available data. Careful educating and monitoring of the study sites will attempt to limit the amount of missing data. Sensitivity analyses, with replacement of missing data, will be performed for the primary efficacy endpoint.

9.13.1.2. Primary Endpoint (Seizure Control)

The primary efficacy endpoint is the percent change in 28-day primary seizure frequency during the 17-week DB phase relative to the baseline. The primary seizure types are defined as countable focal seizures that include progressive hypotonia and impaired awareness, or any countable focal or generalized seizure with a clear motor component. Focal and generalized nonmotor seizures and myoclonic seizures do not count as the primary seizure types.

The analyses of the primary endpoint will be performed on the sum of the individual countable seizures and each series of continuous uncountable seizures (each contributes 1 to the sum).

Post-baseline 28-day seizure frequency will be calculated as the total number of seizures in the 17-week DB treatment phase divided by the number of days with seizure data in the phase, multiplied by 28. Baseline 28-day seizure frequency will be calculated as the total number of seizures in the baseline phase divided by the number of days with seizure data in the phase, multiplied by 28. The difference between the GNX and placebo groups in the percent changes will be tested using the Wilcoxon Rank-Sum statistic. Testing will be conducted in the following

order:

- The primary analysis will be conducted in the ITT Population.
- If nominal statistical significance is achieved in the ITT Population, the primary analysis will be conducted in the biomarker-positive stratum of the ITT population as a secondary endpoint.

In addition, as an exploratory analysis, efficacy will be assessed in the biomarker-negative stratum and compared with the biomarker-positive result.

9.13.1.3. Secondary Efficacy Endpoints

All secondary efficacy endpoints will compare GNX and PBO during the 17-week DB treatment phase relative to the prospective baseline phase, unless specifically indicated otherwise.

9.13.1.3.1. Seizure Control Endpoints

9.13.1.3.1.1. Percent Change in Primary Seizure Frequency

The percent change in 28-day primary seizure frequency during the 17-week DB Phase relative to baseline in biomarker-positive subjects.

The same analysis methods for the primary endpoint will also be applied to this secondary endpoint. Please also refer to Section 9.13.1.2 for the hypothesis testing order.

9.13.1.3.1.2. Percentage of Subjects Experiencing Primary Seizure Reduction

Percentage of subjects experiencing a ≥ 50% reduction in 28-day primary seizure frequency compared to baseline.

9.13.1.3.2. Behavioral/Neuropsychiatric Endpoints

9.13.1.3.2.1. Behavior Rating Inventory of Executive Function (BRIEF, preschool version BRIEF-P)

The Behavior Rating Inventory of Executive Function (BRIEF) is an 86-item questionnaire designed to assess executive function behaviors in the school and home environments in individuals 5-18 years of age. The preschool version (BRIEF-P) is a 63-item modified form and is utilized in individuals 2-5 years of age. The questionnaire is completed by the parents/caregiver/LAR.

BRIEF (BRIEF-P where appropriate) will be assessed as follows: in the DB phase at Visit 2 (baseline/randomization) and Visit 5 (Week 17; also Final DB Visit/First OL Visit in open label phase); in the OL phase at Visit 7 (Week 36) and Visit 9 (Week 68) and thereafter every 16 weeks for the duration of this phase; and at the Final OL Visit.

9.13.1.3.2.2. Aberrant Behavior Checklist - Community (ABC-C)

The ABC-C is a questionnaire designed to assess problematic behavior at home, in educational and work setting, and in residential and community-based facilities.

The ABC-C will be assessed as follows: in the DB phase at Visit 2 (baseline/randomization) and Visit 5 (Week 17; also Final DB Visit/First OL Visit in open label phase); in the OL phase at Visit 7 (Week 36) and Visit 9 (Week 68) and thereafter every 16 weeks for the duration of this phase; and at the Final OL Visit.

9.13.1.3.2.3. Children's Sleep Habit Questionnaire (CSHQ)

The CSHQ is a psychological questionnaire designed to measure sleep behaviors in children and adolescents and is filled out by the parent/caregiver/LAR. An abbreviated version contains 33 items. The first 31 items are scored as 1 = Rarely (0-1 times per week), 2 = Sometimes (2-4 times per week), or 3 = Usually (5 - 7 times per week). Item 32 (Watching TV) and 33 (Riding in car) ask how sleepy the child has appeared during those activities (1 = Not sleepy, 2 = Very sleepy, or 3 = Falls asleep). The questionnaire includes 2 other quantitative questions:

- Child's usual amount of sleep each day
- Number of minutes a night waking usually lasts

The 33 items are partitioned into 8 domains:

1. Bedtime resistance (items 1, 3, 4, 5, 6, 8)
2. Sleep onset delay (item 2)
3. Sleep duration (items 9, 10, 11)
4. Sleep anxiety (items 5, 7, 8, 21)
5. Night wakings (items 16, 24, 25)
6. Parasomnias (items 12-15, 17, 22, 23)
7. Sleep disordered breathing (items 18, 19, 20)
8. Daytime sleepiness (items 26-33)

For scoring, first items 1, 2, 3, 10, 11, and 26 are reversed (4-score). The item scores are then summed within each domain. The domain subtotals, the total of the 33 items, and the 2 other quantitative questions will be summarized with descriptive statistics of the baseline and post-baseline values and the arithmetic changes from baseline. The usual amount of sleep each day will be summarized in hours.

9.13.1.4. Exploratory Efficacy Endpoints

[redacted]

9.13.2. Subgroup Analyses

Other than the within-stratum analyses, no subgroup analyses are planned at this time.

9.13.3. Sensitivity Analyses

Two sensitivity analyses of the primary efficacy endpoint of change in 28-day frequency of the primary seizure types will be performed:

Intermittent (random/sporadic) missing data during the 17-week DB phase and any missing data during the baseline phase will be assumed missing completely at random and the collected data will be used to calculate the 28-day seizure frequencies. For early drug termination prior to the end of the 17-week DB phase, caregivers will be instructed to continue to provide daily seizure records until the end of the 17-week DB phase (hence further preventing missingness).

In the first sensitivity analysis, the following imputation approach will be used for the primary outcome measure when a subject stops recording measurements permanently (anticipated to be zero or minimal in occurrence) prior to the end of the 17-week DB phase: for the missing days, the corresponding median PBO data will be imputed (irrespective of treatment arm), within each stratum, as follows:

- Compute the median 28-day seizure frequency in the PBO arm based on all available PBO measurements during the 17-week DB treatment phase. Label that 'X' and define 'A' to be 'X'/28, (i.e., the daily average on placebo during the 17-week during the DB phase).
- For any days (whether they be on the PBO or GNX arm) that occur AFTER a subject has become lost to follow up, impute 'A' on that day.

The second sensitivity analysis will explore the possibility that subjects who stop recording their seizure counts tend to have higher seizure counts than the other subjects. The imputation method described above will be modified to use the median of the 5 highest counts, rather than the median count, among the PBO subjects with data.

9.13.4. Protections for Multiplicity

To control the family-wise Type I error rate, hypothesis testing of the primary efficacy endpoint will be conducted sequentially in the order specified in Section 9.13.1.2.

9.13.5. Open-Label Period Analyses

All of the analyses for the DB phase, will be repeated for the OL phase with the following differences:

- The results will be presented overall and also classified according to the DB treatment received by subjects.
- Post-baseline seizure endpoints will be derived based on the first day of OL treatment.
- No sensitivity analyses will be performed
- The seizure frequencies during the titration and maintenance phases will not be analyzed.
- The time points for the efficacy, exploratory, and quality of life endpoints will be after 19 weeks, 51 weeks, and every 16 weeks thereafter of OL treatment relative to the prospective baseline phase.
- The differences between the DB 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.

The complete list of differences will be outlined in the SAP.

9.14. Safety Analyses

All safety analyses will be performed in the Safety Population. The results in the DB and OL phases will be summarized separately. In both phases, the results will be summarized by the DB treatment actually received and, for the OL 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.

Adverse events will be tabulated by overall, system organ class, and Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA) coding system. Incidence and percentage of AEs will be presented. Additional tables, with AEs classified by severity and by only those related to drug as assessed by the PI will be presented. Subset listings will be produced for AEs that cause withdrawal and for SAEs. Clinical laboratory tests (hematology, chemistry and urinalysis), vital signs and ECGs will be summarized using descriptive statistics including changes from baseline. In addition, shift tables cross-tabulating the baseline and post-baseline low/normal/high classifications by visit will be provided for the laboratory tests. Physical, neurological and developmental examinations will be summarized using number and percentage of subjects with abnormalities.

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. The Tanner scale is administered following the first dose, only during the OL phase of the study.

The baseline and post-baseline values and the arithmetic changes from baseline of the neurosteroid levels will be summarized using descriptive statistics.

Concomitant AED levels are not mandatory but will be collected per sites' standard of care. A subject listing, including date and time of last AED dose and date and time of AED PK sample, will be provided.

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

9.15. Pharmacokinetic Analyses

A listing of the PK collection times will be provided, but the analyses will be described in a separate report (analyses details will be provided in the SAP).

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. The samples will be drawn

between 1 and 5 hours or between 4 and 8 after the last dose during the double-blind and open label periods. 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.

9.16. Interim Analysis

No formal interim analysis is planned for this study. After all active subjects complete the17-week double-blind phase, the double-blind data in the database will be locked and used to perform endpoint analysis. Data collected during the open label phase will be analyzed separately.

The emerging study data will be reviewed on a regular basis by an independent 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 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. Specific details of the monitoring boundaries are provided in the SAP and the DMC Charter.

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 IP 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 PI 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 PI'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 PI should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The PI will maintain a list of appropriately qualified persons to whom the PI 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 PIs 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 PI 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 PI and any sub-investigators must adhere to the protocol as detailed in this document. The PI 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 PI suspends or terminates the study at their site, the PI will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The PI will also return all IP, containers, and other study materials to the sponsor. Upon study completion, the PI 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, PI, 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 study team and should be handled in accordance with instructions from the Sponsor.

The PI 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 PI 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 PI.

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.

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 PI 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 Diaries (eDiary)

The eDiaries are supplied by the Sponsor designee and should be handled in accordance with instructions from the sponsor. In rare cases when an eDiary completion is not feasible, a paper diary will be used to log daily seizure type and frequency. The Sponsor will provide the paper diary template which should not be modified.

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

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.

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 PI 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 (eg, 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 (eg, 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 PI 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 PI 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 IP; 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/Assent

It is the responsibility of the PI to obtain written informed consent/assent from the subject/parent/caregiver/LAR for all study subjects prior to any study-related procedures, including screening assessments.

All consent documentation must be in accordance with applicable regulations and GCP. Each subject's parent/caregiver/LAR/subject, as applicable, is requested to sign and date the subject's informed consent/assent 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/caregiver/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/caregiver/LAR of the safe, responsible storage and administration of the oral IP.

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 (ie, 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 PI 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 PI 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 PI for sites within the EU, or for multicenter studies, it can be done by the coordinating PI, according to national provisions. The PI 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 (eg, 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 (eg, 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 PI 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 PI may individually publish the study results from the specific site in accordance with this section. The PI 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	

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.

[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.

Source: FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Web link Accessed 08 November 2018:
http://www fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inVivo

12.2. Appendix 2: Clinical Laboratory Tests

Clinical Chemistry	Hematology	Urinalysis	Other
Total Bilirubin[a]	Hemoglobin	pH	Drug Screen[d]
AST (SGOT)[b]	Hematocrit	Color	
ALT (SGPT)[b]	Erythrocytes	Clarity	
BUN	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[c]			
Quantitative serum β-human chorionic growth hormone (β-HCG) serum pregnancy			

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, eGFR = estimated glomerular filtration rate.

[a] If total bilirubin increases to 1.5 x ULN or more during study, the subject will be discontinued.

[b] If AST or ALT increases > 3 × 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.

[c] Subjects with significant renal insufficiency, eGFR < 30 mL/min (calculated using the Cockcroft-Gault formula), will be discontinued if the criterion is met post baseline.

[d] Plasma drug screen for tetrahydrocannabinol (THC) and unapproved cannabidiol (CBD).

12.3. Appendix 3: Examples of Dosing Titration for Oral Suspension

An example of the transition from DB to OL dosing is shown below for a 20-kg subject who was initially randomized to GNX during the DB phase:

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)
Morning dose	21 mg/kg; 8.4 mL	6 mg/kg; 2.4 mL
Afternoon dose	21 mg/kg; 8.4 mL	6 mg/kg; 2.4 mL
Evening dose	21 mg/kg; 8.4 mL	6 mg/kg; 2.4 mL
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 (13 mg/kg TID)
Morning dose	21 mg/kg; 8.4 mL	11 mg//kg; 4.4 mL
Afternoon dose	21 mg/kg; 8.4 mL	11 mg/kg; 4.4 mL
Evening dose	21 mg/kg; 8.4 mL	11 mg/kg; 4.4 mL
Continue dosing from Group A and B as above until end of Day 14		
Days 15-21	63 mg/kg/day (21 mg/kg TID)	48 mg/kg/day (16 mg/kg TID)
Morning dose	21 mg/kg; 8.4 mL	16 mg/kg; 6.4 mL
Afternoon dose	21 mg/kg; 8.4 mL	16 mg/kg; 6.4 mL
Evening dose	21 mg/kg; 8.4 mL	16 mg/kg; 6.4 mL
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)
Morning dose	21 mg/kg; 8.4 mL	21 mg/kg; 8.4 mL
Afternoon dose	21 mg/kg; 8.4 mL	21 mg/kg; 8.4 mL
Evening dose	21 mg/kg; 8.4 mL	21 mg/kg; 8.4 mL
Continue dosing from Group A and B as above until Visit 6, Week 21		
Visit 6, 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)	
Morning dose	21 mg/kg; 8.4 mL	
Afternoon dose	21 mg/kg; 8.4 mL	
Evening dose	21 mg/kg; 8.4 mL	

GNX = ganaxolone, TID = 3 times daily.

An example of the transition from DB to OL dosing is shown below for a 20-kg subject who was initially randomized to PBO during the DB phase:

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; 8.4 mL	6 mg/kg; 2.4 mL
Day 1 afternoon dose	21 mg/kg; 8.4 mL	6 mg/kg; 2.4 mL
Day 1 evening dose	21 mg/kg; 8.4 mL	6 mg/kg; 2.4 mL
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; 8.4 mL	11 mg/kg; 4.4 mL
Day 8 afternoon dose	21 mg/kg; 8.4 mL	11 mg/kg; 4.4 mL
Day 8 evening dose	21 mg/kg; 8.4 mL	11 mg/kg; 4.4 mL
Continue dosing from Group A and B as above until end of Day 14		
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; 8.4 mL	16 mg/kg; 6.4 mL
Day 15 afternoon dose	21 mg/kg; 8.4 mL	16 mg/kg; 6.4 mL
Day 15 evening dose	21 mg/kg; 8.4 mL	16 mg/kg; 6.4 mL
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; 8.4 mL	21 mg/kg; 8.4 mL
Day 15 afternoon dose	21 mg/kg; 8.4 mL	21 mg/kg; 8.4 mL
Day 15 evening dose	21 mg/kg; 8.4 mL	21 mg/kg; 8.4 mL
Continue dosing from Group A and B as above until Visit 6, Week 21		
Visit 6, 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; 8.4 mL	
Day 29 afternoon dose	21 mg/kg; 8.4 mL	
Day 29 evening dose	21 mg/kg; 8.4 mL	

GNX = ganaxolone, TID = 3 times daily.

An example of the transition from DB to OL dosing is shown below for a > 28-kg subject who was initially randomized to GNX during the DB phase:

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; 12 mL	150 mg; 3 mL
Day 1 afternoon dose	600 mg; 12 mL	150 mg; 3 mL
Day 1 evening dose	600 mg; 12 mL	150 mg; 3 mL
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; 12 mL	300 mg; 6 mL
Day 8 afternoon dose	600 mg; 12 mL	300 mg; 6 mL
Day 8 evening dose	600 mg; 12 mL	300 mg; 6 mL
Continue dosing from Group A and B as above until end of Day 14		
Days 15-21	1800 mg/day (600 mg TID)	1350 mg/day (450 mg TID)
Day 15 morning dose	600 mg; 12 mL	450 mg; 9 mL
Day 15 afternoon dose	600 mg; 12 mL	450 mg; 9 mL
Day 15 evening dose	600 mg; 12 mL	450 mg; 9 mL
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; 12 mL	600 mg; 12 mL
Day 15 afternoon dose	600 mg; 12 mL	600 mg; 12 mL
Day 15 evening dose	600 mg; 12 mL	600 mg; 12 mL
Continue dosing from Group A and B as above until Visit 6, Week 21		
Visit 6, 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; 12 mL	
Day 29 afternoon dose	600 mg; 12 mL	
Day 29 evening dose	600 mg; 12 mL	

GNX = ganaxolone, TID = 3 times daily.

An example of the transition from DB to OL dosing is shown below for a > 28-kg subject who was initially randomized to PBO during the DB phase.

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; 12 mL	150 mg; 3 mL
Day 1 afternoon dose	600 mg; 12 mL	150 mg; 3 mL
Day 1 evening dose	600 mg; 12 mL	150 mg; 3 mL
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; 12 mL	300 mg; 6 mL
Day 8 afternoon dose	600 mg; 12 mL	300 mg; 6 mL
Day 8 evening dose	600 mg; 12 mL	300 mg; 6 mL
Continue dosing from Group A and B as above until end of Day 14		
Days 15-21	1800 mg/day (600 mg TID)	1350 mg/day (450 mg TID)
Day 15 morning dose	600 mg; 12 mL	450 mg; 9 mL
Day 15 afternoon dose	600 mg; 12 mL	450 mg; 9 mL
Day 15 evening dose	600 mg; 12 mL	450 mg; 9 mL
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; 12 mL	600 mg; 12 mL
Day 15 afternoon dose	600 mg; 12 mL	600 mg; 12 mL
Day 15 evening dose	600 mg; 12 mL	600 mg; 12 mL
Continue dosing from Group A and B as above until Visit 7, Week 21		
Visit 6, 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; 12 mL	
Day 29 afternoon dose	600 mg; 12 mL	
Day 29 evening dose	600 mg; 12 mL	

GNX = ganaxolone, TID = 3 times daily.