PROTOCOL: 1042-TSC-2001

TITLE:	A Phase 2 Open-label 12-Week Trial of Adjunctive Ganaxolone Treatment (Part A) in Tuberous Sclerosis Complex-related Epilepsy followed by Long-term Treatment (Part B)
DRUG:	Ganaxolone
IND:	044,020
SPONSOR:	Marinus Pharmaceuticals, Inc. 5 Radnor Corporate Center 100 Matsonford Rd, Suite 500 Radnor, PA 19087 USA
PRINCIPAL/ COORDINATING INVESTIGATOR:	
PROTOCOL HISTORY:	Protocol Amendment 2: 11 Jun 2021, Version 3.0 Protocol Amendment 1: 12 May 2020, Version 2.0 Original Protocol: 07 Feb 2020

NCT Number: NCT04285346
This NCT number has been applied to the document for purposes of posting on Clinicaltrials.gov

PROTOCOL SIGNATURE PAGE

Sponsor's (Marinus) Approval

Signature: [redacted]	**Date:** June 14, 2021 | 1:34 PM EDT
	{***Note: Signature date must not precede the approval date***}

Investigator's Acknowledgement

I have read this protocol for Marinus Study 1042-TSC-2001.

Title: A Phase 2 Open-label 12-Week Trial of Adjunctive Ganaxolone Treatment (Part A) in Tuberous Sclerosis Complex-related Epilepsy followed by Long-term Treatment (Part B)

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 Council for Harmonisation guidelines on Good Clinical Practice and with the applicable regulatory requirements.

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

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

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

Signature: _____ **Date:** _____

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments	
Summary of Change(s) Since Last Version of Approved Protocol	
Amendment Number **2**	**Amendment Date** **11 Jun 2021**
Description of Change	**Section(s) Affected by Change**
Protocol version and date updated	Protocol History
Sponsor contact information updated	Emergency Contact Information
Study period (planned)	Study Synopsis
OL extension	Methodology Part B
Formatting update	4.1 Inclusion Criteria
PK sample collection clarification	7.8 Pharmacokinetic Assessments
Unscheduled visits clarification	7.3.5 Unscheduled visits
Study design updated	3.1 Study Design and Flow Chart
Duration of study extended	3.2 Duration and Study Completion Definition
Amendment Number **1**	**Amendment Date** **12 May 2020**
Description of Change	**Section(s) Affected by Change**
Update protocol version and date	Protocol History
Add table for Summary of Changes	Summary of Changes
Add Day 1 and Day 2 Follow-up phone calls	Schedule of Assessments -Part A
Add CGI-I assessments to Baseline Visit	Schedule of Assessments -Part A
Change footnote “m” from screening to baseline	Schedule of Assessments -Part A
Add remote / home visits details	7.1 Study Assessments
Add CGI-I assessments (caregiver and clinician)	7.2.2 Baseline
Add Day 1 and Day 2 Follow-up phone calls	7.2.3 Telephone Follow-up
Change from screening to baseline visit	7.5.2 CGI-C
Add Baseline visit	7.5.3 CGI-I
Plasma drug screen moved to hematology from urinalysis	12.2 Appendix 2

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: safetyTSC2001@marinuspharma.com
Fax: +1 484-679-2138

SPONSOR CONTACTS:

Sponsor Medical Monitor:

[redacted], **MBChB**
[redacted]
Mobile Telephone: [redacted]
Email: [redacted]

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

Back-up Medical Monitor:

[redacted], **MD**
[redacted] Clinical Development
Mobile Telephone: [redacted]
Email: [redacted] (primary contact method)

Sponsor Project Managers:

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

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

Term	Definition
ACTH	Adrenocorticotropic hormone
AE	adverse event
AED	antiepileptic drug
ASM	anti-seizure medication
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
β-HCG	β-human chorionic growth hormone
BP	blood pressure
BUN	blood urea nitrogen
CBD	cannabidiol
CDKL5	cyclin-dependent kinase-like 5
CGI-C	Caregiver Global Impression of Change
CGI-I	Clinical Global Impression – Improvement
C_{max}	maximum plasma concentration
CNS	central nervous system
CRA	clinical research associate
CRO	clinical research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome P450
DB	double-blind
eCRF	electronic case report form
EC	ethics committee
ECG	electrocardiogram
[redacted]	[redacted]
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
FXS	fragile X syndrome
GABA	γ-Aminobutyric acid

Term	Definition
$GABA_A$	γ-Aminobutyric acid type A
GCP	Good Clinical Practice
GNX	ganaxolone
HDPE	high-density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
ICH	International Council for Harmonisation
IND	Investigational New Drug
IP	investigational product
IRB	institutional review board
IS	infantile spasms
ITT	intent-to-treat
IV	intravenous
LAM	lymphangioleiomyomatosis
LAR	legally authorized representative
MedDRA	Medical Dictionary for Regulatory Activities
mTOR	mammalian target of rapamycin
OL	open-label
OLE	open-label extension
PBO	placebo
PCDH19	protocadherin 19
PI	principal investigator
PK	pharmacokinetic(s)
PP	Per-Protocol
Rheb	Ras homolog enriched in brain
RR	respiratory rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase

Term	Definition
SIF/DRF	Seizure Identification and Diagnostic Review Form
TEAE	Treatment-emergent adverse event
THC	tetrahydrocannabinol
THP	tetrahydroprogesterone
TID	three times daily
t_{max}	time of maximum concentration
TSC	Tuberous Sclerosis Complex
ULN	upper limit of normal
US	United States
VNS	Vagus nerve stimulator
WCBP	women of childbearing potential

STUDY SYNOPSIS

Protocol number: 1042-TSC-2001	**Drug:** ganaxolone (GNX)
Title of the study: A Phase 2 open-label 12-week trial of adjunctive ganaxolone treatment (Part A) in tuberous sclerosis complex-related epilepsy followed by long-term treatment (Part B).	
Number of patients (total and for each treatment arm): Approximately 36 tuberous sclerosis complex (TSC) patients will be screened to achieve 30 TSC patients enrolled in Part A.	
Investigators: Multicenter study	
Sites and Regions: Multicenter study to be conducted at approximately 6 sites in the United States	
Study period (planned): March 2020 – January 2022	**Clinical phase:** **2**

Objectives:

Primary:

- To assess preliminary safety and efficacy of GNX as adjunctive therapy for the treatment of primary seizure types in patients with genetically- or clinically-confirmed TSC-related epilepsy through the end of the 12-week treatment period. The primary seizure types (defined later) are identified to be the most common, easily identifiable/countable by a parent/caregiver/legally authorized representative (LAR), and most consequential to the patient's quality of life

Secondary:

- To assess the long-term efficacy of GNX when administered as adjunctive therapy throughout the open-label extension (OLE) period (Part B)
- To assess the long-term safety and tolerability of GNX when administered as adjunctive therapy throughout the OLE period (Part B)

[redacted]

Rationale:

Tuberous sclerosis complex is a multi-system disorder of embryonal cortical development which can impact many organs through the overgrowth of hamartomas, benign, tumorous growths that can occur in the brain and other organs. While the phenotype of TSC can be extremely variable, neurologic manifestations such as epilepsy are seen in up to 90% of TSC patients (Krueger and Northrup, 2013). The condition is caused by inherited mutations in either the *TSC1* gene, located on chromosome 9q34, or the *TSC2* gene located on chromosome 16p13.3. TSC occurs with a frequency of 1:6,000 and a mutation is found in 85% of patients (Jülich and Sahin, 2014). The gene products hamartin (*TSC1*) and tuberin (*TSC2*) form a regulatory complex responsible for limiting the activity of mammalian target of rapamycin (mTOR) complex 1, an important intracellular regulator of growth and metabolism that acts via inhibition of the small GTPase Ras homolog enriched in brain (Rheb) (Krueger and Northrup, 2013). Everolimus, an mTOR inhibitor, has been shown to decrease seizures (French et al., 2016; Mizuguchi et al., 2019).

Tuberous sclerosis complex is one of the most common genetic causes of epilepsy, with seizure semiology that varies by age of onset (Jülich and Sahin, 2014). Infantile spasms (IS) are the most common seizure type presenting in infancy and represent the first manifestation of epilepsy in 50% of patients. In older children and adults, focal impaired awareness seizures (previously known as complex partial seizures) are the most common

(Chu-Shore et al., 2010). Other focal and generalized seizures may also occur, with over 30% of patients developing treatment-refractory epilepsy (Jülich and Sahin, 2014). While seizures have typically been ascribed to tubers and the surrounding cortex, epilepsy in TSC can be considered multifactorial in origin as seizures can originate in other brain areas or can occur in TSC patients without tubers (Jülich and Sahin, 2014; van der Poest Clement et al., 2020).

γ-Aminobutyric acid (GABA)ergic signaling may play a meaningful role in the development and severity of TSC-related epilepsy, possibly due to altered expression of endogenous GABA type A ($GABA_A$) receptor modulators (Di Michele et al., 2003). There is evidence supporting a deficiency of the neuroactive steroid, 3α, 5α-tetrahydroprogesterone (THP), or allopregnanolone, as a contributor to epileptogenesis in TSC. Allopregnanolone is a positive modulator of the $GABA_A$ receptor and has been shown to have antiepileptic effects in experimental animals and humans. There is a decrease in allopregnanolone relative to its functional $GABA_A$ antagonist, 3β-THP, in patients with TSC-related epilepsy but not in TSC patients without epilepsy or in controls (Di Michele et al., 2003). This reduced ratio could alter neuronal excitability mediated by $GABA_A$ receptors, leading to the development of epilepsy. The role of $GABA_A$ receptor mediation is also supported by the efficacy of vigabatrin, a specific and irreversible inhibitor of GABA-aminotransferase, in seizures due to TSC relative to other epilepsies (Di Michele et al., 2003). These findings provide compelling evidence for the potential role of neuroactive steroids with anticonvulsant properties, or analogues such as GNX, in the treatment of TSC-related epilepsy.

Ganaxolone is the 3β-methylated synthetic analog of allopregnanolone, an endogenous positive allosteric modulator of central nervous system (CNS) $GABA_A$ receptors. Ganaxolone has potency comparable to allopregnanolone in activating synaptic and extrasynaptic $GABA_A$ receptors at a site distinct from benzodiazepines and barbiturates (Carter et al., 1997). Ganaxolone has protective activity in diverse rodent seizure models (Bialer et al., 2010; Reddy and Rogwski, 2012). 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 given orally in adults and children (Kerrigan et al., 2000; Laxer et al., 2000; Pieribone et al., 2007; Sperling et al., 2017). Further, GNX reduces seizures in children with IS and refractory pediatric epilepsy. In an open-label (OL) study, pediatric patients aged 2 to 60 months with refractory seizures and a history of IS were treated with GNX doses up to 36 mg/kg for up to 3 months (Kerrigan et al., 2000). Fifteen patients with a history of IS completed treatment. Five of the 15 patients 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 patient became spasm-free and 1 non-responder (with a decrease of < 25%) was spasm-free from Weeks 2 to 7.

A double-blind (DB) study (Study 1042-0500) of GNX in IS was also conducted. In this study, patients aged 4 to 24 months with IS received placebo or GNX doses of up to 54 mg/kg/day for up to 20 days in an incomplete crossover design. A total of 55 of the 57 patients completed treatment, 54 of whom continued GNX treatment in Study 1042-0501, an OLE. Although the GNX group had numerically higher reductions in frequency of spasm clusters, no statistically significant differences were observed in change from baseline between the treatment groups in the frequency of spasm clusters or in any of the secondary efficacy parameters at the end of the DB period (Day 9 ± 1 day).

In addition to its anticonvulsant activity, GNX has been shown to reduce anxiety, hyperactivity, and attention in children with fragile X syndrome who had higher baseline levels of anxiety (Ligsay et al., 2016). Similar behavioral problems occur in individuals with TSC, with rates of approximately 50% for attention deficit hyperactivity disorder and autism (Jülich and Sahin, 2014). It is hypothesized that GNX treatment will increase $GABA_A$-receptor signaling and improve not only seizure control but may also ameliorate the behavioral abnormalities in individuals with TSC.

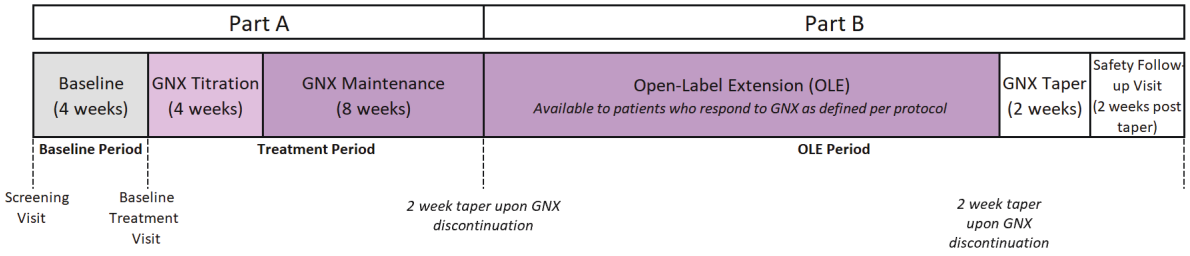
Methodology: This is an OL proof of concept study of adjunctive GNX treatment in patients with a confirmed clinical diagnosis of TSC and/or a mutation in either the *TSC1* or *TSC2* gene. The trial consists of two parts: Part A consists of a 4-week baseline period followed by a 12-week treatment period (4-week titration and 8-week maintenance). For patients not continuing in the OLE period (Part B), a 2-week taper period followed by a 2-week safety period would follow. The main difference between Part A and Part B is the length of treatment, less frequent assessments, and the ability to alter drug doses (both GNX and other antiepileptic drug [AED] treatments which includes initiating and stopping other medications) based on investigator evaluation of the patient's clinical course during Part B. Patients with a seizure frequency reduction rate of ≥ 35% during the 12-week treatment period in Part A compared to baseline may continue into Part B ("OLE eligible"). If the investigator believes there is a medical benefit for the patient who does not meet the seizure reduction criterion to enter the OLE, they must discuss the patient with the sponsor medical monitor and receive sponsor approval for that patient to continue into the OLE.

Part A

- 4-week baseline period
- 4-week titration period
- 8-week maintenance period
- 2-week taper period (For patients who do not complete Part A or after completing Part A but do not continue into Part B)
- 2-week safety follow-up visit post taper (For patients who taper off GNX)

Part B (Optional for OLE-eligible patients)

- OLE period (until the Sponsor markets ganaxolone or terminates the study)
- 2-week taper period (For patients who discontinue GNX due to early termination or completion)
- 2-week safety follow-up visit post taper (For patients who taper off GNX)



GNX = ganaxolone

During the screening visit, each patient's baseline [redacted], will be collected and analyzed for post-study evaluation.

Patient rescreening is allowed as agreed by the sponsor and the investigator unless there is a general concern for patient safety or an inability for the patient to become eligible (e.g., GNX allergy, sensitivity or exposure, non-TSC and/or other ineligible epilepsy, chronic prohibited medical condition or treatment). Subsequent screening should take place at least 30 days from the patient's last visit, unless otherwise noted.

Part A includes a 4-week baseline and 4 weeks of investigational product (IP) titration followed by 8 weeks of dose maintenance followed by 2-week taper for those patients not continuing into the Part B OLE period. After meeting all eligibility criteria, approximately 30 patients aged 2 to 65 years (inclusive) with TSC-related epilepsy will be enrolled to receive GNX for a total of 12 weeks (4-week titration, 8-week maintenance) in addition to their standard anti-seizure medication(s) (ASMs). Patients will be titrated to 63 mg/kg/day (maximum 1800 mg/day) over 4 weeks, and then maintained at that dose for another 8 weeks. Patients who are not able to tolerate 63 mg/kg/day (or maximum 1800 mg/day) may be maintained on a lower dose after discussion with the sponsor medical monitor. A minimum dose of 33 mg/kg/day or 900 mg/day is generally required during the maintenance period.

For Part A, 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. Patients who discontinue GNX should undergo a 2-week taper period, unless otherwise medically indicated. Patients who discontinue GNX before the completion of the maintenance period

will continue to be followed per protocol and, at a minimum, patients will be encouraged to maintain daily seizure diaries until the maintenance period in Part A is completed. These patients will also return to the site 2 weeks after the taper for safety follow-up assessments.

After completing the initial 16-week period, Part A, patients with a seizure reduction of ≥ 35% compared to the 4-week baseline period and who do not have any other contraindications for continued treatment can continue to be treated with GNX in the OLE period (Part B). Patients will continue GNX treatment at the dose that they were taking at completion of Part A. Doses of other ASMs may be adjusted (including tapering and initiating treatments) during Part B based on investigator discretion. Any patient who completes Part A and does not continue in Part B, or discontinues GNX treatment should undergo a 2-week drug de-escalation (taper) period and return to the site 2 weeks later for safety follow-up assessments.

Patients will be required to complete a daily diary to determine GNX's effect on seizures. Days without seizures should also be noted. Additional clinician- and caregiver-administered instruments will be used to assess the efficacy of GNX in TSC, and will include:

- Caregiver Global Impression of Change (CGI-C) - Target Behavior
- Clinical Global Impression – Improvement (CGI-I) caregiver and CGI-I clinician.

Inclusion and Exclusion criteria: Inclusion Criteria (Part A):

1. Clinical or mutational diagnosis of TSC consistent with Northrup and Krueger, 2013.
   a. Molecular confirmation of a pathogenic mutation in *TSC1* or *TSC2*. A pathogenic mutation is defined as a mutation that clearly prevents protein synthesis and/or inactivates the function of the *TSC1* or *TSC2* proteins (e.g., nonsense mutation or frameshift mutations, large genomic deletions) or is a missense mutation whose effect on protein function has been established by functional assessment. The investigator must review the results of the genetic analysis and confirm that the causal relationship to the epilepsy syndrome is likely. OR
   b. Clinical diagnosis of definite TSC which includes two major features or one major feature with ≥ 2 minor features. The investigator must document which of the features (Major or Minor) fulfill the clinical diagnostic criteria.

Major features	Minor features
1. Hypomelanotic macules (≥ 3, at least 5-mm diameter) 2. Angiofibromas (≥ 3) or fibrous cephalic plaque 3. Ungual fibromas (≥ 2) 4. Shagreen patch 5. Multiple retinal hamartomas 6. Cortical dysplasias[a] 7. Subependymal nodules 8. Subependymal giant cell astrocytomas 9. Cardiac rhabdomyoma 10. Lymphangioleiomyomatosis (LAM)[b] 11. Angiomyolipomas (≥ 2)[b]	1. "Confetti" skin lesions 2. Dental enamel pits (≥ 3) 3. Intraoral fibromas (≥ 2) 4. Retinal achromic patch 5. Multiple renal cysts 6. Nonrenal hamartomas

a. Includes tubers and cerebral white matter radial migration lines
b. A combination of the two major clinical features (LAM and angiomyolipomas) without other features that does not meet criteria for a definite diagnosis.

2. Male or female patients aged 2 through 65 years, inclusive.
3. Patient/parent/caregiver 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. Assent for patients over 7 years of age should be obtained, if appropriate.

4. Failure to control seizures despite appropriate trial of 2 or more ASMs at therapeutic doses.
5. Have at least 8 countable/witnessed primary seizures during the 4-week baseline period with at least 1 primary seizure occurring in at least 3 of the 4 weeks of baseline. The primary seizure types are defined as the following: focal motor seizures without impairment of consciousness or awareness, focal seizures with impairment of consciousness or awareness, focal seizures evolving to bilateral, tonic-clonic convulsive seizures, and generalized motor seizures including tonic-clonic, bilateral tonic, bilateral clonic, or atonic/drop seizures. Focal aware non-motor and generalized seizures without motor features, infantile or epileptic spasms, and myoclonic seizures do not count as the primary seizure types.
6. Patient must be approved to participate by the sponsor or its designee (e.g., Epilepsy Consortium) after review of medical history, genetic testing, and patients' seizure types.
7. Patients should be on a stable regimen of ASMs at therapeutic doses for ≥ 1 month prior to the screening visit, without a foreseeable change in dosing for the duration of Part A. Vagus nerve stimulator (VNS), ketogenic diet, and modified Atkins diet should be unchanged for 3 months prior to screening and will not count towards the number of ASMs.
8. Patients with surgically implanted VNS will be allowed to enter the study provided that all of the following conditions are met:
    a. The VNS has been in place for ≥ 1 year prior to the screening visit.
    b. The settings must have remained constant for 3 months prior to the screening visit and remain constant throughout the baseline and Part A.
    c. The battery is expected to last for the duration of baseline and Part A.
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 IP (suspension) with food 3 times daily. (GNX 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 (e.g., 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 (e.g., a spermicidal cream) is acceptable. In patients who are not sexually active, abstinence is an acceptable form of birth control.

Inclusion Criteria (Part B)

1. Patients have experienced ≥ 35% reduction in primary seizure frequency during the Part A treatment period compared to the 4-week Baseline Period.

Exclusion Criteria (Part A):

1. Previous exposure to GNX.
2. Pregnant or breastfeeding.
3. Concurrent use of strong inducers or inhibitors of cytochrome P450 (CYP)3A4/5/7. Any strong inhibitor or inducer of CYP3A4/5/7 must be discontinued at least 28 days before Visit 2, study drug initiation. This does not include approved ASMs.
4. Patients who have been taking felbamate for less than 1 year prior to screening.
5. Patients who test positive for tetrahydrocannabinol (THC) or non-approved cannabidiol (CBD) via plasma drug screen.
6. Chronic use of oral steroid medications, ketoconazole (except for topical formulations), St. John's Wort, or other IPs is not permitted.
7. Adrenocorticotropic hormone (ACTH), prednisone, or other systemically administered (non-inhaled) steroids must be discontinued ≥ 28 days prior to screening. Concomitant topical, inhaled or intranasal steroids are allowed and do not warrant exclusion from the study.

8. Changes in any chronic medications within the month (e.g., 30 days) prior to the screening visit. All concomitant medications must have been at a stable in dose for at least 1-month prior to the screening visit unless otherwise noted.
9. Patient is being considered for epilepsy surgery or has undergone surgery for epilepsy within the 6 months prior to screening.
10. Have an active CNS infection, demyelinating disease, degenerative neurological disease, or CNS disease deemed progressive. This includes tumor growth which in the opinion of the investigator could affect primary seizure control.
11. Have any disease or condition (medical or surgical; other than TSC) 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 patient at increased risk. This may include any illness in the past 4 weeks which in the opinion of the investigator may affect seizure frequency.
12. 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 or baseline visits and confirmed by a repeat test.
13. Total bilirubin levels > 1.5 × ULN at screening or baseline visit and 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.
14. Patients 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.
15. Have been exposed to any other investigational drug within 30 days or fewer than 5 half-lives (whichever is shorter) prior to the screening visit.
16. Unwillingness to withhold grapefruit, Seville oranges, star fruit, or grapefruit containing products from diet 7 days prior to first dose and for the duration of the study.
17. Have had an active suicidal plan/intent or active suicidal thoughts in the past 6 months or have made 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.

Exclusion Criteria (Part B):

1. Patient developed a medical condition that would make it unsafe for patients to received GNX as determined by the investigator.

Number of patients: Approximately 36 TSC patients, aged 2 to 65 inclusive, will be screened to achieve 30 TSC patients enrolled in Part A. Since this is an OL proof of concept study, sample size was not determined by statistical methods.

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 (maximum 1800 mg/day) given as an oral suspension with food. Patients weighing ≤ 28 kg will be dosed on an mg/kg basis. Patients weighing > 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 as follows:

Oral Suspension Dosing[a] for Patients Weighing ≤ 28 kg (62 lbs)[b]			
Dose mg/kg	**Total mg/kg/day**		**Days**
6 TID	18		1-7
11 TID	33		8-14
16 TID	48		15-21
21 TID	63		22-28
Oral Suspension Dosing[a] for Patients Weighing > 28 kg (62 lbs)[c]			
Dose mg	**mL per Dose**	**Total mg/day**	**Days**
150 TID	3	450	1-7

300 TID	6	900	8-14
450 TID	9	1350	15-21
600 TID	12	1800	22-28

TID = 3 times daily.

a. To be administered in 3 divided doses following a meal or snack.
b. Patients weighing ≤ 28 kg will be dosed according to the patient's weight in kilograms.
c. Patients weighing > 28 kg will be dosed on a fixed regimen in increments of 450 mg/day up to 1800 mg/day.

Any patient not tolerating the next dose step can be maintained at the lower dose step for additional days before advancing to the next dose. If the next dose is still not tolerated, the patient can drop back to the next lower dose step. A minimum dose of 33 mg/kg/day or 900 mg/day is generally required following the escalation period, during the maintenance period.

Dose changes including alternative dosing paradigms (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 investigator. For any patient who is unable to be maintained at the minimum dose, the investigator should contact the sponsor medical monitor to discuss continued IP dosing. Patients who discontinue GNX treatment before the completion of the maintenance period in Part A will continue to be followed per protocol and, at a minimum, patients will be encouraged to maintain daily seizure diary entries until Part A is completed.

During Part B, patients who meet all of the inclusion criteria and none of the exclusion criteria will initiate treatment in Part B with GNX at the same dose they were on at the completion of Part A. During Part B, doses of GNX may be adjusted to a maximum of 600 mg three times daily (TID) for patients weighing > 28 kg and a maximum dose of 21/mg/kg TID for patients weighing ≤ 28 kg.

Duration of treatment: After 4 weeks of baseline seizure charting, patients will initiate a 4-week GNX titration period followed by an 8-week GNX maintenance period (Part A). Patients completing Part A and deemed eligible for Part B will continue taking GNX. Patients will have the option to continue longer-term treatment on ganaxolone until commercially available or the study is terminated by the Sponsor. Anyone discontinuing GNX will undergo a 2-week taper and a 2-week follow-up safety visit.

The planned study duration is approximately 64 weeks for patients who stay on the study through Part B.

Criteria for Evaluation:

Seizures: All seizure types and number of seizures will be recorded daily in a diary. Days in which no seizures occur will also be noted. Subsets of seizure types will be defined below.

Primary Efficacy Endpoint: The primary efficacy endpoint is the percent change in 28-day primary seizure frequency through the end of the 12-week treatment period (4-week titration and 8-week maintenance) relative to the 4-week baseline. The primary seizure types are defined as the following: focal motor seizures without impairment of consciousness or awareness, focal seizures with impairment of consciousness or awareness, focal seizures evolving to bilateral, tonic-clonic seizures, and generalized motor seizures including tonic-clonic, bilateral tonic, bilateral clonic, and atonic/drop seizures. Focal aware non-motor and generalized seizures without motor features, infantile or epileptic spasms, and myoclonic seizures are not considered primary seizure types.

Post-baseline 28-day seizure frequency will be calculated as the total number of seizures in the 12-week treatment period (4-week titration and 8-week maintenance periods) divided by the number of days for which seizure data are reported in that period, multiplied by 28. Baseline 28-day seizure frequency will be calculated as the total number of seizures in the baseline period divided by the number of days for which seizure data are reported in the baseline period multiplied by 28. Descriptive statistics will be used to summarize changes in seizure frequency. No inferential statistical testing will be performed.

Secondary Efficacy Endpoints (Seizure control): Derived seizure secondary efficacy endpoints will be based on data through the end of the 12-week treatment period relative to the 4-week prospective baseline period.

- Percentage of patients experiencing a ≥ 50% reduction in 28-day primary seizure frequency through the end of the 12-week treatment period compared to the 4-week Baseline Period.

Secondary Efficacy Endpoints (Other):

- CGI-I, parent/caregiver and clinician
- CGI-C - Target Behavior

[redacted]

Pharmacokinetic Assessments:

The pharmacokinetic (PK) population will include all patients who have received at least 1 dose of GNX 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 Part A and Part B. Pharmacokinetic analyses will be limited to listing of concentrations because sufficient concentration-time data will not be available for noncompartmental analyses such as maximum plasma concentration (C_{max}), area under the concentration versus time curve (AUC), or time of maximum concentration (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 Statistical Analysis Plan.

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, Columbia-Suicide Severity Rating Scale (C-SSRS) if appropriate and frequency, type, and severity of adverse events (AEs) during Part A and Part B. Height and weight will also be measured.

Statistical Methods:

The intent-to-treat (ITT) population comprises all patients who received at least one dose of IP. The ITT population will be the primary population for efficacy analyses. The Per-Protocol (PP) population includes all ITT patients without major protocol violations (defined prior to database lock). Safety will be reported in all patients.

Since this is an OL proof of concept study, no inferential statistical testing will be conducted, and all efficacy outcomes will be descriptive.

Primary Endpoint: Definition and Analysis:

The primary efficacy endpoint (change in seizure frequency) is the percent change in 28-day seizure frequency through the end of the 12-week treatment period (4-week titration and 8-week maintenance) relative to the baseline, based on the primary seizure types. The primary seizure types are defined as the following: focal motor seizures without impairment of consciousness or awareness, focal seizures with impairment of consciousness or awareness, focal seizures evolving to bilateral, tonic-clonic convulsive seizures, and generalized motor seizures including tonic-clonic, bilateral tonic, bilateral clonic, or atonic/drop seizures. Focal aware non-motor and generalized seizures without motor features, infantile or epileptic spasms, and myoclonic seizures do not count as the primary seizure types.

Post-baseline 28-day seizure frequency will be calculated as the total number of seizures in the 12-week treatment periods (4-week titration plus 8-week maintenance period) during Part A divided by the number of days with seizure data in the period, multiplied by 28. Baseline 28-day seizure frequency will be calculated as the total number of primary seizures in the baseline period divided by the number of days with seizure data in the baseline period, multiplied by 28.

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

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

Since this is an OL proof of concept study, all efficacy analyses will be based on descriptive statistics.

Sample Size:

Since this is an OL proof of concept study, sample size was not determined by statistical methods.

Secondary and Exploratory Endpoints - Descriptive Evaluation:

Seizure control:

- Percentage of patients experiencing a ≥ 50% reduction in 28-day primary seizure frequency through the end of the 12-week treatment period compared to the 4-week Baseline Period.

Other:

- CGI-I, parent/caregiver and clinician.
- CGI-C - Target Behavior.

Exploratory Endpoints - Descriptive Evaluation:

All secondary and [redacted]

[redacted]

Safety Analysis: Safety will be reported for all patients. The results in Part A and Part B will be summarized separately and then the combined results in Part A and Part B will be summarized together. 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 investigator will be presented. Subset listings will be produced for AEs that cause withdrawal and for serious adverse events (SAEs). Clinical laboratory tests (hematology, chemistry and urinalysis), vital signs (temperature, BP, pulse rate), weight, and ECGs will be summarized using descriptive statistics including changes from baseline. Change in C-SSRS scores where applicable will be determined. Physical, neurological and developmental examinations will be summarized using number and percentage of patients 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 Part A:
  - Visit 4 (Week 5): between 1 and 5 hours since the last IP dosing
  - Visit 5 (Week 12): between 4 and 8 hours since the last IP dosing
- During Part B: There is no specified time to draw the PK sample and can be drawn when convenient during the study visits.

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

[redacted] **and Concomitant AED levels**: Blood samples will be drawn at screening visit, [redacted] 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. [redacted] and concomitant AED levels will be analyzed according to the SAP.

Interim Analysis: No formal interim analysis is planned.

Table 1: Schedule of Assessments - Part A

			Part A								
	Screen/Baseline					Titration and Maintenance					
WEEK	**-4 (Screening Visit – Start of Baseline)**	**0 (Baseline Treatment Visit)**	**Day 1**	**Day 2**	**Day 3**	**1**	**2, 3, 4**	**5**	**9**	**12**	**16 Taper/Safety Visits[p]**
Visit Windows		**+ 4 days**			**± 1 day**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**
VISIT	**Visit 1[a]**	**Visit 2[o]**	**Phone Follow-up**	**Phone Follow-up**	**Phone Follow-up**	**Visit 3**	**Phone Follow-up**	**Visit 4**	**Phone Follow-up**	**Visit 5**	**Visit 5a**
Informed Consent[b]	X										
Demographics & Medical History	X	X[s]									
Inclusion/Exclusion Criteria	X	X									
Genetic testing	X[c]	X[r]									
Seizure Identification and Diagnostic Review Form (Epilepsy Study Consortium)	X	X									
Vital Signs (BP, HR, RR, and body temperature)	X	X				X		X		X	X
Height / weight	X[d]	X[e]				X[e]		X[e]		X[e]	
Physical/Neurological/ Developmental Exam[t]	X	X				X		X		X	
ECG		X				X		X		X	
Clinical Laboratory Tests[f]	X	X				X		X		X	
Urinalysis	X[g]	X[g]				X		X		X	
Drug Screen[h]	X	X								X	
Pregnancy Test (WCBP)[i]	X	X						X		X	

Table 1: Schedule of Assessments - Part A

			Part A								
	Screen/Baseline					Titration and Maintenance					
WEEK	**-4 (Screening Visit – Start of Baseline)**	**0 (Baseline Treatment Visit)**	**Day 1**	**Day 2**	**Day 3**	**1**	**2, 3, 4**	**5**	**9**	**12**	**16 Taper/Safety Visits[p]**
Visit Windows		**+ 4 days**			**± 1 day**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 3 days**
VISIT	**Visit 1[a]**	**Visit 2[o]**	**Phone Follow-up**	**Phone Follow-up**	**Phone Follow-up**	**Visit 3**	**Phone Follow-up**	**Visit 4**	**Phone Follow-up**	**Visit 5**	**Visit 5a**
Tanner Staging	X										X
IP PK								X[j]		X[j]	
Concomitant AED Review and Levels if Per Standard of Care[k]	X	X				X		X		X	
[redacted]	[redacted]									[redacted]	
Adverse Event	X	X	X	X	X	X	X	X	X	X	X
Seizure and Medication Diary Review[l]	X[l]	X	X	X	X	X	X	X	X	X	X
[redacted]		[redacted]								[redacted]	
CGI-C - Target Behavior		X[m]						X		X	
CGI-I (caregiver)		X						X		X	
CGI-I (clinician)		X						X		X	
C-SSRS (baseline form)[q]		X									
C-SSRS (since previous visit)[q]								X		X	X
Dispense GNX[n]		X						X		X	

AED = antiepileptic drug, BP = blood pressure, CBD = cannabidiol, CGI-C = Caregiver Global Impression of Change, CGI-I = Clinical Global Impression – Improvement, C-SSRS = Columbia-Suicide Severity Rating Scale, D/C = discontinuation, ECG = electrocardiogram, [redacted], GNX = ganaxolone, HR = heart rate, IP = investigational product, LAR = legally authorized representative, PK = pharmacokinetic, RR = respiratory rate, THC = tetrahydrocannabinol, WCBP = women of childbearing potential.

Table 1: Schedule of Assessments - Part A

			Part A								
	Screen/Baseline					Titration and Maintenance					
WEEK	-4 (Screening Visit – Start of Baseline)	0 (Baseline Treatment Visit)	Day 1	Day 2	Day 3	1	2, 3, 4	5	9	12	16 Taper/Safety Visits[p]
Visit Windows		+ 4 days			± 1 day	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days
VISIT	Visit 1[a]	Visit 2[o]	Phone Follow-up	Phone Follow-up	Phone Follow-up	Visit 3	Phone Follow-up	Visit 4	Phone Follow-up	Visit 5	Visit 5a

a. Patient rescreening is allowed as agreed by the sponsor and the investigator unless there is a general concern for patient safety or an inability for the patient to become eligible (e.g., GNX allergy, sensitivity or exposure, non-TSC and/or other ineligible epilepsy, chronic prohibited medical condition or treatment). Subsequent screening should take place at least 30 days from the patient's last visit.
b. Written informed consent/assent must be obtained from patient, parent or LAR before any study assessments are performed. Pediatric assent should be obtained, if appropriate.
c. Previous genetic testing results will be accepted and reviewed to assess if a pathogenic *TSC1* or *TSC2* variant is present. If genetic testing has not previously been performed, then a biological sample will be obtained to complete genetic testing at the sponsor's designated lab. Note: TSC diagnosis does not require pathogenic *TSC1* or *TSC2* mutations if the clinical criteria are met.
d. Height and weight will be measured. Length will be measured if height cannot be obtained.
e. Only weight will be measured. At each visit, dosing will be reviewed and adjusted as needed based on a patient's current weight.
f. Chemistry and Hematology.
g. 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 if possible.
h. A drug screen (plasma) will be performed to test for THC and CBD at screening. If the screening drug test is positive, the patient can be retested, via plasma, after two weeks. A positive drug test during the treatment period will result in early termination.
i. Serum pregnancy test is required for all girls/women of childbearing potential.
j. Population PK will be conducted at these visits (Visit 4: between 1-5 hours since last IP dosing, Visit 5: between 4-8 hours since the last IP dosing).
k. Concomitant AEDs or their dose must be stable for 1 month prior to screening and cannot be changed at any time prior to Visit 4, but may be adjusted during Part B.
l. Caregiver given seizure and medication diary and instructions for use.
m. During the baseline visit, the investigator and parent/caregiver/LAR will decide on a domain and identify the specific behavior that the patient exhibits that denotes the domain. This behavior will be used at subsequent visits to assess change after the initiation of IP.
n. Patients who discontinue IP early will be encouraged to continue with all procedures and scheduled visits.
o. The 4 weeks between Screening Visit and Baseline Treatment Visit can be no less than 28 days and no more than 32 days.
p. Only for patients who do not continue into Part B. This will occur after 2 weeks of taper and 2 weeks after completion of treatment.
q. Only for patients ≥ 7 years old if appropriate. Otherwise clinical judgment will be used.
r. Only for patients that were Screened without previous genetic testing results and had a genetic test performed at the sponsor's designated lab.

Table 1: Schedule of Assessments - Part A

			Part A								
	Screen/Baseline					Titration and Maintenance					
WEEK	-4 (Screening Visit – Start of Baseline)	0 (Baseline Treatment Visit)	Day 1	Day 2	Day 3	1	2, 3, 4	5	9	12	16 Taper/Safety Visits[p]
Visit Windows		+ 4 days			± 1 day	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days
VISIT	Visit 1[a]	Visit 2[o]	Phone Follow-up	Phone Follow-up	Phone Follow-up	Visit 3	Phone Follow-up	Visit 4	Phone Follow-up	Visit 5	Visit 5a

s. Review of medical history only.
t. Developmental examination is limited to pediatric patients 2 to 17 years of age, inclusive.

Table 2: Schedule of Assessments - Part B

Part B								
	Final Part A Visit/ First Part B Visit	**Open-Label Extension (Visits will be every 8 weeks with a telephone follow-up in-between)**					**Final OLE Visit or Taper Visit**	**Safety Follow-up Post-taper**
WEEK	**12**	**16**	**20**	**24**	**28**	**32**	**36 or early D/C**	**2 weeks post last dose**
Visit Windows		**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 3 days**
VISIT	**Visit 5**	**Phone follow-up**	**Visit 6**	**Phone follow-up**	**Visit 7**	**Phone follow-up**	**Visit 8 (Week 36)[g] or Visit X (early D/C)**	**Visit X**
Confirm patient is "OLE eligible" (≥ 35% reduction in seizure frequency)	X							
Vital signs (BP, HR, RR, and body temperature)	X		X		X		X	X
Weight[a]	X		X		X		X	
Physical/Neurological/ Developmental Exam	X		X		X		X	X
ECG	X				X		X[d]	
Clinical Laboratory Tests[b]	X		X		X		X	X
Urinalysis	X				X		X	X
Drug Screen	X				X			
Pregnancy Test (WCBP)[c]	X		X		X		X	X
Tanner Staging							X[d]	
IP PK[e]	X		X		X		X	X
Concomitant AED Review and levels if per standard of care	X		X		X		X	X

Table 2: Schedule of Assessments - Part B

Part B								
	Final Part A Visit/ First Part B Visit	**Open-Label Extension (Visits will be every 8 weeks with a telephone follow-up in-between)**					**Final OLE Visit or Taper Visit**	**Safety Follow-up Post-taper**
WEEK	**12**	**16**	**20**	**24**	**28**	**32**	**36 or early D/C**	**2 weeks post last dose**
Visit Windows		**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 3 days**
VISIT	**Visit 5**	**Phone follow-up**	**Visit 6**	**Phone follow-up**	**Visit 7**	**Phone follow-up**	**Visit 8 (Week 36)[g] or Visit X (early D/C)**	**Visit X**
[redacted]	[redacted]						[redacted]	
Adverse Event	X	X	X	X	X	X	X	X
Seizure and Medication Diary Review	X	X	X	X	X	X	X	X
[redacted]	[redacted]						[redacted]	
CGI-C - Target Behavior	X						X	
CGI-I (caregiver)	X						X	
CGI-I (clinician)	X						X	
C-SSRS (since last visit form)[f]	X		X		X		X	
Dispense GNX	X		X		X		X	

AED = antiepileptic drug, BP = blood pressure, CGI-C = Caregiver Global Impression of Change, CGI-I = Clinical Global Impression – Improvement, C-SSRS = Columbia-Suicide Severity Rating Scale, D/C = discontinuation, ECG = electrocardiogram, [redacted], GNX = ganaxolone, HR = heart rate, IP = investigational product, OLE = open-label extension, PK = pharmacokinetic, RR = respiratory rate, WCBP = women of childbearing potential.

a. Weight will be measured at every visit, except the safety follow-up visit.
b. Chemistry and Hematology.
c. Serum pregnancy test is required for all girls/women of childbearing potential.
d. Conduct at Week 36/Visit 8 or the last open-label extension visit if prior to Week 36/Visit 8.
e. PK samples can be drawn when convenient during the study visits.

Table 2: Schedule of Assessments - Part B

Part B								
	Final Part A Visit/ First Part B Visit	**Open-Label Extension (Visits will be every 8 weeks with a telephone follow-up in-between)**					**Final OLE Visit or Taper Visit**	**Safety Follow-up Post-taper**
WEEK	**12**	**16**	**20**	**24**	**28**	**32**	**36 or early D/C**	**2 weeks post last dose**
Visit Windows		**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 3 days**
VISIT	**Visit 5**	**Phone follow-up**	**Visit 6**	**Phone follow-up**	**Visit 7**	**Phone follow-up**	**Visit 8 (Week 36)[g] or Visit X (early D/C)**	**Visit X**

f. Only for patients ≥ 7 years old if appropriate. Otherwise clinical judgment will be used.

g. Consistent with V8 (Week 36) or Visit X, patients can be seen at Investigator's discretion for unscheduled visits.

1. BACKGROUND INFORMATION

1.1. Indication and Current Treatment Options

Tuberous Sclerosis Complex (TSC) is a multi-system disorder of embryonal cortical development which can impact many organs through the overgrowth of hamartomas, benign, tumorous growths that can occur in the brain and other organs. While the phenotype of TSC can be extremely variable, neurologic manifestations such as epilepsy are seen in up to 90% of TSC patients. (Krueger and Northrup, 2013). The condition is caused by inherited mutations in either the *TSC1* gene, located on chromosome 9q34, or the *TSC2* gene located on chromosome 16p13.3. Tuberous Sclerosis Complex occurs with a frequency of 1:6,000 and a mutation is found in 85% of patients (Jülich and Sahin, 2014). The gene products hamartin (*TSC1*) and tuberin (*TSC2*) form a regulatory complex responsible for limiting the activity of mammalian target of rapamycin (mTOR) complex 1, an important intracellular regulator of growth and metabolism that acts via inhibition of the small GTPase Ras homolog enriched in brain (Rheb) (Krueger and Northrup, 2013). Everolimus, an mTOR inhibitor, has been shown to decrease seizures (French et al., 2016; Mizuguchi et al., 2019).

Tuberous Sclerosis Complex is one of the most common genetic causes of epilepsy, with seizure semiology that varies by age of onset (Jülich and Sahin, 2014). Infantile spasms (IS) are the most common seizure type presenting in infancy and represent the first manifestation of epilepsy in 50% of patients. In older children and adults, focal impaired awareness seizures (previously known as complex partial seizures) are the most common (Chu-Shore et al., 2010). Other focal and generalized seizures may also occur, with over 30% of patients developing treatment-refractory epilepsy (Jülich and Sahin, 2014). While seizures have typically been ascribed to tubers and the surrounding cortex, epilepsy in TSC can be considered multifactorial in origin as seizures can originate in other brain areas or can occur in TSC patients without tubers (Jülich and Sahin, 2014; van der Poest Clement et al., 2020).

Treatment options depend on the type and severity of seizures. Vigabatrin is widely accepted as the first-line treatment for IS associated with TSC. For other seizure types, conventional antiepileptic drugs (AEDs) such as valproic acid, topiramate, and oxcarbazepine are often used as first-line AEDs in TSC although there are no data supporting TSC-specific efficacy. Additionally, there are disease-modifying drugs that target inhibition of the mTOR pathway such as everolimus. A randomized clinical trial demonstrated efficacy of everolimus on seizure frequency reduction and is Food and Drug Administration (FDA)-approved for treatment of focal-onset seizures associated with TSC. More recently, cannabidiol (CBD) (EPIDIOLEX®) demonstrated seizure reduction efficacy in a randomized controlled trial.

1.2. Product Background and Clinical Information

Ganaxolone (GNX) 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 γ-Aminobutyric acid (GABA) agents by interacting with both synaptic and extra-synaptic GABA type A ($GABA_A$) receptors and at binding sites distinct from benzodiazepines. Whereas benzodiazepines might lose their inhibitory action, GNX does not because it selectively binds to $GABA_A$ receptors containing the α and δ subunits. By enhancing

synaptic and extrasynaptic $GABA_A$ receptor function, GNX provides an alternative mechanism in the treatment of seizures.

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 (IV)-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 et al., 1997; Kaminski et al., 2004; Reddy et al., 2004).

The completed GNX clinical program comprises 20 Phase 1 studies in healthy subjects and 20 Phase 2 studies in adults with epilepsy, children with seizure disorders, children with fragile X syndrome (FXS), adults with post-traumatic stress disorder and adults with migraine. In these studies, the efficacy, safety, tolerability, pharmacokinetics (PK), and PD of GNX were evaluated with an oral dosing duration ranging from 1 day up to more than 2 years, using doses from 50 to 2000 mg/day. Additionally, 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 were evaluated in healthy subjects (Ganaxolone, 2019).

As of 10 Oct 2019, 1557 patients and healthy volunteers have received at least 1 dose of GNX across the 40 completed studies. This includes 319 patients in Phase 1 and 1238 patients in Phase 2/3 studies.

In 20 completed Phase 1 studies, 319 healthy subjects received GNX oral doses of 50 to 2000 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 patients have received GNX in studies of adult patients with epilepsy, pediatric patients with seizure disorders, pediatric patients with FXS, adult patients with post-traumatic stress disorder, and adult patients with migraine.

The ongoing GNX clinical program consists of 6 Phase 2/3 studies evaluating GNX in women with postpartum depresssion, children with refractory epilepsy including protocadherin 19 (PCDH19) epilepsy, cyclin dependent kinase-like 5 (CDKL5) deficiency disorder and other rare genetic epilepsies, and in adolescents and adults with SE. Additionally, two Phase 1 studies designed to evaluate metabolites of GNX in healthy lactating females and healthy males are ongoing.

In addition to the company-sponsored studies, 18 patients were treated with GNX in completed studies not sponsored by Marinus. These included 16 patients who received oral GNX doses from 400 to 1200 mg/day in a smoking cessation study. In addition, [redacted]

[redacted]

The overall frequency of treatment-emergent adverse events (TEAE) in company-sponsored placebo (PBO)-controlled studies was 61.7% (613/993 patients) in patients who received GNX and 51.8% (330/637 patients) in patients who received PBO. The most frequently reported TEAEs in GNX-treated patients were somnolence, dizziness, fatigue, and headache. All of these events, except for headache, occurred more frequently in GNX-treated patients than PBO-treated patients. Central nervous system (CNS)-related events appeared to be dose-related, with the majority of these events occurring at doses ≥ 500 mg and were anticipated based on the mechanism of action of GNX. 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 patients treated with GNX and 0.5% of patients treated with PBO exhibited elevated liver function tests during the study (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] > 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 patients receiving PBO and 1.7% of patients 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 patients in 6 cases (0.6%) compared to no cases (0%) in PBO-treated patients. Most rashes improved either while the drug was continued or following discontinuation. Two patients 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 (IP).

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 Lennox Gastaut syndrome, is clinically complete and analysis is ongoing.

Approximately 250 pediatric patients aged 4 months to 17 years (data cutoff 10 Oct 2019) have received at least 1 dose of GNX. The largest cohorts received 12 to 54 mg/kg/day, although some patients received doses as high as 63 mg/kg/day or 1800 mg/day for adolescents.

The majority of the pediatric patients were refractory epilepsy patients who had uncontrolled seizures despite trying other AEDs (range 1-8). Overall, GNX was generally safe and well tolerated. In the incomplete crossover Study 1042-0500 (N = 56; all patients received GNX during the trial), 39 patients with IS treated with GNX doses up to 54 mg/kg/day for up to 20 days reported at least 1 TEAE. The most frequently reported AEs (≥ 8% of patients) were vomiting (7 patients), somnolence (5 patients), and cough (5 patients). Most AEs were mild or

moderate; 1 severe AE of lethargy occurred in 1 GNX patients. 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 patients (aged 5-17 years) with FXS who were treated with GNX up to 36 mg/kg/day (maximum 1800 mg/day) or PBO, the percentage of patients 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 patients who received GNX included fatigue (29/59 patients; 49.2%), somnolence (20/59 patients; 33.9%), vomiting (8/59 patients; 13.6%), decreased appetite (8/59 patients; 13.6%), aggression (6/59 patients; 10.2%) and rash (5/59 patients; 8.5%). Both fatigue (49.2% vs 20.4%) and somnolence (33.9% vs 5.6%) occurred more frequently in GNX-treated patients compared with PBO-treated patients, respectively.

Among patients who received PBO, headache (6 patients; 11.1%) and agitation (8 patients; 14.8%) were reported more frequently compared with GNX-treated patients. Severe TEAEs were reported for 3/59 (5.1%) GNX patients and 1/54 (1.9%) PBO patients. Severe events in the GNX group were somnolence and fatigue in 1 patient each and agitation and aggression in 1 patient.

To date, AEs have been consistent with the GABAergic mechanism of GNX or the underlying condition. 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

GABAergic signaling may play a meaningful role in the development and severity of TSC-related epilepsy, possibly due to altered expression of endogenous $GABA_A$ receptor modulators (Di Michele et al., 2003). There is evidence supporting a deficiency of the neuroactive steroid, 3α, 5α-tetrahydroprogesterone (THP), or allopregnanolone, as a contributor to epileptogenesis in TSC. Allopregnanolone is a positive modulator of the $GABA_A$ receptor and has been shown to have antiepileptic effects in experimental animals and humans. There is a decrease in allopregnanolone relative to its functional $GABA_A$ antagonist, 3β-THP, in patients with TSC-related epilepsy but not in TSC patients without epilepsy or in controls (Di Michele et al., 2003). This reduced ratio could alter neuronal excitability mediated by $GABA_A$ receptors, leading to the development of epilepsy. The role of $GABA_A$ receptor mediation is also supported by the efficacy of vigabatrin, a specific and irreversible inhibitor of GABA-aminotransferase, in seizures due to TSC relative to other epilepsies (Di Michele et al., 2003). These findings provide compelling evidence for the potential role of neuroactive steroids with anticonvulsant properties, or analogues such as GNX, in the treatment of TSC-related epilepsy.

Ganaxolone is the 3β-methylated synthetic analog of allopregnanolone, an endogenous positive allosteric modulator of CNS $GABA_A$ receptors. Ganaxolone has potency comparable to allopregnanolone in activating synaptic and extrasynaptic $GABA_A$ receptors at a site distinct from benzodiazepines and barbiturates (Carter et al., 1997). Ganaxolone has protective activity in diverse rodent seizure models (Bialer et al., 2010; Reddy and Rogwski, 2012). 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 given orally in adults and children (Kerrigan et al., 2000; Laxer et al., 2000; Pieribone et al., 2007; Sperling et al., 2017). Further, GNX reduces seizures in children with IS and refractory pediatric epilepsy. In an OL study, pediatric patients aged 2 to 60 months with refractory seizures and a history of IS were treated with GNX doses up to 36 mg/kg for up to 3 months (Kerrigan et al., 2000). Fifteen patients with a history of IS completed treatment. Five of the 15 patients 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 patient became spasm-free and 1 non-responder (with a decrease of < 25%) was spasm-free from Weeks 2 to 7.

A DB study (Study 1042-0500) of GNX in IS was also conducted. In this study, patients aged 4 to 24 months with IS received PBO or GNX doses of up to 54 mg/kg/day for up to 20 days in an incomplete crossover design. A total of 55 of the 57 patients completed treatment, 54 of whom continued GNX treatment in Study 1042-0501, an open-label extension (OLE). Although the GNX group had numerically higher reductions in frequency of spasm clusters, no statistically significant differences were observed in change from baseline between the treatment groups in the frequency of spasm clusters or in any of the secondary efficacy parameters at the end of the DB period (Day 9 ± 1 day).

In addition to its anticonvulsant activity, GNX has been shown to reduce anxiety, hyperactivity, and attention in children with FXS who had higher baseline levels of anxiety (Ligsay et al., 2016). Similar behavioral problems occur in individuals with TSC, with rates of approximately 50% for attention deficit hyperactivity disorder and autism (Jülich and Sahin, 2014).

It is hypothesized that GNX treatment will increase and improve $GABA_A$-receptor mediated signaling by boosting the signaling capacity of existing receptors and improve not only seizure control but may also ameliorate the behavioral abnormalities in individuals with TSC.

This present study is planned to assess preliminary safety and efficacy of GNX as adjunctive therapy for the treatment of primary seizure types in patients with genetically- or clinically-confirmed TSC-related epilepsy through the end of the 12-week treatment period. Pharmacokinetic assessments and population PK analyses will also be performed during this time. The 12-week treatment period (4-week titration and 8-week maintenance periods) will be followed by an optional long-term OLE period. Efficacy, safety and tolerability, and PK assessments will continue to be performed.

2.2. Study Objectives

2.2.1. Primary Objective

The primary objective of this study is to assess preliminary safety and efficacy of GNX as adjunctive therapy for the treatment of primary seizure types in patients with genetically- or clinically-confirmed TSC-related epilepsy through the end of the 12-week treatment period. The

primary seizure types (defined later) are identified to be the most common, easily identifiable/countable by a parent/caregiver/legally authorized representative (LAR), and most consequential to the patient's quality of life.

2.2.2. Secondary Objectives

The secondary objectives of this study are the following:

- To assess the long-term efficacy of GNX when administered as adjunctive therapy throughout the OLE period (Part B).
- To assess the long-term safety and tolerability of GNX when administered as adjunctive therapy throughout the OLE period (Part B).

[redacted]

3. STUDY DESIGN

3.1. Study Design and Flow Chart

This is an OL proof of concept study of adjunctive GNX treatment in patients with a confirmed clinical diagnosis of TSC and/or a mutation in either the *TSC1* or *TSC2* gene. The trial consists of two parts: Part A consists of a 4-week baseline period followed by a 12-week treatment period (4-week titration and 8-week maintenance). For patients not continuing in the OLE period (Part B), a 2-week taper period followed by a 2-week safety period would follow. The main difference between Part A and Part B is the length of treatment, less frequent assessments, and the ability to alter drug doses (both GNX and other AED treatments which includes initiating and stopping other medications) based on investigator evaluation of the patient's clinical course during Part B. Patients with a seizure frequency reduction rate of ≥ 35% during the 12-week treatment period in Part A compared to baseline may continue into Part B ("OLE eligible"). If the investigator believes there is a medical benefit for the patient who does not meet the seizure reduction criterion to enter the OLE, they must discuss the patient with the sponsor medical monitor and receive sponsor approval for that patient to continue into the OLE.

Part A

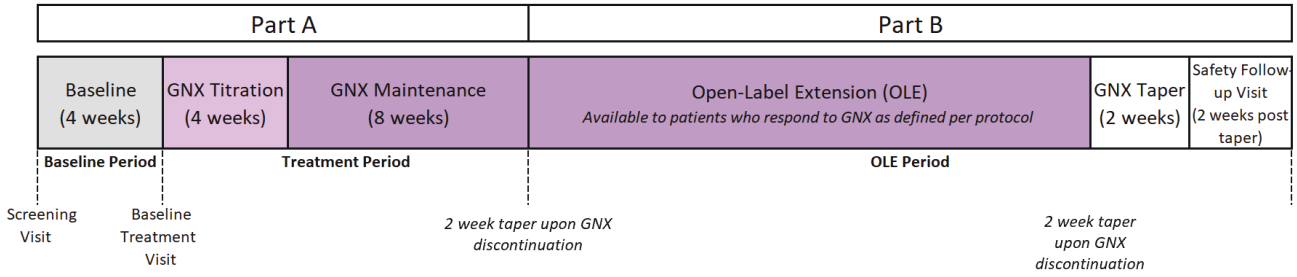
- 4-week baseline period

- 4-week titration period
- 8-week maintenance period
- 2-week taper period (For patients who do not complete Part A or after completing Part A but do not continue into Part B)
- 2-week safety follow-up visit post taper (For patients who taper off GNX)

Part B (Optional for OLE-eligible patients)

- OLE period (until the Sponsor markets ganaxolone or terminates the study
- 2-week taper period (For patients who discontinue GNX due to early termination or completion)
- 2-week safety follow-up visit post-taper (For patients who taper off GNX)

Figure 1: Study Design



GNX = ganaxolone

During the screening visit, each patient's baseline [redacted] will be collected and analyzed for post-study evaluation.

Patient rescreening is allowed as agreed by the sponsor and the investigator unless there is a general concern for patient safety or an inability for the patient to become eligible (e.g., GNX allergy, sensitivity or exposure, non-TSC and/or other ineligible epilepsy, chronic prohibited medical condition or treatment). Subsequent screening should take place at least 30 days from the patient's last visit, unless otherwise noted.

Part A includes a 4-week baseline and 4 weeks of IP titration followed by 8 weeks of dose maintenance followed by 2-week taper for those patients not continuing into the Part B OLE period. After meeting all eligibility criteria, approximately 30 patients aged 2 to 65 years (inclusive) with TSC-related epilepsy will be enrolled to receive GNX for a total of 12 weeks (4-week titration, 8-week maintenance) in addition to their standard anti-seizure medication(s) (ASMs). Patients will be titrated to 63 mg/kg/day (maximum 1800 mg/day) over 4 weeks, and then maintained at that dose for another 8 weeks. Patients who are not able to tolerate 63 mg/kg/day (or maximum 1800 mg/day) may be maintained on a lower dose after discussion with the sponsor medical monitor. A minimum dose of 33 mg/kg/day or 900 mg/day is generally required during the maintenance period.

For Part A, 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. Patients who discontinue GNX should undergo a 2-week taper period, unless otherwise medically indicated. Patients who discontinue GNX before the completion of the maintenance period will continue to be followed per protocol and, at a minimum, patients will be encouraged to maintain daily seizure diaries until the maintenance period in Part A is completed. These patients will also return to the site 2 weeks after the taper for safety follow-up assessments.

After completing the initial 16-week period, Part A, patients with a seizure reduction of ≥ 35% compared to the 4-week baseline period and who do not have any other contraindications for continued treatment can continue to be treated with GNX in the OLE period (Part B). Patients will continue GNX treatment at the dose that they were taking at completion of Part A. Doses of other ASMs may be adjusted (including tapering and initiating treatments) during Part B based on investigator discretion. Any patient who discontinues GNX treatment should undergo a 2-week drug de-escalation (taper) period and return to the site 2 weeks later for safety follow-up assessments.

Patients will be required to complete a daily diary to determine GNX's effect on seizures. Days without seizures should also be noted. Additional clinician- and caregiver-administered instruments will be used to assess the efficacy of GNX in TSC, and will include:

- Caregiver Global Impression of Change (CGI-C) – Target Behavior
- Clinical Global Impression – Improvement (CGI-I) caregiver and CGI-I clinician.

3.2. Duration and Study Completion Definition

After 4 weeks of baseline seizure charting, patients will initiate a 4-week GNX titration period followed by an 8-week GNX maintenance period (Part A). Patients completing Part A and deemed eligible for Part B will continue taking GNX for an additional 24 weeks of treatment. Anyone discontinuing GNX will undergo a 2-week taper and a 2-week follow-up safety visit. Patients who discontinue IP treatment before the completion of the maintenance period in Part A will continue to be followed per protocol and at minimum maintain daily seizure diary entry until the maintenance period is completed.

The planned study duration will be approximately 64 weeks for patients who stay on the study through Part B, or until ganaxolone is commercially available.

3.3. Sites and Regions

This multicenter study is to be conducted at approximately 6 sites in the United States (US).

3.4. Discussion of Study Design

Dosing will be based on doses that have been shown to be safe in children and adults in multiple studies with normal volunteers and individuals with epilepsy. In this current study, patients will receive OL GNX, prescribed in increments of 15 mg/kg/day up to 63 mg/kg/day given as an oral suspension with food, during a 4-week titration period, 8-week maintenance period, and optional extension period. Patients weighing ≤ 28 kg will be dosed on an mg/kg basis. Patients weighing > 28 kg will be dosed on a fixed regimen in increments of 450 mg/day up to 1800 mg/day.

Ganaxolone will be administered during the 4-week titration period as follows:

1. For patients weighing ≤ 28 kg (62 lbs):

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

2. For patients weighing > 28 kg (62 lbs):

- 150 mg TID (450 mg/day) suspension - Days 1-7
- 300 mg TID (900 mg/day) suspension - Days 8-14
- 450 mg TID (1350 mg/day) suspension - Days 15-21
- 600 mg TID (1800 mg/day) suspension - Days 22-28

Any patient not tolerating the next dose step can be maintained at the lower dose step for additional days before advancing to the next dose. If the next dose is still not tolerated, the patient can drop back to the next lower dose step. A minimum dose of 33 mg/kg/day or 900 mg/day is generally required following the escalation period and during the maintenance period.

Patients will initiate treatment in Part B with GNX at the same dose they were on at the completion of the maintenance period. During the extension period, doses of GNX may be adjusted to a maximum of 600 mg TID for patients weighing > 28 kg and a maximum dose of 21 mg/kg TID for patients ≤ 28 kg.

4. STUDY POPULATION

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

4.1. Inclusion Criteria (Part A)

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

1. Clinical or mutational diagnosis of TSC consistent with Northrup and Krueger, 2013.
   a. Molecular confirmation of a pathogenic mutation in *TSC1* or *TSC2*. A pathogenic mutation is defined as a mutation that clearly prevents protein synthesis and/or inactivates the function of the *TSC1* or *TSC2* proteins (e.g., nonsense mutation or frameshift mutations, large genomic deletions) or is a missense mutation whose effect on protein function has been established by functional assessment. The investigator must review the results of the genetic analysis and confirm that the causal relationship to the epilepsy syndrome is likely. OR

b. Clinical diagnosis of definite TSC which includes two major features or one major feature with ≥ 2 minor features. The investigator must document which of the features (Major or Minor) fulfill the clinical diagnostic criteria.

Major features	Minor features
1. Hypomelanotic macules (≥ 3, at least 5-mm diameter) 2. Angiofibromas (≥ 3) or fibrous cephalic plaque 3. Ungual fibromas (≥ 2) 4. Shagreen patch 5. Multiple retinal hamartomas 6. Cortical dysplasias[a] 7. Subependymal nodules 8. Subependymal giant cell astrocytomas 9. Cardiac rhabdomyoma 10. Lymphangioleiomyomatosis (LAM)[b] 11. Angiomyolipomas (≥ 2)[b]	1. "Confetti" skin lesions 2. Dental enamel pits (≥ 3) 3. Intraoral fibromas (≥ 2) 4. Retinal achromic patch 5. Multiple renal cysts 6. Nonrenal hamartomas

a. Includes tubers and cerebral white matter radial migration lines
b. A combination of the two major clinical features (LAM and angiomyolipomas) without other features that does not meet criteria for a definite diagnosis.

2. Male or female patients aged 2 through 65 years, inclusive.
3. Patient/parent/caregiver 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. Assent for patients over 7 years of age should be obtained, if appropriate.
4. Failure to control seizures despite appropriate trial of 2 or more ASMs at therapeutic doses.
5. Have at least 8 countable/witnessed primary seizures during the 4-week baseline period with at least 1 primary seizure occurring in at least 3 of the 4 weeks of baseline. The primary seizure types are defined as the following: focal motor seizures without impairment of consciousness or awareness, focal seizures with impairment of consciousness or awareness, focal seizures evolving to bilateral, tonic-clonic convulsive seizures, and generalized motor seizures including tonic-clonic, bilateral tonic, bilateral clonic, or atonic/drop seizures. Focal aware non-motor and generalized seizures without motor features, infantile or epileptic spasms, and myoclonic seizures do not count as the primary seizure types.
6. Patient must be approved to participate by the sponsor or its designee (e.g., Epilepsy Consortium) after review of medical history, genetic testing, and patients' seizure types.

7. Patients should be on a stable regimen of ASMs at therapeutic doses for ≥ 1 month prior to the screening visit, without a foreseeable change in dosing for the duration of Part A. Vagus nerve stimulator (VNS), ketogenic diet, and modified Atkins diet should be unchanged for 3 months prior to screening and will not count towards the number of ASMs.
8. Patients with surgically implanted VNS will be allowed to enter the study provided that all of the following conditions are met:
    a. The VNS has been in place for ≥ 1 year prior to the screening visit.
    b. The settings must have remained constant for 3 months prior to the screening visit and remain constant throughout the baseline and Part A.
    c. The battery is expected to last for the duration of baseline and Part A.
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 IP (suspension) with food 3 times daily. (GNX 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 (e.g., 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 (e.g., a spermicidal cream) is acceptable. In patients who are not sexually active, abstinence is an acceptable form of birth control.

4.1.1. Inclusion Criterion (Part B)

1. Patients have experienced ≥ 35% reduction in primary seizure frequency during the Part A treatment period compared to the 4-week Baseline Period.

4.2. Exclusion Criteria (Part A)

Patients are excluded from the study if any of the following criteria apply:

1. Previous exposure to GNX.
2. Pregnant or breastfeeding.
3. Concurrent use of strong inducers or inhibitors of cytochrome P450 (CYP)3A4/5/7. Any strong inhibitor or inducer of CYP3A4/5/7 must be discontinued at least 28 days before Visit 2, study drug initiation. This does not include approved ASMs.
4. Patients who have been taking felbamate for less than 1 year prior to screening.
5. Patients who test positive for tetrahydrocannabinol (THC) or non-approved CBD via plasma drug screen.

6. Chronic use of oral steroid medications, ketoconazole (except for topical formulations), St. John's Wort, or other IPs is not permitted.
7. Adrenocorticotropic hormone (ACTH), prednisone, or other systemically administered (non-inhaled) steroids must be discontinued > 28 days prior to screening. Concomitant topical, inhaled or intranasal steroids are allowed and do not warrant exclusion from the study.
8. Changes in any chronic medications within the month (e.g., 30 days) prior to the screening visit. All concomitant medications must have been at a stable in dose for at least 1-month prior to the screening visit unless otherwise noted.
9. Patient is being considered for epilepsy surgery or has undergone surgery for epilepsy within the 6 months prior to screening.
10. Have an active CNS infection, demyelinating disease, degenerative neurological disease, or CNS disease deemed progressive. This includes tumor growth which in the opinion of the investigator could affect primary seizure control.
11. Have any disease or condition (medical or surgical; other than TSC) 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 patient at increased risk. This may include any illness in the past 4 weeks which in the opinion of the investigator may affect seizure frequency.
12. An AST/serum glutamic oxaloacetic transaminase (SGOT) or ALT/serum glutamic pyruvic transaminase (SGPT) >3 × the ULN at screening or baseline visits and confirmed by a repeat test.
13. Total bilirubin levels > 1.5 × ULN at screening or baseline visit and 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.
14. Patients 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.
15. Have been exposed to any other investigational drug within 30 days or fewer than 5 half-lives (whichever is shorter) prior to the screening visit.
16. Unwillingness to withhold grapefruit, Seville oranges, star fruit, or grapefruit containing products from diet 7 days prior to the first dose and for the duration of the study.
17. Have had an active suicidal plan/intent or active suicidal thoughts in the past 6 months or have made 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.

4.2.1. Exclusion Criterion (Part B)

1. Patient developed a medical condition that would make it unsafe for patients to received GNX as determined by the investigator.

4.3. Restrictions

Patients must abstain from the use of alcohol, and from consuming grapefruit, Seville oranges, starfruit, or grapefruit containing products from 7 days prior to the first dose and for the duration of the study.

4.4. Reproductive Potential

4.4.1. Female Contraception

Sexually active girls/women of childbearing potential should be using a medically acceptable form of birth control and have a negative quantitative serum β-HCG test collected at the initial screening visit. Girls/women of childbearing potential must be advised to use medically acceptable birth control throughout the study period and for 30 days after the last dose of IP. 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 (e.g., 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 (e.g., a spermicidal cream) is acceptable. Contraceptive measures such as Plan B™, sold for emergency use after unprotected sex, are not acceptable methods for routine use. Patients who are not sexually active, abstinence is an acceptable form.

4.4.2. Male Contraception

Male patients must agree to take all necessary measures to avoid causing pregnancy in their sexual partners during the study and for 3 months after the last dose of IP. Medically acceptable contraceptives include surgical sterilization (such as a vasectomy) and a condom used with a spermicidal gel or foam.

Male patients should not donate sperm during the study and for 30 days after the last dose of IP. Patients who are not sexually active, abstinence is an acceptable form.

4.5. Discontinuation of Patients

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

If the IP is discontinued at any time, patients should follow the 2-week taper schedule unless otherwise medically indicated such as drug-induced rash. If the patient discontinues during the maintenance period of Part A, evaluations listed for Taper and Safety Visit (Section 7.2.8) are to be performed as completely as possible. If the patient discontinues during the OLE period (Part B), evaluations listed for the Taper Visit (Section 7.3.2) and Safety Follow-up Post Taper

Visit (Section 7.3.4) are to be performed as completely as possible. Comments (spontaneous or elicited) or complaints made by the patient 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. Patient Withdrawal Criteria

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

- Patient is found to have entered the study in violation of the protocol;
- Patient requires the use of a disallowed concomitant medication;
- Patient's condition changes after entering the clinical investigation so that the patient no longer meets the inclusion criteria or develops any of the exclusion criteria;
- Patient or parent/LAR withdraws consent or assent to participate in the study;
- Patient is noncompliant with the procedures set forth in the protocol;
- Patient experiences an AE/SAE that warrants withdrawal from the study;
- Laboratory, medical, or clinical finding for which clinical intervention should take precedence over study participation; or
- It is the investigator's opinion that it is not in the patient's best interest to continue in the study.

Decisions to discontinue the study will be made at each participating site by the investigator. If feasible, the reason for discontinuation should be discussed with the sponsor's medical monitor prior to patient's discontinuation. Patients who discontinue IP during the maintenance period of Part A will continue to record daily seizure frequency at minimum until the completion of the maintenance period.

4.5.2. Reasons for Early Discontinuation

The reason for early discontinuation must be determined by the investigator and recorded in the patient's source documents and on the eCRF. If a patient 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:

- AE
- Protocol violation/protocol deviation
- Withdrawal by patient or parent/LAR
- Lost to follow-up
- Lack of efficacy

- Death
- Physician decision
- Other (must be specified in the patient source document and eCRF)

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

A minimum of 3 documented attempts must be made to contact any patient 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 patient's last known address via courier or mail (with an acknowledgment of receipt request) asking that they return to the site for final safety evaluations and return any unused IP. If contact is made but the patient refuses or is unable to return to the site for the final safety follow-up visit, it should be documented in the eCRF.

4.6. Patient Numbering

During the screening visit, each patient will be assigned a unique 6-digit patient number by the site. The patient number will consist of a 3-digit clinical investigational site number assigned by the sponsor, followed by a 3-digit patient number (e.g., 001) assigned by the study staff. This patient number will also serve as the screening number. The unique 6-digit patient number will serve as the patient ID and be used to track the patient throughout the study.

The clinical site is responsible for maintaining a current log of patient number assignments and bottle numbers of the IP administered to each patient. The unique patient 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 investigator should assess all concomitant medications at every visit, and at the screening visit in particular to ensure that the patient 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 five 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 Informed Consent/Assent and the date of the last dose of IP. Concomitant treatment information must be recorded on the appropriate eCRF page. Concomitant topical and intranasal steroids for dermatologic reactions and allergic rhinitis are allowed as needed and do not warrant exclusion from study. If the patient is currently taking an excluded medication at the time of the screening

visit, then the patient must undergo a washout period equivalent to 5 half-lives of the drug before they may enter the prospective 4-week baseline period.

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

5.2.1. Concomitant AED Medications

Patients in the study should be on a stable regimen of AED medications at therapeutic doses for ≥ 1 month prior to the screening visit, and cannot be changed at any time prior to Visit 5 during Part A, but may be adjusted during Part B.

Vagus nerve stimulator, ketogenic diet, and modified Atkins diet should be unchanged for 3 months prior to screening and will not count towards the number of ASMs.

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

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

The use of felbamate is allowed provided that the patient has been maintained on a stable dose of felbamate for at least 1 year, and has had stable liver function (AST/ALT) and hematology during the course of treatment, and is expected to remain constant throughout the 12-week treatment period.

5.3. Rescue Medications

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

5.4. Excluded Medications

Excluded medications include all steroid medications, other IPs, as well as ketoconazole, and St. John's wort. Concurrent use of ACTH, prednisone or other glucocorticoid is not permitted, nor use of moderate or strong inducers or inhibitors of CYP3A4/5/7. Patients on ACTH, prednisone, or other systemically (non-inhaled) administered steroids should be off the product greater than 28 days prior to screening. Any strong inhibitor or inducer of CYP3A4/5/7 must be discontinued at least 28 days before Visit 2, study drug initiation. A list of CYP3A4/5/7 inhibitors and inducers is included in Section 12.1. Concomitant topical and intranasal steroids for dermatologic reactions and allergic rhinitis are allowed as needed and do not warrant exclusion from the study.

Products containing THC or non-approved CBD are excluded in the treatment period (Part A) of the study but allowed in the OLE period (Part B). Tetrahydrocannabinol or non-approved CBD should be washed out for at least 6 weeks. Patients with a positive result on THC at the

screening and baseline visit will be excluded. Patients with a positive result on CBD without a prescription for an approved CBD would also be excluded.

6. INVESTIGATIONAL PRODUCT

6.1. Identity of Investigational Product

Drug name: GNX suspension

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 [redacted] to [redacted], and is sweetened with sucralose and flavored with artificial cherry.

Strength: 50 mg/mL suspension

Ganaxolone will be supplied at a concentration of 50 mg/mL (GNX equivalent) in 120 mL bottles, containing 110 mL GNX.

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).

6.1.1. Blinding the Treatment Assignment

This is an OL study.

6.2. Administration of Investigational Products

6.2.1. Allocation of Patients to Treatment

All eligible patients will receive treatment with GNX in this OL study.

6.2.2. Dosing

Ganaxolone will 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. Patients weighing ≤ 28 kg will be dosed on an mg/kg basis. Patients weighing > 28 kg will be dosed on a fixed regimen in increments of 450 mg/day up to 1800 mg/day. All IP prescribed per day will be administered in 3 divided doses following a meal or snack. Ganaxolone is to be administered during the 4-week titration period as follows:

Table 3: Oral Suspension Dosing[a] for Patients Weighing ≤ 28 kg (62 lbs)[b]

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

TID = three times daily

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

b. Patients weighing ≤ 28 kg will be dosed according to the patient's weight in kilograms.

Table 4: Oral Suspension Dosing[a] for Patients Weighing > 28 kg (62 lbs)[b]

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

TID = three times daily

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

b. Patients weighing > 28 kg will be dosed on a fixed regimen in increments of 450 mg/day up to 1800 mg/day.

Any patient not tolerating the next dose step can be maintained at the lower dose step for additional days before advancing to the next dose. If the next dose is still not tolerated, the patient can drop back to the next lower dose step. A minimum dose of 33 mg/kg/day or 900 mg/day is generally required following the escalation period, during the maintenance period.

Dose changes including alternative dosing paradigms (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 investigator. For any patient who is unable to be maintained at the minimum dose, the investigator should contact the sponsor medical monitor to discuss continued IP dosing. Patients who discontinue GNX treatment before the completion of the maintenance period in Part A will continue to be followed per protocol and, at a minimum, patients will be encouraged to maintain daily seizure diary entries until Part A is completed.

Patients who meet all of the inclusion criteria and none of the exclusion criteria will initiate treatment in Part B with GNX at the same dose they were on at the completion of Part A. During Part B, doses of GNX may be adjusted to a maximum of 600 mg TID for patients weighing > 28 kg and a maximum dose of 21 mg/kg TID for patients weighing ≤ 28 kg.

6.2.2.1. De-escalation Period

Any patient who discontinues IP treatment should undergo a 2-week drug de-escalation (taper) period, unless otherwise medically indicated such as drug-induced rash. The schedule will be dependent on the maintenance dose. Typically, doses will be reduced by 15 mg/kg/day or 450

mg/day every 3 days until the patient is completely off IP. Patients should then return for a post-taper safety follow-up visit.

6.2.3. Dose Administration

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

Ganaxolone oral suspension will be administered through an oral dosing syringe administered by parents/caregivers TID, following the morning, noon, and evening meal or snack. Each dose should be separated by a minimum of 4 hours and a maximum of 12 hours. A missed dose of IP may be taken up to 4 hours before the next scheduled dose; otherwise, the missed dose should not be given.

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

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

Please use a new dosing syringe and adapter every day. Dosing syringes should be cleaned with hot water rinse and air-drying between first, second, and third daily doses.

Patients 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. Patients will be advised that the IP might affect mental alertness. They will also be cautioned that non-adherence to the dosing instructions (e.g., increasing the dose, taking the IP doses too close together) could produce side effects.

6.2.4. Missing a Dose

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 patient misses 2 days in a row or more, the site should be contacted to determine whether any adjustment in IP is needed.

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

6.3. Labeling, Packaging, Storage, and Handling

6.3.1. 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 patient by name, without consultation with the sponsor

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

6.3.2. Packaging

Ganaxolone will be supplied as an oral suspension formulation.

Ganaxolone for oral suspension formulation will be provided to the site as individual suspension bottles containing 110 mL in 120-mL high-density polyethylene (HDPE) bottles. Ganaxolone will be supplied at a concentration of 50 mg/mL.

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

6.3.3. Storage

The investigator 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). Excursions between 5°C (for less than 24 hours) and 40°C are acceptable. If a temperature excursion below 5°C or above 40°C (41°F to 104°F) occurs, Marinus must be notified.

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 investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by an in-house system, by a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (i.e., certified minimum/maximum 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 patients 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.

6.4. Investigational Product Accountability

Investigators will be provided with sufficient amounts of the IP to carry out this protocol for the agreed number of patients. The investigator 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 investigator has overall responsibility for administering/dispensing IP. Where permissible, tasks may be delegated to a qualified designee (e.g., a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

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

The patient'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 (e.g., 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, patient-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 clinical research organization [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, patient-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.

6.5. Patient Compliance

Patient compliance will be tracked through the 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 assessed by inspecting the seizure and medication diary entries and returned supplies with queries as necessary. Parent/caregiver will be re-educated on the importance of adhering to daily seizure, IP and non-study AED recording as needed. Patients that fall below 80% compliance at 2 consecutive visits during the maintenance period will not be in the Per-Protocol (PP) population.

7. STUDY PROCEDURES

7.1. Study Assessments

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

Study Assessments can be conducted at the institution of the site Investigator or remotely at the patient's home. All assessments can be conducted remotely with the use of telemedicine video tools used by the site staff; and providing traveling nurses to take vital signs, draw blood samples, and collect specimens. [redacted] and ECGs can be completed by a mobile vendor that is contracted to perform these tasks.

7.2. Study Procedures (Part A: Treatment Period)

7.2.1. Screening Period

7.2.1.1. Screening (Visit 1, Week -4)

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

- Informed consent from parent/LAR (or patient assent)
- Demographics and medical history
- Review of inclusion/exclusion criteria
- Review previous genetic testing results to evaluate pathogenic or likely pathogenic *TSC1* or *TSC2* variant. If genetic testing has not previously been performed, then a biological sample will be obtained to complete genetic testing at the sponsor's designated lab. Note: Tuberous Sclerosis Complex diagnosis does not require pathogenic *TSC1* or *TSC2* mutations if the clinical criteria are met.
- Seizure Identification and Diagnostic Review Form (SIF/DRF) (Epilepsy Study Consortium)

- Vital signs (to include blood pressure [BP], heart rate [HR], respiratory rate [RR], and body temperature).
- Height and weight. Length will be measured if height cannot be obtained.
- Physical, neurological, and developmental examination (developmental examination is limited to pediatric patients 2 to 17 years of age, inclusive)
- Clinical laboratory tests (chemistry and hematology)
- 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) for THC and CBD. If the screening drug test is positive, the patient can be retested after two weeks.
- Serum pregnancy test for all girls/women of childbearing potential
- Tanner staging
- Concomitant AED review and levels if per standard of care
- [redacted]
- AEs
- Seizure and medication diary set up and review. Caregiver given seizure diary and instructions for use.

A screen failure is a patient for whom informed consent/assent has been obtained and has failed to meet the inclusion criteria and/or met at least one of the exclusion criteria and has not been administered the IP.

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

7.2.2. Baseline (Visit 2, Week 0 + 4 days)

The 4 weeks between the Screening Visit and the Baseline Visit can be no less than 28 days and no more than 32 days. The following study procedures/assessments are to be completed prior to IP administration:

- Review of inclusion/exclusion criteria
- Medical history review
- Review genetic testing results for patients that were screened without previous genetic testing results and had a genetic test performed at the sponsor's designated lab
- SIF/DRF (Epilepsy Study Consortium) approval
- Vital signs (to include BP, HR, RR, and body temperature)

- Weight
- Physical, neurological, and developmental examination (developmental examination is limited to pediatric patients 2 to 17 years of age, inclusive)
- ECG
- Clinical laboratory tests (chemistry and hematology)
- Urinalysis (If the urine sample was not collected at screening, it must be collected at baseline)
- Drug screen (plasma) for THC and CBD
- Serum pregnancy test for all girls/women of childbearing potential
- Concomitant AED review and levels if per standard of care
- AEs
- Seizure and medication diary review
- [redacted]
- CGI-C (parent/caregiver/LAR identified behavioral target). During the baseline visit, the investigator and parent/caregiver/LAR will decide on a domain and identify the specific behavior that the patient exhibits that denotes the domain. This behavior will be used at subsequent visits to assess change after the initiation of IP.
- CGI-I (parent/caregiver/LAR and clinician)
- Columbia-Suicide Severity Rating Scale (C-SSRS) (baseline form) for patients ≥ 7 years old if appropriate. Otherwise clinical judgment will be used.
- Dispense IP

7.2.3. Telephone Follow-up (Day 1, 2 and 3 + 1 days)

A telephone follow-up visit will be conducted each of the 3 (± 1) days after the Week 0 Baseline Visit to assess the following:

- AEs
- Seizure and medication diary review

7.2.4. Titration Period (Visit 3, Week 1 ± 3 days)

The following study procedures/assessments will be completed at Week 1 (± 3 days):

- Vital signs (to include BP, HR, RR, and body temperature)
- Weight
- Physical, neurological, and developmental examination (developmental examination is limited to pediatric patients 2 to 17 years of age, inclusive)
- ECG

- Clinical laboratory tests (chemistry and hematology)
- Urinalysis
- Concomitant AED review and levels if per standard of care
- AEs
- Seizure and medication diary review

7.2.5. Titration Period (Phone Follow-ups, Weeks 2, 3, and 4 ± 3 days)

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

- AEs
- Seizure and medication diary review

7.2.6. Maintenance Period (Visits 4 and 5, Weeks 5 and 12 ± 3 days)

The following study procedures/assessments will be completed at Weeks 5 and 12 (± 3 days):

- Vital signs (to include BP, HR, RR, and body temperature)
- Weight
- Physical, neurological, and developmental examination (developmental examination is limited to pediatric patients 2 to 17 years of age, inclusive)
- ECG
- Clinical laboratory tests (chemistry and hematology)
- Urinalysis
- Drug screen (plasma) for THC and CBD (Visit 5 [Week 12])
- Serum pregnancy test for all girls/women of childbearing potential
- IP PK sample (Visit 4 [Week 5], between 1-5 hours after last IP dose and Visit 5 [Week 12], between 4-8 hours after last IP dose)
- Concomitant AED review and levels if per standard of care
- [redacted]
- AEs
- Seizure and medication diary review
- [redacted]
- CGI-C (parent/caregiver/LAR identified behavioral target)
- CGI-I (parent/caregiver/LAR and clinician)
- C-SSRS (since previous visit). Only for patients ≥ 7 years old if appropriate, otherwise clinical judgement will be used.

- Dispense IP

7.2.7. Maintenance Period (Phone Follow-up, Week 9 ± 3 days)

A telephone follow-up visit will be conducted at Week 9 (± 3 days) to assess the following:

- AEs
- Seizure and medication diary review

7.2.8. Taper and Safety Visits (Visit 5a, Week 16 ± 3 days)

For patients who do not continue into study Part B, the following assessments will be completed after 2 weeks of taper and 2 weeks after completion of treatment (± 3 days):

- Vital signs (to include BP, HR, RR, and body temperature)
- Tanner staging
- AEs
- Seizure and medication diary review
- C-SSRS (since previous visit). Only for patients ≥ 7 years old if appropriate, otherwise clinical judgement will be used.

7.3. Study Procedures (Part B: OLE Period)

7.3.1. First OLE Visit (Visit 5, Week 12)

Patients who complete Part A with a seizure reduction of ≥ 35% compared to the 4-week baseline period and who do not have any other contraindications for continued treatment will continue to be treated with GNX in the OLE period (Part B) of the study. Ganaxolone patients will continue GNX treatment at the dose that they were on at the completion of Part A. The following study procedures/assessments will be completed during the final maintenance period visit in Part A (Visit 5, Week 12):

- Confirm patient OLE eligibility (≥ 35% reduction in seizure frequency)
- Vital signs (to include BP, HR, RR, and body temperature).
- Height and weight. Length will be measured if height cannot be obtained.
- Physical, neurological, and developmental examination (developmental examination is limited to pediatric patients 2 to 17 years of age, inclusive)
- ECG
- Clinical laboratory tests (chemistry and hematology)
- Urinalysis
- Drug screen (plasma) for THC and CBD
- Serum pregnancy test for all girls/women of childbearing potential
- IP Population PK sample (drawn when convenient during the visits)

- Concomitant AED review and levels if per standard of care
- [redacted]
- AEs
- Seizure and medication diary review
- [redacted]
- CGI-C (parent/caregiver/LAR identified behavioral target)
- CGI-I (parent/caregiver/LAR and clinician)
- C-SSRS (since previous visit). Only for patients ≥ 7 years old if appropriate, otherwise clinical judgement will be used.
- Dispense IP

7.3.2. OLE Period and Final OLE Visit or Taper Visit (Visits 6, 7, and 8 [or Early Discontinuation], Weeks 20, 28, and 36 [or Early Discontinuation] ± 7 days)

The following study procedures/assessments will be completed during the OLE period of the study at Visits 6, 7, and 8 (± 7 days):

- Vital signs (to include BP, HR, RR, and body temperature)
- Weight
- Physical, neurological, and developmental examination (developmental examination is limited to pediatric patients 2 to 17 years of age, inclusive)
- ECG (Visit 7, Week 28 and Visit 8, Week 36)
- Clinical laboratory tests (chemistry and hematology)
- Urinalysis (Visit 7, Week 28 and Visit 8, Week 36)
- Drug screen (plasma) for THC and CBD (Visit 7, Week 28)
- Serum pregnancy test for all girls/women of childbearing potential
- Tanner staging (Visit 8, Week 36)
- IP PK sample (drawn when convenient during the visits)
- Concomitant AED review and levels if per standard of care
- [redacted]
- AEs
- Seizure and medication diary review
- [redacted]
- CGI-C (Visit 8, Week 36, parent/caregiver/LAR identified behavioral target)
- CGI-I (Visit 8, Week 36, parent/caregiver/LAR and clinician)

- C-SSRS (since previous visit). Only for patients ≥ 7 years old, otherwise clinical judgement will be used.
- Dispense IP

7.3.3. Telephone Follow-up (Weeks 16, 24 and 32 ± 7 days)

A telephone follow-up visit will be conducted at Weeks 16, 24, and 32 (± 7 days) of the OLE period to assess the following:

- AEs
- Seizure and medication diary review

7.3.4. Safety Follow-up Post Taper (Visit X, 2 Weeks Post Last Dose ± 3 days)

The following study procedures/assessments to be completed during the Safety Follow-up Post Taper Visit (± 3 days):

- Vital signs (to include BP, HR, RR, and body temperature)
- Physical, neurological, and developmental examination (developmental examination is limited to pediatric patients 2 to 17 years of age, inclusive)
- Clinical laboratory tests (chemistry and hematology)
- Urinalysis
- Serum pregnancy test for all girls/women of childbearing potential
- IP PK sample (drawn when convenient during the visits)
- Concomitant AED review and levels if standard of care
- AEs
- Seizure and medication diary review

7.3.5. Unscheduled Visits

Unscheduled visits can occur between regularly scheduled visits. For patients who are remaining in Part B (on the OLE)after Visit 8, unscheduled visits may take place as decided by Investigator, but no longer than six months after the prior visit, or prior to exiting the study. Unscheduled Visits assessments will be conducted at the discretion of the PI. These assessments may include vital signs, laboratory testing, etc.

7.4. Screening and Diagnosis

Potential patients will be pre-identified by the site because of a previous TSC diagnosis based on clinical features and/or genetic testing results and those still experience refractory seizures.

7.4.1. 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 parent/caregiver/LAR has been appropriately obtained.

7.4.2. Drug Screen

A drug screen (plasma) will be performed to test for THC and non-approved CBD at Visit 1 (screening). If the screening drug test is positive, a confirmatory retest, via plasma, will be performed after 2 weeks. A positive drug test during the treatment phase will result in early termination.

7.4.3. Demographics and Medical History

Demographics including age, gender, ethnicity and race will be collected. In addition to the genetic evaluation of pathogenic or likely pathogenic *TSC1/TSC2* variant, relevant medical history including but limited to the age of seizure onset, other physical disabilities such as scoliosis, visual impairment, sensory problems and gastrointestinal difficulties will also be assessed. The patient'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 patient's Medical History will be performed again at Visit 2 (baseline).

7.4.4. Genetic Testing

Genetic testing to assess if the patient has a pathogenic or likely pathogenic *TSC1/TSC2* variant will be conducted by the sponsor's central genetic laboratory if the patient does not have previous genetic testing. Previous genetic testing results are acceptable for review.

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

7.4.5. Seizure Identification and Diagnostic Review

Per the inclusion criteria, enrollment into the study will be based on the presence and frequency of the primary seizure types. The primary seizure types are defined as the following: focal motor seizures without impairment of consciousness or awareness, focal seizures with impairment of consciousness or awareness, focal seizures evolving to bilateral, tonic-clonic convulsive seizures, and generalized motor seizures including tonic-clonic, bilateral tonic, bilateral clonic, or atonic/drop seizures. Focal and generalized nonmotor seizures, infantile or epileptic spasms, and myoclonic seizures do not count as the primary seizure types.

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 IP dosing.

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

7.5. Efficacy Assessments

Efficacy as determined by a reduction in seizures will be evaluated by collecting daily seizure type and frequency in a seizure diary. Days in which no seizures occur will also be noted.

Changes in seizure intensity/duration, CGI-I, as well as changes in behavior and neuropsychiatric symptoms will be assessed by a variety of clinician and caregiver administered instruments.

7.5.1. Seizure Type and Frequency

Parent/caregiver/LAR will record daily seizure frequency denoting seizure type and frequency in a seizure diary. Primary seizure types of focal motor seizures without impairment of consciousness or awareness, focal seizures with impairment of consciousness or awareness, focal seizures evolving to bilateral, tonic-clonic convulsive seizures, and generalized motor seizures including tonic-clonic, bilateral tonic, bilateral clonic, or atonic/drop seizures will be counted towards the primary endpoint.

Patients or parent/caregiver/LAR are to record administration of IP and background AEDs in the daily seizure calendar. Compliance with IP treatment will be assessed by inspecting the patients' diary/seizure calendar and returned supplies with queries as necessary. Patients that fall below 80% compliance at 2 consecutive visits during the maintenance period will not be included in the PP population.

7.5.2. Caregiver Global Impression of Change (CGI-C - Target Behavior)

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

Caregiver Global Impression of Change - Target Behavior will be assessed at Baseline (Visit 2, Week 0), Visit 4 (Week 5), and Visit 5 (Week 12) in the treatment period (Part A), and will be assessed at Visit 8 (Week 36) and the Final Visit or Taper Visit of the OLE period (Part B).

7.5.3. Clinical Global Impression – Improvement (CGI-I)

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

Clinical Global Impression – Improvement (parent/caregiver/LAR and clinician) will be assessed at Baseline (Visit 2, Week 0), Visit 4 (Week 5), and Visit 5 (Week 12) in the treatment period (Part A), and will be assessed at Visit 8 (Week 36) and the Final Visit or Taper Visit of the OLE period (Part B).

7.6. Exploratory Efficacy Assessments

[redacted]

[redacted]

7.7. Safety Assessments

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

7.7.1. Adverse Events

Details regarding AEs and SAEs are provided in Section 8.

7.7.2. Vital Signs

Vital signs including HR (bpm), RR (breaths/minute), body temperature (C/F), BP (mmHg) will be collected at every clinic visit.

7.7.3. Height and Weight

Height will be collected at Visit 1 (screening). Length will be measured if height cannot be obtained. Weight will be collected at Visit 1 (screening), Visit 2 (baseline), Visit 3 (Week 1), and every clinic visit thereafter, including the Final OLE Visit or Taper Visit and Safety Follow-up Post Taper Visit.

7.7.4. 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 (applicable only to pediatric patients 2 to 17 years of age, inclusive) 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

7.7.5. 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 patient is enrolled in the treatment period.

Electrocardiograms will be performed at Visit 2 (baseline), Visit 3 (Week 1), Visit 4 (Week 5), and Visit 5 (Week 12) in the treatment period (Part A), and will be assessed at Visit 7 (Week 28) and the Final OLE Visit or Taper Visit in the OLE period (Part B).

7.7.6. Clinical Laboratory Tests

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

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, patient should be followed with weekly laboratory repeat testing and continue in study if levels trending down. Patient 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 patient will be discontinued.
- Patients 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 investigator, then the sponsor's medical monitor should be contacted.

Urinalysis will be conducted at Visit 1 (screening) or Visit 2 (baseline), Visit 3 (Week 1), Visit 4 (Week 5), and Visit 5 (Week 12) in the treatment period (Part A), and Visit 7 (Week 28), Visit 8 (Week 36), the Final Visit or Taper Visit, and the Safety Follow-up or Post Taper Visit in the OLE period (Part B).

An attempt will be made to collect a urine sample at screening in order to perform the study-related urinalysis. Otherwise, the urine sample for the urinalysis can be collected at baseline.

7.7.7. 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. Patients will be evaluated and rated as Tanner I, Tanner II, Tanner III, Tanner IV, and Tanner V. Tanner staging will occur at Visit 1 (screening) and Visit 5a (only for patients who do not continue into Part B) of the treatment period (Part A), and at the Final OLE Visit or Taper Visit (Part B).

7.7.8. Investigational Product PK

Please refer to Section 7.8 for additional details regarding PK assessments.

7.7.9. Concomitant AED Levels

Concomitant AED levels are not mandatory but will be collected per sites' standard of care. If AED levels are available for Visit 1 (screening), Visit 2 (baseline), Visit 3 (Week 1), Visit 4 (Week 5) and Visit 5 (Week 12), and throughout the OLE period of the study at the time points noted in Table 1 and Table 2, the results, date and time of last AED dose and date and time of AED PK sample will be recorded in the eCRF.

7.8. Pharmacokinetic Assessments

Blood sampling for PK evaluation must be performed at the precise protocol scheduled time. Actual sampling time(s) must be accurately recorded in the source document and appropriate eCRF.

One blood sample will be obtained at Visit 4 (Week 5), and Visit 5 (Week 12) in the treatment period (Part A), and at Visit 6 (Week 20), Visit 7 (Week 28), Visit 8 (Week 36), Final OLE Visit or Taper Visit, and Safety Follow-up Post Taper Visit of the OLE period (Part B).

A population PK approach addressing the relationship between GNX PK parameters and individual characteristics will be implemented at Visit 4 (Week 5) and Visit 5 (Week 12) in the treatment period.

During Part A:

- Visit 4 (Week 5): between 1 and 5 hours since the last IP dosing.
- Visit 5 (Week 12): between 4 and 8 hours since the last IP dosing.

During Part B:

There is no specified time to draw the PK sample and can be drawn when convenient during the study visit. Exact time of sample withdrawal and IP intake will be recorded in the eCRF.

7.8.1. 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 laboratory manual for processing instructions.

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 patient 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 Council for Harmonisation [ICH] Guidance E2A March 1995).

All AEs are collected from the time the informed consent/assent is signed until the defined follow-up period. This includes events occurring during the screening period 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 patient's health has returned to baseline status or all variables have returned to normal), regardless of whether the patient is still participating in the study. Closure indicates that an outcome is reached, stabilization is achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1. Severity Categorization

The severity of AEs must be recorded during the course of the event, including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pretreatment events, after initiation of the IP, must be recorded as new AEs (e.g., if a patient 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 patient.

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 investigator 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." Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the IP and the occurrence of the AE, 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 patient's medical condition, other therapies, or accident.
Not related	The event can be readily explained by other factors, such as the patient'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 period, there are abnormal clinical laboratory, vital sign, or ECG values that were not present in the pretreatment findings observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (e.g., concomitant disease) is found for the abnormal values.

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

8.1.6. Pregnancy

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

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

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

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

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE to the Marinus Safety Department or delegate as outlined in Section 8.2.2 of the protocol using the Marinus Clinical Study Serious Adverse Event Form. The test date of the first positive serum 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 (e.g., to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society.
- **Misuse:** Intentional use of an 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. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of patient's missing doses of the IP are not considered reportable as medication errors.

Medication errors should be collected and reported 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 patients should be supervised by the parent/caregiver/LAR.

8.2. Serious Adverse Event Procedures

8.2.1. Reference Safety Information

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

8.2.2. Reporting Procedures

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

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

8.2.3. Serious Adverse Event Definition

An SAE is any untoward medical occurrence (whether considered to be related to 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 patient 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 patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4. Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the parent/caregiver/LAR signs the informed consent/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 investigator at any interval after the study has completed must be reported to the Marinus Safety Department within 24 hours of the first awareness of the event.

8.2.5. Serious Adverse Event Onset and Resolution Dates

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

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

8.2.6. Fatal Outcome

Any SAE that results in the patient'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 patient's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the patient's death or any ongoing events at the time of death, unless another IP action was previously taken (e.g., 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 patient never received the IP). The IP action of "withdrawn" should not be selected solely as a result of the patient'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 US and the CRO is responsible for notifying the relevant regulatory authorities in rest of world of related, unexpected SAEs.

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

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

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1. Data Collection

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

The patient's parent/caregiver/LAR must enter the information required by the protocol in the diary. 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 patients' parent/caregiver/LAR and qualified site personnel. When a data discrepancy warrants correction, the correction will be made by the patients' 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 patient's parent/caregiver/LAR signs informed consent/assent, it is expected that all diary entries will be made daily and no longer than 48 hours after each day.

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

9.2. Clinical Data Management

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

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

9.3. Statistical Analysis Process

The study will be analyzed by the sponsor or its agent. The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information, such as patient 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.

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

9.4. Sample Size Calculation and Power Considerations

Approximately 36 TSC patients, aged 2 to 65 inclusive, will be screened to achieve 30 TSC patients enrolled in Part A. Since this is an OL proof of concept study, sample size was not determined by statistical methods.

9.5. Analysis Populations

The intent-to-treat (ITT) population comprises all patients who receive at least one dose of IP. The ITT population will be the primary population for efficacy analyses. The PP population includes all ITT patients without major protocol violations (defined prior to database lock). Safety will be reported for all patients.

9.6. Efficacy Analyses

Since this is an OL proof of concept study, no inferential statistical testing will be conducted. All efficacy outcomes will be assessed descriptively with point estimates and 95% confidence intervals.

9.6.1. Primary Efficacy Endpoint

The primary efficacy endpoint (change in seizure frequency) is the percent change in 28-day seizure frequency through the end of the 12-week treatment period (4-week titration and 8-week maintenance) relative to the baseline, based on the primary seizure types. The primary seizure types are defined as the following: focal motor seizures without impairment of consciousness or awareness, focal seizures with impairment of consciousness or awareness, focal seizures evolving to bilateral, tonic-clonic convulsive seizures, and generalized motor seizures including tonic-clonic, bilateral tonic, bilateral clonic, or atonic/drop seizures. Focal aware non-motor and generalized seizures without motor features, infantile or epileptic spasms, and myoclonic seizures do not count as the primary seizure types.

Post-baseline 28-day seizure frequency will be calculated as the total number of seizures in the 12-week treatment periods (4-week titration plus 8-week maintenance period) during Part A divided by the number of days with seizure data in the period, multiplied by 28. Baseline 28-day seizure frequency will be calculated as the total number of primary seizures in the baseline period divided by the number of days with seizure data in the baseline period, multiplied by 28.

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

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

The percentages of seizure-free days will be based on the primary seizure types (primary seizure-free-days) and infantile/epileptic spasms (infantile/epileptic spasms free days).

9.6.2. Secondary Efficacy Endpoints

In addition to evidence about effects of GNX on 28-day seizure frequency, the clinical trial will assess GNX's effects on several secondary endpoints that capture important symptoms and activities of daily living that are meaningfully compromised by TSC. The behavioral/neuropsychiatric secondary endpoints will provide information about the overall

impact of GNX on the treatment of patients with TSC. The CGI-C and the CGI-I are 7-point scales, and the number and percentage of patients with each score will be summarized. The scores range from 1 = very much improved to 7 = very much worse.

Derived seizure secondary efficacy endpoints will be based on data through the end of the 12-week treatment period relative to the 4-week baseline period.

9.6.2.1. Secondary Efficacy: Seizure control

- Percentage of patients experiencing a ≥ 50% reduction in 28-day primary seizure frequency through the end of the 12-week treatment period compared to the 4-week Baseline Period

9.6.2.2. Secondary Efficacy: Other

- CGI-I, parent/caregiver and clinician
- CGI-C – Target Behavior

9.6.3. Exploratory Efficacy Endpoints

All secondary and [redacted]

[redacted]

9.6.4. Subgroup Analyses

A subgroup analysis of the primary endpoint is not planned at this time.

9.7. Safety Analyses

Safety will be reported for all patients. The results in Part A and Part B will be summarized separately and then the combined results in Part A and Part B will be summarized together. 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 investigator 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 (temperature, BP, pulse rate), weight, and ECGs will be summarized using descriptive statistics including changes from baseline. Change in C-SSRS scores where applicable will be determined. Physical, neurological and developmental examinations will be summarized using number and percentage of patients with abnormalities.

9.8. Other Analyses

[redacted] and concomitant AED levels will be analyzed according to the SAP.

9.9. Pharmacokinetic Analyses

The PK population will include all patients who have received at least 1 dose of GNX and who have had at least 1 sample collected and a valid bioanalytical result obtained.

Pharmacokinetic analyses will be limited to listing of concentrations because sufficient concentration-time data will not be available for noncompartmental analyses such as maximum plasma concentration (C_{max}), area under the concentration versus time curve (AUC), or time of maximum concentration (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.

9.10. Interim Analysis

No formal interim analysis is planned.

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, 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(R2) (2016), 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 patients' medical records, diaries/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 investigator must undertake to perform the study in accordance with ICH GCP Guideline E6(R2) (2016) and applicable regulatory requirements and guidelines.

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

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

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

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

10.2.2. Protocol Adherence and Investigator Agreement

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

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

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

10.2.3. Documentation and Retention of Records

10.2.3.1. Electronic Case Report Forms (eCRF)

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

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

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

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

The clinical research associate (CRA)/study monitor will 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 investigator or designee as stated in the site delegation log. Overwriting of this information or use of liquid correction fluid is not allowed.

10.2.3.2. Seizure and Medication Diaries

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

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

The CRA/study monitor will verify the contents of the diary 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 patient's medical file, the patient's electronic or paper seizure diaries, and original clinical laboratory reports.

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

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

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

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (e.g., the US FDA, European Medicines Agency, United Kingdom 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 European Medicines Agency, the United Kingdom Medicines and Healthcare Products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.3.5. Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries, such as a grant to fund ongoing research, compensation in the form of equipment, or retainer for ongoing consultation or honoraria; any proprietary interest in 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 investigator to obtain written informed consent/assent from the parent/caregiver/LAR for all study patients prior to any study-related procedures, including screening assessments. As the disease under consideration is a condition for which the patients will not be capable of signing consent/assent for themselves, a parent/caregiver/LAR will be required to sign upon identification of the patient for participation.

All consent documentation must be in accordance with applicable regulations and GCP. Each patient's parent/caregiver/LAR, as applicable, is requested to sign and date the patient's informed consent/assent form or a certified translation, if applicable, after they have received and read (or been read) the written patient information and received an explanation of what the study involves, including but not limited to the objectives, potential benefits and risk, inconveniences, and the patient's rights and responsibilities. A copy of the informed consent/assent documentation (i.e., a complete set of patient information sheets and fully executed signature pages) must be given to the patient's parent/guardian/LAR, as applicable. This document may require translation into the local language. Signed consent forms must remain in each patient'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 investigator provides the sponsor with a copy of the consent form that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national

provisions) prior to study start that another party (i.e., sponsor or coordinating PI) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample patient 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

It is the responsibility of the investigator to submit this protocol, the informed consent/assent document (approved by the sponsor or their designee), relevant supporting information, and all types of patient 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/assent documents and amendments to the protocol unless there is a patient safety issue.

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

The investigator is responsible for keeping the IRB/EC informed of the progress of the study and of any changes made to the protocol at least once a year. The investigator must also keep the local IRB/EC informed of any SAEs and significant AEs.

10.4. Privacy and Confidentiality

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

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

After the patient'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 patients' identities.

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

The results of studies—containing patient unique identifying numbers, relevant medical records, and possibly initials and dates of birth—will be recorded. They may be transferred to, and used in, other countries that may not afford the same level of protection that applies within the countries where this study is conducted. The purposes of any such transfer would include to

support regulatory submissions, to conduct new data analyses to publish or present the study results, and to answer questions asked by regulatory or health authorities.

10.5. Study Results/Publication Policy

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

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

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

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

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single-site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors

current standards. Participation as an investigator does not confer any rights to authorship of publications.

11. REFERENCES

Bialer M., Johannessen SI, Levy RH, Perucca E, Tomson T, White HS. Progress report on new antiepileptic drugs: A summary of the Tenth Eilat Conference (EILAT X). Epilepsy Res. 2010;92(2-3):89-124.

Carter RB, Wood PL, Wieland S, Hawkinson JE, Belelli D, Lambert JJ, White HS, Wolf HH, Mirsadeghi S, Tahir SH, Bolger MB, Lan NC, Gee KW. Characterization of the anticonvulsant properties of ganaxolone (CCD 1042; 3alpha-hydroxy- 3beta-methyl-5alpha-pregnan-20-one), a selective, high-affinity, steroid modulator of the gamma-aminobutyric acid(A) receptor. J Pharmacol Exp Ther. 1997;280(3):1284-95.

Chu-Shore J, Major P, Camposano S, et al. The natural history of epilepsy in tuberous sclerosis complex. Epilepsia 2010;51:1236-41.

Di Michele F, Verdecchia M, Dorofeeva M, et al. $GABA_A$ receptor active steroids are altered in epilepsy patients with tuberous sclerosis. J Neurol Neurosurg Psychiatry. 2003;74:667-70.

French JA, Lawson JA, Yapici et al. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomized, double-blind placebo-controlled study. Lancet. 2016;388:2153-63.

Ganaxolone Investigator's Brochure. Marinus Pharmaceuticals, Inc., Dated 03 Dec 2019.

International Council for Harmonisation Guidance E2A March 1995. Accessed 20-Feb-2018. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf

Jülich K, Sahin M. Mechanism-based treatment in tuberous sclerosis complex. Pediatric Neurol. 2014;50:290-6.

Kaminski RM, Livingood MR, Rogawski MA. Allopregnanolone analogs that positively modulate GABA receptors protect against partial seizures induced by 6-Hz electrical stimulation in mice. Epilepsia. 2004;45(7):864-7.

Kerrigan JF, Shields WD, Nelson TY, Bluestone DL, Dodson WE, Bourgeois BF, Pellock JM, Morton LD, Monaghan EP. Ganaxolone for treating intractable infantile spasms: a multicenter, open-label, add-on trial. Epilepsy Res. 2000;42(2-3):133-9.

Krueger DA, Northrup H. Tuberous sclerosis complex surveillance and management: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatric Neurol. 2013;49:255-65.

Laxer K, Blum D, Abou-Khalil BW, Morrell MJ, Lee DA, Data JL, Monaghan EP. Assessment of ganaxolone's anticonvulsant activity using a randomized, double-blind, presurgical trial design. Ganaxolone Presurgical Study Group. Epilepsia. 2000;41(19):1187-94.

Ligsay A, Van Dijck A, Kooy RF, and Hagerman R. Ganaxolone in Children with FXS. International FXS Conference San Antonio, TX 2016.

Mizuguchi M, Ikeda H, Kagitani-Shimono et al. Everolimus for epilepsy and autism spectrum disorder in tuberous sclerosis complex: EXIST-3 substudy in Japan. Brain & Development. 2019;41:1-10.

Northrup H, Krueger DA. Tuberous sclerosis complex diagnostic criteria update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatric Neurol. 2013;49:243-54.

Pieribone VA, Tsai J, Soufflet C, Rey E, Shaw K, Giller E, Dulac O. Clinical evaluation of ganaxolone in pediatric and adolescent patients with refractory epilepsy. Epilepsia. 2007;48(10):1870-4.

Reddy DS, Castaneda DC, O'Malley BW, Rogawski MA. Anticonvulsant activity of progesterone and neurosteroids in progesterone receptor knockout mice. J Pharmacol Exp Ther. 2004;310(1):230-9.

Reddy DS, Rogwski MA. Neurosteroids — Endogenous regulators of seizure susceptibility and role in the treatment of epilepsy (Chapter 77). In, Jasper's Basic Mechanisms of the Epilepsies, Fourth Edition (Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AV, eds.), Contemporary Neurology Series 80, Oxford University Press. 2012; pp. 984–1002.

Sperling MR, Klein P, Tsai J. Randomized, double-blind, placebo-controlled phase 2 study of ganaxolone as add-on therapy in adults with uncontrolled partial-onset seizures. Epilepsia. 2017;58(4):558-64.

van der Poest Clement E, Jansen, F.E., Braun, K.P.J. et al. Update on Drug Management of Refractory Epilepsy in Tuberous Sclerosis Complex. Pediatric Drugs (2020). https://doi.org/10.1007/s40272-019-00376-0

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	

AUC = area under the concentration versus time curve, CYP = cytochrome P450

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 (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).
d. Withdrawn from the United States market because of safety reasons.
e. A strong inducer for CYP3A is defined as an inducer that results in ≥ 80% decrease in the AUC of a substrate for CYP3A.
f. In vivo inducer of P-glycoprotein.

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

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

12.2. Appendix 2: Clinical Laboratory Tests

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

[1]AST = aspartate aminotransferase, SGOT = serum glutamic oxaloacetic transaminase
[2]ALT = alanine aminotransferase, SGPT = serum glutamic pyruvic transaminase
[3]BUN = blood urea nitrogen
[4]eGFR = estimated glomerular filtration rate
[5]Plasma drug screen for THC, CBD

12.3. Appendix 3: Dosing Instructions for Oral Suspension

GANAXOLONE 1042-TSC-2001 STUDY
DOSING INSTRUCTIONS FOR ORAL SUSPENSION
(OPEN-LABEL DOSE TITRATION, OPEN-LABEL MAINTENANCE, OPEN-LABEL EXTENSION, AND TAPER)

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

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

Example 1:
For a 15 kg child, please dose the following:

Dose Titration / Dose Maintenance / Dose Extension/Dose Taper (Please circle study period)

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

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

Dose Titration / Dose Maintenance / Dose Extension/ Dose Taper (Please circle period)

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

Please take the study medication as outlined below:

Dose Titration / Dose Maintenance / Dose Extension / Dose Taper (Please circle study period)

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

SHAKE THE BOTTLE WELL BEFORE DISPENSING

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

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

Use the dosing syringe provided. Do not use a household spoon. A new dosing syringe and adapter should be used every day. Dosing syringes should be cleaned with hot water rinse and air-drying between first, second, and third daily doses.

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

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

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

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

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

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

Some people may report feeling dizzy or tired, or experiencing other problems after taking the study medication, ganaxolone. These side effects usually go away after 2 or 3 days. If you experience any side effects from the study medication that interfere with your daily activities or if you have any questions, please contact your study doctor at the telephone number below to see if a dose adjustment is necessary.

Study Doctor: _____

Telephone Number: _____

DocuSign

Certificate Of Completion

Envelope Id: FAF5E8829E3D415081B1E865796694DA
Status: Completed
Subject: Please DocuSign: 1042-TSC-2001 Ganaxolone Ph 2 Protocol Amdt 2_Final_2021-06-11.pdf
Source Envelope:
Document Pages: 88
Signatures: 1
Certificate Pages: 1
Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Enabled
Time Zone: (UTC-05:00) Eastern Time (US & Canada)

Envelope Originator:
[redacted]
5 Radnor Corporate Center, 100 Mastonford Road
Suite 500
Radnor, PA 19087
[redacted]
IP Address: [redacted]

Record Tracking

Status: Original
6/14/2021 9:57:49 AM
Holder: [redacted]
Location: DocuSign

Signer Events	Signature	Timestamp
[redacted]	[redacted]	Sent: 6/14/2021 10:00:50 AM Viewed: 6/14/2021 1:34:26 PM Signed: 6/14/2021 1:34:32 PM
Marinus Pharmaceuticals Security Level: Email, Account Authentication (None)	Signature Adoption: Drawn on Device Using IP Address: [redacted]	

Electronic Record and Signature Disclosure:
Not Offered via DocuSign

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	6/14/2021 10:00:50 AM
Certified Delivered	Security Checked	6/14/2021 1:34:26 PM
Signing Complete	Security Checked	6/14/2021 1:34:32 PM
Completed	Security Checked	6/14/2021 1:34:32 PM

Payment Events	Status	Timestamps