TITLE PAGE

Protocol Title: A Phase 3, Double-blind, Randomized, Placebo-controlled Trial of Adjunctive Ganaxolone (GNX) Treatment in Children and Adults with Tuberous Sclerosis Complex (TSC)-related Epilepsy (TrustTSC)

Protocol Number: 1042-TSC-3001

Compound: Ganaxolone

Brief Title: Adjunctive GNX treatment compared with placebo in children and adults with TSC-related epilepsy

Indication: TSC-related epilepsy

Study Phase: Phase 3

Sponsor Name: Marinus Pharmaceuticals Inc.

Legal Registered Address: 5 Radnor Corporate Center
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Regulatory Agency Identifier Numbers:

Registry	**ID**
IND	155634
EudraCT	2021-003441-38

Protocol version/date	**Document Version**	**Approval Date**
	Protocol Amendment 3; v4.0	12 Sep 2023
	Protocol Amendment 2; v3.1	08 Dec 2022
	Protocol Amendment 2; v3.0	07 Dec 2022
	Protocol Amendment 1; v2.0	01 Feb 2022
	Original (v1.0 [superseded])	16 Sep 2021

CONFIDENTIALITY NOTICE

Sponsor Signatory:

Protocol Number: 1042-TSC-3001

Protocol Title: A Phase 3, Double-blind, Randomized, Placebo-controlled Trial of Adjunctive Ganaxolone (GNX) Treatment in Children and Adults with Tuberous Sclerosis Complex (TSC)-related Epilepsy (TrustTSC)

I, the undersigned, have approved of the clinical trial protocol with the date of 12 Sep 2023.

DocuSigned by:
[redacted]
EBD8EF65167C44A...

September 13, 2023 | 2:43 PM EDT

[redacted], MD
[redacted], Clinical Development

Date

Medical Monitor Name and Contact Information is provided Section 10.2.

INVESTIGATOR AGREEMENT

Protocol Number: 1042-TSC-3001

Protocol Title: A Phase 3, Double-blind, Randomized, Placebo-controlled Trial of Adjunctive Ganaxolone (GNX) Treatment in Children and Adults with Tuberous Sclerosis Complex (TSC)-related Epilepsy (TrustTSC)

I have read the protocol, including all appendices, and I agree that it contains all the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in compliance with current Good Clinical Practice (GCP) standards as defined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for GCP, all applicable national, state, and local laws and regulations, and the applicable Institutional Review Board/Independent Ethics Committee (IRB/IEC) and other institutional requirements.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by Marinus Pharmaceuticals Inc, or specified designees. I will discuss the material with them to ensure that they are fully informed about ganaxolone (GNX), understand this study, and are able to comply.

_____ _____

Investigator Name (printed) Signature

_____

Date

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments		
Summary of Changes Since Last Version of Approved Protocol		
Amendment Number **3**	**Amendment Date** **12 Sep 2023**	**Applicable To** **Global**
Rationale for the Amendment The following changes are made in this global protocol amendment from version 3.0 to version 4.0 to: • Include updated information regarding completed and ongoing clinical studies. • Editorial updates throughout. • Sample size, subject age, and inclusion criteria were updated. • References to interim analysis were removed as no interim analysis was performed. • SAE contact details were updated. • Country-specific amendment for China/North America has been combined with the global protocol. •		
Description of Changes		**Section(s) Affected by Change**
Minor editorial updates throughout for administrative changes, grammar, consistency, and clarity.		Throughout the document
Updated Protocol amendment date and version.		Protocol header, Title page
Updated rationale text to clarify the completion of Study 1042-TSC-2001.		Section 1.1, Section 2.2.2.1.1.
Participant number was updated.		Section 1.1, Section 4.1.2
Inclusion criteria number 3 was updated.		Section 1.1, Section 5.1
Inclusion criteria number 6 was made clearer.		Section 1.1, Section 5.1
Midazolam added to approved rescue medications.		Section 6.6.1
Added text to clarify that assessments conducted by travelling nurses only applies to sites located within the United States.		Section 8
Clarification regarding laboratory testing added.		Section 8.3.6
Deleted: '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.'		Section 8.4
Deleted "Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs."		Section 8.4.1
Added text that [redacted] will not be performed in China.		Section 1.3, Section 8.7, Section 10.6, Section 10.7
Updated language for safety monitoring contact.		Section 8.4, Section 8.4.1, Section 8.4.4.1,

	Section 8.4.8, Section 8.4.9, Section 10.2.1.
Interim analysis removed. With the smaller sample size, the interim analysis will not read out before the entire cohort is expected to be enrolled. As a result, there is no benefit of the interim analysis.	Section 1.1, Section 9.4
Sample size determination updated. The original efficacy assumption (22%) for the power analysis were unnecessarily conservative. The current sample size of 128 retains a 90% power if a treatment effect of 25% is assumed.	Section 9.4
Sponsor project managers updated	Section 10.2.2.2

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments		
Summary of Changes Since Last Version of Approved Protocol		
Amendment Number **2.1**	**Amendment Date** **08 Dec 2022**	**Applicable To** North America (United States and Canada) and China
Rationale for the Amendment The following changes are made in this protocol amendment from version 3.0 (applicable to Europe [EU], Middle East and North Africa [MENA] and Oceania [OC]) to version 3.1 (applicable to North America [United States and Canada] and China) to: • Revise inclusion criteria to include participants aged 1 to 65 years of age. • Specify that [redacted] will not be permitted under this protocol in China. • Specified that investigational product will be stored in accordance with applicable requirements under the Controlled Substance Act and Drug Enforcement Administration regulations.		
Description of Changes		**Section(s) Affected by Change**
Revised inclusion criterion 2 to include participants aged 1 to 65 years of age. Deleted: • Male or female participants aged 2 through 65 years, inclusive. Added: • Male or female participants aged 1 through 65 years, inclusive.		Section 1.1 and Section 5.1
Specified that [redacted] will not be permitted under this protocol in China.		Section 1.3 (footnote), Section 8.7, Section 10.6, and Section 10.7
Addition of the rationale for selecting participants aged 1 through 65 years, inclusive. Added: • This study plans to enroll participants as young as 1 year of age. Based on the known clearance pathway of GNX (which is primarily CYP3A4/5) and CYP3A4 maturation by the age of 1 month, the dosing strategy for pediatric participants 1 to 2 years was guided by a recently completed		Section 4.3

population PK analysis which incorporated allometric principles. The similarity of model maximum plasma concentration (C_{max}) and the area under the plasma concentration-time curve (AUC) with the proposed dosing regimen across a range of doses administered in previous clinical trials in participants 2 years of age and older coupled with the known maturation of CYP3A4 indicates that a similar exposure will be achieved in participants 1 to 2 years of age with the proposed dosing regimen.	
Specified that investigational product will be stored in accordance with applicable requirements under the Controlled Substance Act and Drug Enforcement Administration regulations.	Section 6.3.1

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments		
Summary of Changes Since Last Version of Approved Protocol		
Amendment Number **2**	**Amendment Date** **07 Dec 2022**	**Applicable To** Europe (EU), Middle East and North Africa (MENA), and Oceania (OC)
Rationale for the Amendment The following changes are made in this global protocol amendment from version 2.0 to version 3.0 to: • Revise inclusion criteria to include participants aged 2 to 65 years of age. • Add a section on contraception use to include acceptable barrier methods and donation of sperm and ova. • Add details on pregnancy testing. • Elaborate on dose adjustments and rescue medications. • Update endpoint analyses to incorporate analyses related to European Medicines Agency (EMA). • Add details on blood volumes approval by investigator for participants < 15 kg weight. • The dosing instructions for the oral suspension were updated to match the package insert.		
Description of Changes		**Section(s) Affected by Change**
Minor editorial updates throughout for grammar, consistency, and clarity. Removed "sexually active girls" when referring to women of childbearing potential (WOCBP). Replaced the term anti-epileptic drugs (AEDs) with the preferred term anti-seizure medication (ASM) per Tuberous Sclerosis Complex (TSC) Alliance. Replaced "subjects" with "participants". Updated definition of the abbreviation mTOR from "mammalian target of rapamycin" to the preferred definition "mechanistic target of rapamycin" per TSC Alliance.		Throughout the document
Updated Protocol amendment date and version in the header		Protocol header
Added updates to the list of abbreviations		List of Abbreviations
[redacted]		
Updated information of the Investigational Product (IP) background and Clinical Development Program updated with current available information to align with the current updated version of the Investigator's Brochure (IB).		Section 1.1, Section 2.2.2, and Section 2.2.2.1
Specified that version 2 of the Short Form 36 (SF-36) will be used.		Section 1.1 (footnote), Section 1.3 (footnote), Section 3 (footnote), Section 8.2.8, and Section 10.15
Updates to inclusion criterion 1: • Criteria for clinical or mutational diagnosis of TSC updated from Northrup and Krueger, 2013 to Northrup et al. 2021: updates in major and minor features for clinical diagnosis of definite TSC.		Section 1.1 and Section 5.1

Updates to inclusion criterion 2: • Male or female participants aged 2 through 65 years, inclusive. Updates to inclusion criterion 3. Removal of inclusion criterion 4. Updates to inclusion criterion 7: • Requirements amended to state the requirement that at least 8 primary endpoint seizures are required in the first 28 days following the screening visit. Updates to inclusion criterion 9: • Vagal nerve stimulator (VNS) requirement changed from 1 year to 6 months.	
Minor clarification in exclusion criterion 5. Addition of 2 new exclusion criterions (18 and 19): 18. Participants deprived of their liberty by a judicial or administrative decision, or for psychiatric treatment, or participants admitted to a health or social services facility for purposes other than research. 19. Participants receiving traditional Chinese medicine therapies within the prior 28 days of the screening.	Section 1.1 and Section 5.2
Combined definitions of seizure types that do not count towards the primary endpoint: Replaced: a. Focal aware seizures without motor features. b. Focal and generalized nonmotor seizures (eg, absence or focal nonmotor seizures with or without impairment of awareness). With a. Focal or generalized nonmotor seizures (eg, absence seizures or focal nonmotor seizures with or without impairment of awareness).	Section 1.1, Section 3, Section 5.1, Section 8.1.1.3, Section 8.2.1, and Section 9.3.2
Updated general considerations to differentiate primary and secondary endpoint analyses for the Food and Drug Administration (FDA) and EMA.	Section 1.1, Section 3, Section 9.3.1, Section 9.3.2, Section 9.3.3, Section 9.3.3.2
Revised contraception information throughout the protocol. Removal of abstinence as an acceptable form of birth control. Deleted: • Participants who are not sexually active, abstinence is an acceptable form.	Section 1.1, Section 5.1, Section 5.3.2, Section 10.5.1, Section 10.5.2, and Section 10.5.3
Minor update to schema: • “Enter Open-label extension (OLE)”changed to “Crossover to OLE”.	Section 1.2
Schedule of Activities (SOA) updated to remove Seizure Identification and Diagnostic Review Form (SIF/DRF) from baseline visit. Visit header for Part B of SOA updated to specify which visits are phone visits.	Section 1.3
Specified that a urine drug screen could be performed if a plasma sample is difficult or impossible to obtain.	Section 1.3 (footnote)
Specified that a urine drug screen could be performed if a plasma sample is difficult or impossible to obtain.	Section 1.3 (footnote)
Specified that the Pediatric Quality of Life – Family Impact Module (Peds-QL-FIM) for past 1 month is for baseline visit, and past 7 days is for on-study visits.	Sections 1.3 and Section 8.2.7

Included pregnancy testing at in person visits, Revised text for pregnancy testing, including pregnancy testing at in person visits and indicating what type of pregnancy test (serum or urine) will occur during the study visits.	Section 1.3, Section 8.3.4, Section 8.3.8, and Section 10.3
Clarified that [redacted] is not required but may be conducted.	Section 1.3 (footnote) and Section 8.7
Specified that [redacted] will not be permitted under this protocol in Israel.	Section 1.3 (footnote), Section 8.7, Section 10.6, and Section 10.7
Number of study sites updated to 80-85.	Section 4.1.3
Removed information related to justification of enrolling participants as young as 1 year of age.	Section 4.3
Rescreening criteria updated to state that the medical monitor should be contacted for subsequent screening.	Section 5.4
Storage conditions updated to include a new window of temperature to store the IP in °F and °C.	Section 6.1 and Section 6.3.1
Dosing modifications language updated to indicate the approaches to ganaxolone (GNX) dosing to manage tolerability.	Section 6.2
Text “stratified for concomitant cannabidiol (CBD) use” replaced with “stratified for current CBD use”.	Section 6.4.1.1 and Section 8.1.1
Updated text for rescue medication to include additional information on seizure clusters and to include rescue medications permitted for the study.	Section 6.6.1
Revised text to include laboratory parameters for discontinuation.	Section 7.2
Removed 12-lead electrocardiogram (ECG) assessment to be completed by a mobile vendor.	Section 8
Section revised to include information on the process of identification for participants. Added: • The process of identification of participants is performed by the investigator. If an investigator is seeing a patient with TSC in their clinic who is having 8 or more seizures per month, they will make a judgment regarding whether the benefits of clinical trial participation may outweigh the risks of clinical trial participation (with any alternative treatments taken into account). If the clinician feels that they do, then they will explain the study to the participant (or legally authorized representative [LAR]). If the participant/LAR is fully informed and provides consent, then this will be documented, and the screening activities can begin. Note for Investigational Sites in the United Kingdom (UK): National Health Service (NHS) sites in the UK will be aware of the study by virtue of the investigators participating in the site initiation visit, and being trained on the study design, conduct, and participant protection policies.	Section 8.1.1
Specified that only the numbered items in the Sleep Habit Questionnaire (ie, the items that are scored) will be asked to the participant´s parent/caregiver/LAR.	Section 8.2.5 and Section 10.12.1

Text revised to change CKD-EPI formula to calculate estimated glomerular filtration rate (eGFR) with Cockcroft-Gault formula or pediatric glomerular filtration rate (GFR) calculator or Bedside Schwartz. Total blood volume collected from participants corrected from 45 mL to 60 mL. Added details on blood volumes approval by investigator for participants < 15 kg weight. Added: • Note: For participants < 15 kg the maximum blood volume taken during a single day or during a 4-week period may exceed recommendations; therefore, for all participants < 15 kg, the medical monitor should be consulted regarding which labs can be omitted. For all participants, regardless of weight, if additional labs are required, the medical monitor should be consulted to ensure that recommended blood volume limits are not unnecessarily exceeded.	Section 8.3.4
Addition of a new section to include Suspected Unexpected Serious Adverse Reaction (SUSAR) language.	Section 8.4.4.1
Clarification made for the multiplicity adjustment. Added: • The testing will stop if the result is non-statistically significant. All other non-key secondary and [redacted]	Section 9.1.1
Added the evaluation of the primary endpoint for the EMA.	Section 9.3.2
Amended the definition of primary seizure type.	Section 9.3.2
Updated the sensitivity analyses to be different for EMA and FDA. Deleted: • To examine the primary outcome measure when a participant stops recording measurements permanently prior to the end of the double-blind phase using the imputation approach outlined in the Statistical Analysis Plan (SAP). • To explore the possibility that participants who stop recording their seizure counts tend to have higher counts than the other participants. • To examine the primary outcome measure by using modified intent-to-treat (mITT) population. Added: • For the first sensitivity analysis, intermittent (random/sporadic) missing data during the double-blind phase and any missing data during the baseline phase will be assumed missing completely at random and the collected data will be used to calculate the 28-day seizure frequencies. • The second sensitivity analysis is to explore the possibility that participants who stop recording their seizure counts tend to have higher counts than the other participants. • The third sensitivity analysis will be performed on participants who achieved their maintenance dose at the start of the maintenance period. This analysis will exclude those participants who are still titrated continuously during maintenance period. • The fourth sensitivity analysis will be performed for the primary outcome measure by using the mITT population. • The fifth sensitivity analysis will be performed for the primary outcome measure by excluding all intercurrent events.	Section 9.3.2.1

Updated subgroup analyses. Deleted: • Age groups (1 to 6 years; 7 to 12 years; […]). Added: • Age groups (2 to 6 years; 7 to 12 years; […]).	Section 9.3.7
Updated Informed consent form (ICF) processes to include that minor participants must be re-consented if they reach the age of majority during the course of the study and to delete any reference of separate section in the ICF for optional [redacted] Added: • Minor participants must be re-consented if they reach the age of majority during the course of the study, in order to continue participating. Deleted: • The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow [redacted] Participants who decline to participate in this optional research will not provide this separate signature.	Section 10.1.3
Updated sample storage period to 1 year instead of 2 years.	Section 10.1.12
Updated Study/Site Termination. Added: • The decision to terminate a study may be for business reasons or for safety reasons. A decision to terminate for safety reasons may be driven by any data collected on the IP which negatively influences the risk/benefit assessment.	Section 10.1.10.2
Contact details for Marinus Project Managers updated.	Section 10.2.2.2
Added an alternative pregnancy testing in Table 3.	Section 10.3
Excluded references to future use of [redacted] samples and clarify that not [redacted] will be performed in Israel. Deleted: • DNA samples will be used for research related to TSC and related diseases. They may also be used to develop tests/assays, including diagnostic tests related to GNX and TSC. [redacted] may consist of the analysis of one or more candidate genes or the analysis of [redacted] throughout the genome or analysis of the entire genome (as appropriate). • The samples may be analyzed as part of a multistudy assessment of [redacted] involved in the response to study intervention of this class to understand the study disease or related conditions. Added: • No [redacted] will be performed in Israel.	Section 10.6
Reference for not collecting race ethnicity in France removed.	Section 10.7
Updated dosing instructions for the oral suspension to match the package insert.	Section 10.8
Updated SF-36 questionnaire to a more comprehensible format for participants.	Section 10.15

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **01 Feb 2022**	**Global/Country/ Site-Specific** **Global**
Rationale for the Amendment The rationale for the major changes in this protocol amendment are as follows: • The availability of new Phase 2 data raised the question of a cannabidiol (CBD) interaction. As a result, patients taking CBD will be monitored closely for adverse events (AEs), and specifically sedation-related AEs throughout the study. Patients were also stratified according to concomitant CBD use. • The allowance of an additional 2 weeks of titration after the 4 weeks titration period at the start of the maintenance period was removed as were specific dosing paradigms for participants taking Epidiolex > 10 mg/kg/day. This change will ensure that all patients will have the same target dose regardless of their background CBD therapy.		
Description of Changes		**Section(s) Affected by Change**
Minor editorial updates throughout for grammar, consistency, and clarity.		Throughout the document
Protocol date and version added to the header.		Protocol header
Protocol short name 'TrustTSC' added to the protocol title.		Title page, sponsor signatory, Investigator agreement and Section 1.1
The Investigational New Drug (IND) number was updated and the EudraCT number was added.		Title page
Updated the key secondary efficacy endpoint. Added: • Number (%) of participants considered treatment responders during the maintenance phase.		Section 1.1, Section 3, Section 9.3.3

Updated the overall study design so that there was no longer an additional allowance for titration during the maintenance period and to remove specific dosing paradigms for patients taking Epidiolex > 10 mg/kg/day as this will ensure all patients have the same target dose regardless of background therapy.
Removed:
• With 2 additional weeks allowed, if necessary, for tolerance and use of concomitant cannabidiols (Epidiolex/Epidyolex) as follows.
• For participants not taking concomitant Epidiolex or taking Epidiolex at a dose of 10 mg/kg/day or less, the target dose is:
  • 63 mg/kg/day for those weighing 28 kg or less, or
  • 1800 mg/day for those weighing more than 28 kg.
• For participants taking concomitant Epidiolex at a dose greater than 10 mg/kg/day, the target dose is:
  • 42 mg/kg/day for those weighing 28 kg or less, or
  • 1200 mg/day for those weighing more than 28 kg.
• The reduction of the GNX target dose for patients on cannabidiol > 10 mg/kg/day is based on
		Section 1.1, Section 1.2, Section 4.1, Section 4.3, Section 6.2, Section 8.1.2

• Incorporates a lower target dose for participants receiving concomitant Epidiolex, and a titration schedule with smaller increments in initial dosing for all participants • Any participant may extend upward titration of IP into the first 2 weeks of the maintenance period based on tolerability and the desire to attempt additional seizure control, following which they must maintain the attained dose for the duration of the double-blind phase • Dose adjustments to manage AEs, including alternative dosing paradigms Added: • 63 mg/kg/day with a maximum daily dose of 1800 mg (for patients > 28 kg) • The phase 2 data for GNX in TSC raised the question of a CBD interaction • Patients taking CBD should be monitored closely for any sedation-related AEs throughout • Any dose adjustments that are not part of the prespecified titration schedule	
Revised the text on study duration for participants to remove the extension of the 4 weeks titration period into the maintenance period. Removed: Any participant may extend upward titration of IP into the first 2 weeks of the maintenance period based on tolerability and the desire to attempt additional seizure control, following which they must maintain the dose for the duration of the double-blind phase.	Section 1.1, Section 4.1.1
Updated the synopsis to include the eligibility criteria from the main body of the protocol.	Section 1.1
Revised the text throughout the protocol to specify that subjects will be stratified based on whether the patient is taking concomitant CBD or not.	Section 1.1, Section 4.2, Section 6.4.1, Section 8.1.1
The schedule of activities was amended as follows: • A concomitant medication review was added in Part A. • Footnote k and l were updated for clarity. • Informed consent for open label extension (OLE) entry was updated, and a corresponding footnote was added. • Concomitant AED levels were added to Part B and a corresponding footnote was added. • A concomitant medication review was added in Part B. • The dispensing of investigational product was updated and corresponding footnote added.	Section 1.3
Updated the scientific rationale for study design to include stratification according to concomitant CBD use. Added: • In order to facilitate subgroup analysis, randomization will be stratified with respect to whether the participant is taking concomitant CBD or not.	Section 4.2
Revised the exclusion criteria to specify exclusion of patients with hepatic, biliary, and renal impairment if this was sufficient to affect patient safety.	Section 5.2
Deleted the dose titration table for patients receiving concomitant Epidiolex as all patients will be titrated to 63 mg/kg/day up to a maximum daily dose of 1800 mg.	Section 6.1

Updated the dose modification section to specify that all patients were dosed at 63 mg/kg/day up to a maximum daily dose of 1800 mg for participants > 28 kg regardless of concomitant Epidiolex use. Also added dosing requirements for patients who continue in the OLE. Added: In Part B, for participants who continue to the OLE, the total daily dose that the participant was taking at the completion of Part A will be maintained. The titration schedule in Table 2 will be followed until the target total daily dose for the participant is reached.	Section 6.2
Updated the requirements for discontinuation of study intervention to remove mention of drug-induced rash.	Section 7.1
Removed the additional 2 weeks of dose titration, for tolerance, that was specified and in additional to the standard 4 weeks dose titration period.	Section 8.1.2
Updated details for the physical/neurological/developmental examinations to specify this was applicable from ages 1 to 17 years instead of 2 to 17 years.	Section 8.3.1
Updated to specify concomitant anti-epileptic drug (AED) levels will be obtained centrally and collected at Visit 17 for patients who continue in the OLE. Added: • Participants who continue in the OLE will also have the above concomitant AED levels collected at Visit 17 (Week 20)	Section 8.3.6
Updated the drug screen section to state that this could be performed at any time during the study at the investigator's discretion and that concomitant use of THC and non-approved CBD was not permitted. Added: The plasma drug screen can be performed at any time during the study per the investigator's discretion. Concomitant use of THC and non-approved CBD is not permitted on study and will result in participant withdrawal from the study.	Section 8.3.7
Updated the multiplicity adjustment to specify that statistical hypothesis testing will be performed on 4 rather than the previously stated 3 key secondary endpoints as an additional endpoint has been added as part of this amendment.	Section 9.1.1
Updated the specified analysis sets to include the modified intent-to-treat (ITT) and amended the ITT set so that it no longer required patients to have received at least 1 dose of the IP. The exclusion of subjects from the efficacy analyses who failed to reach at least 50% of their respective target dose was also removed. Added: Modified Intent-to-treat (mITT) set - All randomized participants who receive at least 1 dose of the IP. Participants will be summarized within the treatment group to which they were randomized. This population will be used for sensitivity analysis for efficacy.	Section 9.2
Updated the sensitivity analyses planned for the primary efficacy endpoint to include 3 rather than 2 analyses. Added: • To examine the primary outcome measure by using mITT population.	Section 9.3.2.1

Updated secondary endpoint analysis to add an additional analysis for treatment responders during the maintenance period. Added: • Treatment responders are defined as those participants with ≥ 50% reduction from baseline in primary endpoint seizure frequency during given period.	Section 9.3.3
Revised male contraception requirements to state these should be continued for 30 days after the last dose of IP.	Section 10.5.2
Updated the dosing instruction for oral suspension in Appendix 8 to remove the example dose titration and maintenance tables and to add instructions for Part A (double-bind dose titrate, maintenance and taper) and Part B (double-blind crossover to open-label extension period). The patient instructions were also updated to match the package insert.	Section 10.8
Revised the title for Clinical Global Impression – Improvement (CGI-I) in Appendix 10 to specify that this was to be used for Clinicians as well as for Caregivers.	Section 10.10

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LIST OF ABBREVIATIONS

ACTH	adrenocorticotropic hormone
ADAMS	Anxiety, Depression, and Mood Scale
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANOVA	Analysis of Variance
ASM	anti-seizure medication
AST	aspartate aminotransferase
β-HCG	β-human chorionic growth hormone
BP	blood pressure
CBD	cannabidiol
CDD	cyclin-dependent kinase-like 5 deficiency disorder
CGI-CSID	Caregiver Global Impression of Change in Seizure Intensity/Duration
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression - Severity
CIOMS	Council for International Organizations of Medical Sciences
CNS	central nervous system
CRF	case report form
CRO	contract research organization
[redacted]	
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DMC	Data Monitoring Committee
ECG	electrocardiogram
EEG	electroencephalogram
eCRF	electronic case report form
eDiary	electronic seizure diary
eGFR	estimated glomerular filtration rate
ELDQOL	Epilepsy and Learning Disabilities Quality of Life
EMA	European Medicines Agency
EU	Europe
FDA	Food and Drug Administration

FXS	fragile X syndrome
GABA	γ-aminobutyric acid
GFR	glomerular filtration rate
GCP	Good Clinical Practice
GNX	ganaxolone
HR	heart rate
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP/IP	Investigational (Medicinal) Product
IRB	Institutional Review Board
IS	infantile spasm
ITT	intent-to-treat
IV	intravenous(ly)
IWRS	Interactive Web Response System
LAM	Lymphangioleiomyomatosis
LAR	legally authorized representative
MENA	Middle East and North Africa
MRI	magnetic resonance imaging
mITT	modified intent-to-treat
mTOR	mechanistic target of rapamycin
mTORC1	mechanistic target of rapamycin complex 1
NHS	National Health Service
OC	Oceania
OL	open-label
OLE	open-label extension
PCDH	protocadherin
PD	Pharmacodynamic(s)
Peds-QL-FIM	Pediatric Quality of Life – Family Impact Module
PI	principal investigator
PK	pharmacokinetic(s)
PP	Per-Protocol
PPD	postpartum depression
PRN	pro re nata (as needed)
PTSD	post-traumatic stress disorder
QTL	quality tolerance limit

RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SE	status epilepticus
SF-36	Short Form 36
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIB	suicidal ideation and behavior
SIF/DRF	Seizure Identification and Diagnostic Review Form
SOA	schedule of activities
SOC	system organ class
SQS	Sleep Quality Scale
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
THP	tetrahydroprogesterone
tid	3 times a day
TSC	Tuberous Sclerosis Complex
TSC1	hamartin
TSC2	tuberin
UK	United Kingdom
ULN	upper limit of normal
US	United States
VNS	vagal nerve stimulator
WOCBP	women of childbearing potential

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:
A Phase 3, Double-blind, Randomized, Placebo-controlled Trial of Adjunctive Ganaxolone (GNX) Treatment in Children and Adults with Tuberous Sclerosis Complex (TSC)-related Epilepsy (TrustTSC).

Brief Title:
Adjunctive GNX Treatment Compared with Placebo in Children and Adults with TSC-related Epilepsy.

Indication: TSC-related epilepsy.

Rationale:
TSC is a multi-system disorder of embryonal cortical development that can affect many organs through the overgrowth of benign tumors known as hamartomas. While the disease phenotype can be extremely variable, neurologic manifestations such as epilepsy can be seen in up to 90% of patients with TSC (Krueger and Northrup, 2013). The condition is caused by inherited mutations in either the *TSC1* (hamartin) gene, located on chromosome 9q34, or the *TSC2* (tuberin) 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 TSC1 and TSC2 form a regulatory complex responsible for limiting the activity of mechanistic target of rapamycin complex 1 (mTORC1), an important intracellular regulator of growth and metabolism via its inhibition of the small GTPase Rheb (Krueger and Northrup, 2013). Everolimus (Afinitor®), amTORC1 inhibitor, has been shown to decrease seizures (Mizuguchi et al, 2019; French et al, 2016). More recently, cannabidiol (CBD; Epidiolex®) demonstrated seizure reduction efficacy in a randomized controlled trial (Thiele et al, 2021).

TSC is one of the most common genetic causes of epilepsy, with seizure type and characteristics that vary by age (Jülich and Sahin, 2014). Infantile spasm (IS) is the most common seizure type presenting in infancy and represents the first manifestation of epilepsy in 50% of patients. In older children and adults, focal impaired awareness seizures (previously classified as complex partial seizures) are the most common (Chu-Shore et al., 2010); other focal and generalized seizures may also occur. Over 30% of patients develop treatment-refractory epilepsy (Jülich and Sahin, 2014). While seizures have typically been ascribed to cortical or subcortical tubers and subependymal nodules, 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).

Gamma-aminobutyric acid (GABA) appears to play a central role in the development of TSC-related epilepsy, possibly due to altered expression of endogenous $GABA_A$ receptor modulators (Di Michele et al, 2003). The $3\alpha_5$-reduced-tetrahydroprogesterone (THP) metabolites of progesterone, including 3α, 5α-THP (allopregnanolone), are positive allosteric modulators of the $GABA_A$ receptor. In contrast, $3\beta_5$-THP acts as functional antagonists of the $GABA_A$ receptor

by reducing the ability of $3\alpha_5$-THP to exert a potentiating effect on the $GABA_A$ receptor. Di Michele et al, 2003 have demonstrated decreases in allopregnanolone and 3α, 5β-THP relative to $3\beta_5$-THP enantiomers in patients with TSC-related epilepsy but not in patients with TSC without epilepsy or in controls. This change in the ratio of $3\alpha_5$- and $3\beta_5$-THP enantiomers could alter neuronal excitability mediated by $GABA_A$ receptors and predispose to the development of epilepsy in TSC. The role of $GABA_A$ receptor mediation is also supported by the greater efficacy of vigabatrin, a specific and irreversible inhibitor of GABA-aminotransferase leading to increased synaptic GABA levels, in seizures due to TSC relative to other epilepsies (Curatolo et al, 2001). These findings provide compelling evidence for the potential role of neuroactive steroids in the treatment of TSC-related epilepsy.

GNX is the 3β-methylated synthetic analog of allopregnanolone, an endogenous allosteric modulator of central nervous system (CNS) $GABA_A$ receptors. GNX has potency and efficacy comparable to allopregnanolone in activating synaptic and extrasynaptic $GABA_A$ receptors at a site distinct from benzodiazepines and barbiturates (Carter et al, 1997). GNX has protective activity in diverse rodent seizure models (Reddy and Rogwski, 2012; Bialer et al, 2010). Clinical studies have demonstrated that GNX has anticonvulsant activity with an acceptable safety and tolerability profile in the dose range of 900 to 1800 mg in adults and children (Sperling et al, 2017; Laxer et al, 2000; Kerrigan et al, 2000; Pieribone et al, 2007). Further, GNX reduces seizures in children with IS and refractory pediatric epilepsy. In an open-label study (OL), pediatric participants 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). There were 15 participants with a history of IS who completed treatment; 5 of the 15 participants 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%. There was 1 participant who became spasm-free and 1 non responder (with a decrease of < 25%) was spasm-free from Weeks 2 to 7.

In addition to its anticonvulsant activity, GNX has been shown to reduce anxiety, hyperactivity, and attention in children with fragile X syndrome (Ligsay et al, 2016). Similar behavior problems occur in individuals with TSC, with rates of approximately 50% for attention deficit/hyperactivity disorder and autistic spectrum disorder (Jülich and Sahin, 2014).

In TSC-related epilepsy, Study 1042-TSC-2001 was a Phase 2, single arm study with GNX. The primary objective was to assess the preliminary safety and efficacy of GNX as adjunctive therapy for the treatment of seizures in participants aged 2 to 65 years with genetically or clinically confirmed TSC-related epilepsy. The study consisted of a 4-week baseline followed by a treatment phase, consisting of a 4-week titration and 8-week maintenance period. The primary efficacy endpoint was the percent reduction in countable, TSC-associated seizures from the baseline through the end of the Period A treatment phase. Review of data for the primary endpoint showed a median 16.6% reduction in 28-day primary endpoint seizure frequency relative to the 4-week baseline period, with 30.4% of patients achieving a 50% or more seizure reduction. The clinical study report (CSR) for this study was completed on 08 Mar 2023.

It is hypothesized that the augmentation of $GABA_A$-receptor mediated signaling with GNX treatment will reduce seizures in patients with TSC. Changes in neurobehavioral symptoms, mood, sleep and quality of life will also be assessed.

Objectives and Endpoints:

Objectives
Primary Objective
• To assess the safety and efficacy of GNX compared to placebo as adjunctive therapy for seizures associated with TSC in children and adults as assessed by the change from baseline[a] in the frequency of countable major motor and focal seizures (primary endpoint seizures[b]) during the double-blind phase.
Secondary Objectives
• To determine the percentage of change from baseline[a] in 28-day primary endpoint seizure[b] frequency during the maintenance period. • To assess the change in focal seizure frequency from baseline[a] during the double-blind phase. • To assess changes in mood, behavior, and quality of life using the following: o ADAMS. o Peds-QL-FIM. o SF-36. o ELDQOL . • To assess overall clinical outcome using the CGI-I scores by the clinician and the parent(s)/caregiver(s)/LAR(s). • To evaluate the changes in seizure intensity and duration using the CGI-CSID.
Safety Objectives
• To assess the safety and tolerability of GNX compared with placebo as adjunctive therapy.
Endpoints
Primary Endpoint
• The primary efficacy endpoint is the percentage change from baseline[a] in 28-day primary endpoint seizure[b] frequency during the double-blind phase.
Secondary Endpoints
Key Secondary Efficacy Endpoints: • Percentage change from baseline[a] in 28-day primary endpoint seizure[b] frequency during the maintenance period (FDA). For EMA this is the primary endpoint. • Number (%) of participants considered treatment responders[c] during the double-blind phase (FDA). For the EMA, this endpoint will be evaluated over the maintenance period only. • Number (%) of participants considered treatment responders[c] during the maintenance period. • CGI-I at the last scheduled visit in the double-blind phase. **Secondary Efficacy Endpoints (Behavior/Neuropsychiatric/Quality of life):** • Change from baseline in ADAMS total score and sub-score. • Change from baseline in quality-of-life scales: Peds-QL-FIM, SF-36, and ELDQOL. **Secondary Efficacy Endpoints (Seizure Control):**

- Change from baseline[a] in the percentage of seizure-free days during the double-blind phase, based on primary endpoint seizure[b] type (FDA). For the EMA, this endpoint will be evaluated over the maintenance period only.
- Change from baseline[a] in the CGI-CSID at the end of the double-blind phase (FDA). For the EMA, this endpoint will be evaluated over the maintenance period only.
- Participants with a ≥ 25% and ≥ 75% reduction from baseline in primary endpoint seizure[b] frequency during the double-blind phase (FDA). For the EMA, this endpoint will be evaluated over the maintenance period only.
- Participants with a ≥ 25%, ≥ 50%, and ≥ 75% reduction from baseline[a] in primary endpoint seizure[b] frequency during the maintenance period.
- Responder analysis for primary endpoint seizures[b] and all seizures during the double-blind phase using the following response categories: ≤ 0%, > 0% to < 25%, ≥ 25% to < 50%, ≥ 50% to < 75%, and ≥ 75% to 100% (FDA). For the EMA, this endpoint will be evaluated over the maintenance period only.
- Percent change in 28-day frequency of all seizures.
- Change from baseline[a] in the percentage of seizure-free days, based on all seizure types.
- Change from baseline[a] in the longest seizure-free interval, based on primary endpoint seizure type[b] and all seizure types.

Safety Endpoints

- Incidence and severity of AEs, SAEs, and withdrawals and dose-reductions due to AEs
- Other measures of safety including physical/neurological/developmental examinations, vital sign measurements (eg, blood pressure, heart rate, respiratory rate, and body temperature), 12-lead ECGs, clinical laboratory tests, and suicidal ideation and behavior risk monitoring.

The primary and secondary endpoints (unless otherwise defined) for the United States FDA will be based on the double-blind phase (titration and maintenance period). The primary and secondary endpoints (unless otherwise defined) for the EMA will be based on the maintenance period only.

ADAMS = Anxiety, Depression, and Mood Scale; AE = adverse event; CGI-CSID = Clinical Global Impression of Change in Seizure Intensity/Duration; CGI-I = Clinical Global Impression of Improvement; ECG = electrocardiogram; ELDQOL = Epilepsy and Learning Disabilities Quality of Life; EMA = European Medicines Agency; FDA = Food and Drug Administration; GNX = ganaxolone; LAR = legally authorized representative; Peds-QL-FIM = Pediatric Quality of Life - Family Impact Module;; SAE = serious adverse events; SF-36 = Short Form 36 (version 2); TSC = Tuberous Sclerosis Complex.

a Baseline is defined as the first 28 days following screening.

b Primary endpoint seizure types are defined as the following: focal motor seizures without impairment of consciousness or awareness, focal seizures with impairment of consciousness or awareness with motor features, focal seizures evolving to bilateral, tonic-clonic convulsive seizures, and generalized motor seizures including tonic-clonic, bilateral tonic, bilateral clonic, or atonic/drop seizures. Seizures must have a motor component sufficiently prominent and distinct to clearly establish the observed symptoms as epileptic in origin. Seizures that do not count towards the primary endpoint include: focal or generalized nonmotor seizures (eg, absence seizures or focal nonmotor seizures with or without impairment of awareness), infantile or epileptic spasms, and myoclonic seizures.

c Treatment responders are defined as those participants with a ≥ 50% reduction from baseline in primary endpoint seizure frequency during the double-blind or maintenance phase.

Overall Design:
This is a Phase 3, global, double-blind, randomized, placebo-controlled study of adjunctive GNX treatment in children and adults with TSC-related epilepsy. The study consists of a 4-week prospective baseline phase, defined as the first 28 days following screening, followed by a double-blind phase consisting of a 4-week titration period and a 12-week maintenance period.

Participants eligible for inclusion in this double-blind study must have inadequately controlled seizures after exposure to at least 2 anti-seizure medication (ASMs) administered at adequate doses and for adequate durations, with approximately 8 seizures per month in the 2 months prior to screening and seizure-free periods of not more than 1 week.

Procedures specific to this protocol and not otherwise considered standard of care, will not be performed until written informed consent from the participant or their parent(s)/legally authorized representative (s) (LARs), as appropriate, has been appropriately obtained.

An interactive response technology system will be used to randomize participants, dispense drug, track treatment, and maintain the blind throughout the duration of the study.

Participants or their parent(s)/caregiver(s)/LAR(s) are expected to complete electronic seizure diary (eDiary) entries to document the number and type(s) of seizures daily throughout the study. A variety of clinician and caregiver administered instruments will be used to assess efficacy, and will include:

- Clinical Global Impression - Severity (CGI-S).
- Clinical Global Impression of Improvement (CGI-I) by parent(s)/caregiver(s)/LAR(s) and clinician.
- Caregiver Global Impression of Change in Seizure Intensity/Duration (CGI-CSID).
- [redacted]
- Anxiety, Depression, and Mood Scale (ADAMS).
- Pediatric Quality of Life – Family Impact Module (Peds-QL-FIM).
- Short Form 36 (SF-36).
- Epilepsy and Learning Disabilities Quality of Life (ELDQOL).

The titration schedule is as follows:

- Start – Day 1.
- Titration 1 – Day 7.
- Titration 2 – Day 14.
- Titration 3 – Day 21.
- Final titration – Day 28.
- Maintenance begins on Day 29 (Start of Week 5).

GNX (or matching volumes of placebo suspension) will be titrated at approximately weekly intervals over 4 weeks to a maximum dose based on the participant's starting weight 63 mg/kg/day with a maximum daily dose of 1800 mg (for patients more than 28 kg).

The Phase 2 data for GNX in TSC raised the question of a CBD interaction. In the trial of 23 treated patients, approximately half were on cannabidiol, and there was an association between higher CBD doses and increased somnolence. Given the small sample size, more definitive conclusions were not possible. As a result, patients taking CBD should be monitored closely for any sedation-related adverse events (AEs) throughout this Phase 3 protocol. Participants may have the dose of investigational product (IP) temporarily or permanently decreased at any point in the maintenance period to manage tolerability.

Any dose adjustments that are not part of the prespecified titration schedule should be discussed with the sponsor medical monitor prior to making the change. If it is not possible to contact the medical monitor prior to the dose adjustment, the medical monitor should be notified as soon as possible after making the change.

The maximum dose for all participants is 1800 mg/day. The total double-blind phase (titration and maintenance periods) should not exceed 16 weeks.

Participants who discontinue the IP should undergo a 2-week taper period. The taper period may be shortened at the discretion of the investigator as clinically indicated. Participants who discontinue the IP before the scheduled completion of the study will return to the site 2 weeks after the end of taper to complete the safety follow-up assessments.

Following completion of the double-blind phase, participants who are compliant with study conduct will have the option to enroll and be treated with GNX in a separate open-label extension study (OLE), 1042-TSC-3002. All participants entering the OLE will have their dose of study medication adjusted in a double-blind cross-titration over 4 weeks such that all are receiving GNX at study completion. Participants who do not continue in the OLE will undergo a 2- to 4-weeks double-blind down-titration and taper if discontinuing IP (See Figure 1).

Disclosure Statement:
This is a randomized, double-blind, placebo-controlled, 2-arm treatment study that is participant, caregiver, and investigator blinded.

Number of Participants:
Approximately 200 participants with TSC will be screened with the aim of randomizing approximately 128 participants (64 per arm), aged 1 to 65 years (inclusive). For Europe (EU), Middle East and North Africa (MENA), and Oceania (OC) Male or Female participants aged 2 through 65 years, inclusive. Participants will be randomized (1:1) to either GNX or placebo as adjunctive therapy with their standard ASMs.

Note: Enrolled means the participant, or their LAR(s), has agreed to participate in the study following completion of the informed consent process and screening. Potential participants who are screened for the purpose of determining eligibility for the study, but who subsequently are not eligible for study entry, are not considered enrolled, unless otherwise specified by the protocol.

Eligibility Criteria:
Participants are eligible to be included in the study only if all the following inclusion criteria are met:

1. Clinical or mutational diagnosis of TSC consistent with (Northrup et al, 2021):
   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 (eg, 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 principal investigator (PI) or designee 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 2 major features or 1 major feature with ≥ 2 minor features.

Major features	Minor features
Hypomelanotic macules (≥ 3, at least 5-mm diameter)	"Confetti" skin lesions
Angiofibroma (≥ 3) or fibrous cephalic plaque	Dental enamel pits (≥ 3)
Ungual fibromas (≥ 2)	Intraoral fibromas (≥ 2)
Shagreen patch	Retinal achromic patch
Multiple retinal hamartomas	Multiple renal cysts
Multiple cortical tubers and/or radial migration lines	Nonrenal hamartomas
Subependymal nodules (≥ 2)	Sclerotic bone lesions
Subependymal giant cell astrocytoma	
Cardiac rhabdomyoma	
Lymphangioleiomyomatosis (LAM)*	
Angiomyolipomas (≥ 2)*	

* A combination of the 2 major clinical features (LAM and angiomyolipomas) without other features does not meet criteria for a definite diagnosis.

The investigator must document which of the features (major or minor) fulfill the clinical diagnostic criteria.

2. Male or female participants aged 1 through 65 years, inclusive. For Europe (EU), Middle East and North Africa (MENA), and Oceania (OC) Male or Female participants aged 2 through 65 years, inclusive.
3. Participant/parent(s) or LAR(s) willing and able 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. If the participant is not qualified nor able to provide written informed consent based on age, developmental stage, intellectual capacity, or other factors, parent(s)/LAR(s) must provide consent for study participation, if appropriate.

4. Failure to control seizures despite appropriate trial of 2 or more ASMs at therapeutic doses and for adequate duration of treatment per PI judgment.
5. Participants should be on a stable regimen of ASMs (including moderate or strong inducer or inhibitor ASM eg, carbamazepine, phenytoin, etc.) at therapeutic doses for ≥ 28 days prior to the screening visit, and without a foreseeable change in dosing for the duration of the study. (Note: Minor dose adjustment to address tolerability and safety events may be allowed on case-by-case basis and it should be discussed with the study medical monitor.)
6. A history of at least 8 countable seizures per month in the 2 months prior to screening with no more than 1 seizure free week in each month. This includes seizures of any kind.
7. Have at least 8 primary endpoint seizures in the first 28 days following the screening visit. The primary endpoint seizure types are defined as the following:
   a. Focal motor seizures without impairment of consciousness or awareness
   b. Focal seizures with impairment of consciousness or awareness with motor features
   c. Focal seizures evolving to bilateral, tonic-clonic seizures
   d. Generalized motor seizures including tonic-clonic, bilateral tonic, bilateral clonic, or atonic/drop seizures.

   Seizures that **do not count** towards the primary endpoint include:
   a. Focal or generalized nonmotor seizures (eg, absence seizures or focal nonmotor seizures with or without impairment of awareness)
   b. Infantile or epileptic spasms
   c. Myoclonic seizures
8. Participants with surgically implanted vagal nerve stimulator (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 ≥ 6 months prior to the screening visit
   b. The settings must have remained constant for 3 months prior to the screening visit and are expected to remain constant throughout the study
   c. The battery is expected to last for the duration of the study.
9. Parent(s)/caregiver(s)/LAR(s) or the participant, as appropriate, is (are) willing and able to maintain an accurate and complete daily seizure eDiary for the duration of the study.
10. Willing and able to take IP (suspension) as directed with food 3 times a day (tid).
11. WOCBP 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 and baseline visits. Childbearing potential is defined as a female who is biologically capable of becoming pregnant. Medically acceptable methods of birth control include intrauterine devices (that have been in place for at least 1 month prior to the screening visit), hormonal contraceptives (eg, combined oral contraceptives, patch, vaginal ring, injectables, and implants), and surgical sterilization (such as oophorectomy or tubal ligation). When used consistently and correctly, “double-barrier” methods of contraception can be used as an effective alternative to highly effective contraception methods. Contraceptive measures such as Plan B™, sold for emergency use after unprotected sex, are not acceptable methods for routine use.

12 Male participants must agree to use highly effective contraceptive methods during the study and for 30 days after the last dose of IP. Highly effective methods of contraception include surgical sterilization (such as a vasectomy) and adequate "double-barrier" methods.

Note: The Epilepsy Study Consortium will review and classify all seizure types reported by the investigator, incorporating the medical history, [redacted] seizure description, and historical records (including electroencephalogram [EEG], when available). This review and classification does not need to be completed prior to study entry but should be completed in parallel, and may complete after the participant has been enrolled in the study.

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

1. Previous exposure to GNX.
2. Pregnant or breastfeeding.
3. Participants who have been taking felbamate for less than 1 year prior to screening.
4. Participants taking CBD preparations other than Epidiolex®.
5. A positive result on drug screen for CBD or tetrahydrocannabinol (THC) at Visit 1 (screening), with the exception of results that are fully explained by prescribed Epidiolex®, which can be adjusted by the investigator in the event of any AEs.
6. Concurrent use of adrenocorticotropic hormone (ACTH), prednisone or other glucocorticoid is not permitted, nor use of the strong inducers of cytochrome P450 3A4 (CYP3A4), rifampin and St. John's Wort.

   Participants on ACTH, prednisone, or other systemically (non-inhaled or topical) administered steroids should be off the product > 28 days prior to screening.

   Rifampin and St. John's Wort must be discontinued at least 28 days before Visit 2, study drug initiation.

   Note:

   a. Use of concomitant intranasal or pro re nata (PRN) topical steroids for dermatologic reactions and allergic rhinitis are allowed during the study.
   b. This exclusion criterion does not prohibit the use of approved ASMs.
7. Changes in any chronic medications within the 4 weeks prior to the screening visit. All chronic concomitant medications must be relatively stable in dose for at least 4 weeks prior to the screening visit unless otherwise noted. Small dose adjustment to manage tolerability and safety events is permitted and should be discussed with the study medical monitor.
8. Participants who have epilepsy surgery planned during the study or who have undergone surgery for epilepsy within the 6 months prior to screening.
9. An active CNS infection, demyelinating disease, degenerative neurological disease, or CNS disease deemed progressive as evaluated by brain magnetic resonance imaging (MRI). This includes tumor growth which in the opinion of the investigator could affect primary endpoint seizure control.
10. Any disease or condition (medical or surgical; other than TSC) at the screening visit that might compromise the hematologic, cardiovascular (including any cardiac conduction

defect), 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 participant at increased risk or interfere with the assessment of safety/efficacy. This may include any illness in the past 4 weeks which in the opinion of the investigator may affect seizure frequency.

11. Hepatic impairment sufficient to affect patient safety, or 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.
12. Biliary impairment sufficient to affect patient safety, or total bilirubin levels > 1.5 × ULN at screening or baseline visit and confirmed by a repeat test. In cases of Gilbert's Syndrome, resulting in stable levels of total bilirubin greater than ULN, the medical monitor can determine if a protocol exception can be made.
13. Renal impairment sufficient to affect patient safety, or estimated glomerular filtration rate (eGFR) < 30 mL/min (calculated using the Cockcroft-Gault formula or pediatric glomerular filtration rate [GFR] calculator or Bedside Schwartz), will be excluded from study entry or will be discontinued if the criterion is met post baseline (Levey et al, 2006). Cases of temporary renal insufficiency should be discussed with the medical monitor to determine the participant's study continuation.
14. Exposed to any other investigational drug or investigational device within 30 days or fewer than 5 half-lives prior to the screening visit. For therapies in which half-life cannot be readily established, the Sponsor's medical monitor should be consulted.
15. Unwillingness to avoid excessive alcohol use throughout the study.
16. Have active suicidal plan/intent, active suicidal thoughts or a suicide attempt in the past 6 months.
17. Known sensitivity or allergy to any component in the IP(s), progesterone, or other related steroid compounds.
18. Participants deprived of their liberty by a judicial or administrative decision, or for psychiatric treatment, or participants admitted to a health or social services facility for purposes other than research.
19. Participants receiving traditional Chinese medicine therapies within the prior 28 days of the screening.

Intervention Groups and Duration:
Eligible participants will collect 4 weeks of prospective baseline seizure data prior to starting treatment. Participants will be randomized (1:1) to double-blind treatment with GNX or placebo. Stratification of randomization will be performed based on whether the patient is taking concomitant CBD or not. GNX is to be titrated to the target dose over 4 weeks. The total double-blind phase (titration and maintenance periods) should not exceed 16 weeks.

Participants who complete the study may be eligible to participate in the OLE. However, participants who discontinue IP should undergo a 2-week or shorter taper period, as clinically indicated, and complete the safety follow-up assessments 2 weeks after the final dose.

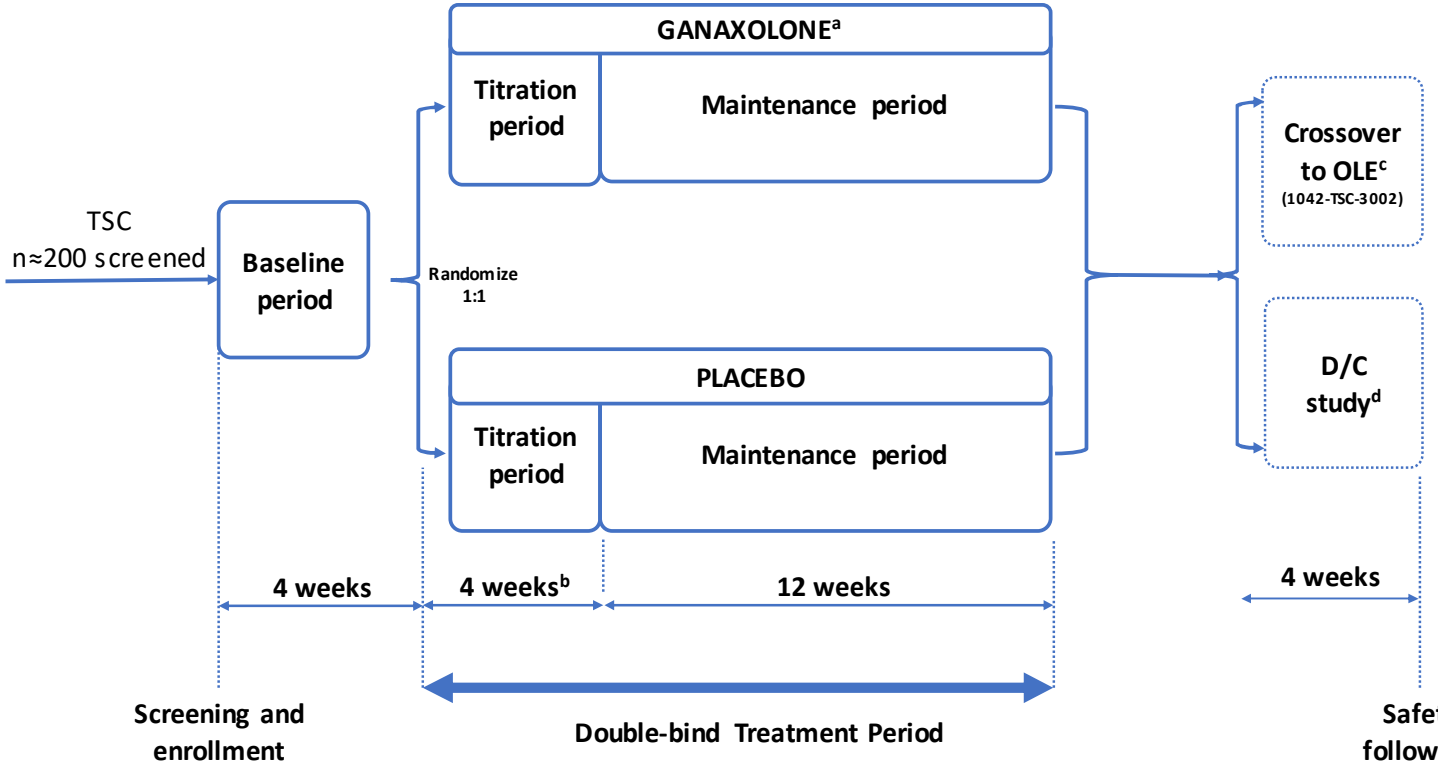
Data Monitoring/Other Committee:
The Data Monitoring Committee (DMC) will review emerging study data on a periodic basis.

The DMC is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the sponsor regarding the stopping of a study for safety concerns. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.

The mission of the DMC will be to safeguard the interests of study participants and to enhance the integrity and credibility of the trial. To enable the DMC to achieve their mission, the DMC will have periodic access to unblinded safety data and data regarding quality of trial conduct and will ensure the confidentiality of these data is preserved. A DMC Charter will provide the principles and guidelines for the DMC process.

1.2 Schema

Figure 1. Study Schematic Diagram



DC = double-blind down cross-titration; GNX = ganaxolone; IP = investigational product; OLE = open-label extension; TSC = Tuberous Sclerosis Complex.

a GNX or matching volumes of placebo suspension will be titrated at approximately weekly intervals over 4 weeks: The target dose is: 63 mg/kg/day for those weighing 28 kg or less, or 1800 mg/day for those weighing more than 28 kg.

b The participant may have the dose of IP temporarily or permanently decreased at any point in the maintenance period to manage tolerability.

c All participants entering the OLE will have their dose of study medication adjusted in a double-blind cross-titration over 4 weeks such that all are receiving GNX at study completion.

d Participants who do not continue in the OLE will undergo a 2- to 4-weeks double-blind down titration and taper if discontinuing IP and safety follow-up visit at the end of 4 weeks

1.3 Schedule of Activities

Table 1. Schedule of Activities – Screening/Baseline and Double-blind Phase (Titration and Maintenance Periods) Plus Part A for Participants who Do Not Continue in the OLE or Part B for Participants who Continue in the OLE

Screening/Baseline and Double-blind Phase (Titration and Maintenance Periods)													Part A: Participants who Do Not Continue in the OLE
	Screening/Baseline		Double-blind Phase (Titration + Maintenance Periods)										End of Study/Safety Follow-up Visit/[a] Discontinuation
WEEK (All dates are relative to the first dose)	**-4 (Screening)**	**Baseline and First Dose on Day 1 (Randomization)**	**Day 4**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 9**	**Wk 11**	**Wk 13**	**Wk 16**	**Wk 20**
Visit and Visit Window		**+ 6 days**	**± 1 day**	**± 1 day**	**All windows for these visits are ± 3 days**								**± 7 days**
(visits are either in person or telehealth)	**V1**	**V2**	**V3 Phone**	**V4**	**V5 Phone**	**V6 Phone**	**V7 Phone**	**V8**	**V9**	**V10 Phone**	**V11 Phone**	**V12 or ET**	**V13A**
Screening and Diagnosis													
Informed Consent[b]	X												
Demographics and Medical History	X	X[c]											
Historical Seizure Calendar Review	X												
Inclusion/ Exclusion Criteria	X	X											
[redacted]	X												
Seizure Identification and Diagnostic Review Form (Epilepsy Study Consortium)	X												

Screening/Baseline and Double-blind Phase (Titration and Maintenance Periods)													Part A: Participants who Do Not Continue in the OLE
	Screening/Baseline		Double-blind Phase (Titration + Maintenance Periods)										End of Study/Safety Follow-up Visit/[a] Discontinuation
WEEK (All dates are relative to the first dose)	**-4 (Screening)**	**Baseline and First Dose on Day 1 (Randomization)**	**Day 4**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk9**	**Wk 11**	**Wk 13**	**Wk 16**	**Wk 20**
Visit and Visit Window (visits are either in person or telehealth)		**+ 6 days**	**± 1 day**	**± 1 day**	**All windows for these visits are ± 3 days**								**± 7 days**
	V1	**V2**	**V3 Phone**	**V4**	**V5 Phone**	**V6 Phone**	**V7 Phone**	**V8**	**V9**	**V10 Phone**	**V11 Phone**	**V12 or ET**	**V13A**
Safety Assessments													
Vital Signs (BP, HR, and RR), Body temperature, Height, and Weight	X	X		X				X	X			X	X
Physical/Neurological/ Developmental Exam[e]	X												
Physical/Neurological/ Developmental Exam Follow-up		X		X				X	X			X	
12-lead ECG	X	X		X				X				X	
Clinical Laboratory Tests[f]	X	X		X				X	X			X	
Urinalysis	X[g]	X[g]		X								X	
Drug screen[h]	X												
Pregnancy Test (WOCBP)[i]	X	X		X				X	X			X	X
Tanner Staging	X												X
Investigational Product PK[j]								X	X			X	
Concomitant ASM Levels[k]	X							X				X	

Screening/Baseline and Double-blind Phase (Titration and Maintenance Periods)													Part A: Participants who Do Not Continue in the OLE
	Screening/Baseline		Double-blind Phase (Titration + Maintenance Periods)										End of Study/Safety Follow-up Visit/[a] Discontinuation
WEEK (All dates are relative to the first dose)	**-4 (Screening)**	**Baseline and First Dose on Day 1 (Randomization)**	**Day 4**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk9**	**Wk 11**	**Wk 13**	**Wk 16**	**Wk 20**
Visit and Visit Window (visits are either in person or telehealth)		**+ 6 days**	**± 1 day**	**± 1 day**	**All windows for these visits are ± 3 days**								**± 7 days**
	V1	**V2**	**V3 Phone**	**V4**	**V5 Phone**	**V6 Phone**	**V7 Phone**	**V8**	**V9**	**V10 Phone**	**V11 Phone**	**V12 or ET**	**V13A**
Concomitant ASM Level Review (if collected per standard of care)[l]	X	X		X				X	X			X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS (baseline form)[m]		X											
C-SSRS (since previous visit)[l]				X				X	X			X	X
Efficacy Assessments													
Seizure eDiary review	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI-S		X											
CGI-CSID				X				X	X			X	
CGI-I by Parent(s)/Caregiver(s)/LAR(s) and Clinician				X				X	X			X	
Exploratory Assessments													
[redacted]													

Screening/Baseline and Double-blind Phase (Titration and Maintenance Periods)													Part A: Participants who Do Not Continue in the OLE
	Screening/Baseline		Double-blind Phase (Titration + Maintenance Periods)										End of Study/Safety Follow-up Visit/[a] Discontinuation
WEEK (All dates are relative to the first dose)	**-4 (Screening)**	**Baseline and First Dose on Day 1 (Randomization)**	**Day 4**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk9**	**Wk 11**	**Wk 13**	**Wk 16**	**Wk 20**
Visit and Visit Window (visits are either in person or telehealth)		**+ 6 days**	**± 1 day**	**± 1 day**	**All windows for these visits are ± 3 days**								**± 7 days**
	V1	**V2**	**V3 Phone**	**V4**	**V5 Phone**	**V6 Phone**	**V7 Phone**	**V8**	**V9**	**V10 Phone**	**V11 Phone**	**V12 or ET**	**V13A**
ADAMS		X		X				X	X			X	
Peds-QL–FIM[p]		X						X	X			X	
ELDQOL		X		X				X	X			X	
SF-36		X		X				X	X			X	
Investigational Product													
Randomization		X											
Dispense IP		X						X	X			X	

ADAMS = Anxiety, Depression, and Mood Scale; ASM = anti-seizure medication; BP = blood pressure; CBD = cannabidiol; CGI-CSID = Caregiver Global Impression of Change in Seizure Intensity/Duration; CGI-I = Clinical Global Impression of Improvement; CGI-S = Clinical Global Impression of Improvement; eCRF = Electronic case report form; [redacted] C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; eDiary = electronic seizure diary; ELDQOL = Epilepsy and Learning Disabilities Quality of Life; ET = early termination; HR = heart rate; IP = investigational product; LAR = legally authorized representative; OLE = open-label extension; Peds-QL–FIM = Pediatric Quality of Life - Family Impact Module; PI = principal investigator; PK = pharmacokinetic; QOL = quality of life; RR = respiratory rate; SF-36 = Short Form 36 (version 2); SQS = Sleep Quality Scale; THC = tetrahydrocannabinol; WOCBP = women of childbearing potential.

a. Only for participants who discontinue treatment, either early or at Visit 12 prior to down-titration as they are not continuing in the OLE study. This visit will occur 2 weeks after the last dose of IP.

b. Written informed consent/assent must be obtained from participant/parent(s)/caregiver(s)/LAR(s) before any study assessments are performed.

c. Review of medical history only.

[redacted]

e. Developmental examination is limited to pediatric participants 1 to 17 years of age, inclusive.

f. Chemistry and Hematology (See Section 8.3.4)
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.
h. A plasma (or urine, if plasma is difficult or impossible to obtain) drug screen will be performed to test for THC and non-approved CBD at Visit 1 (screening). A positive test for CBD or THC will exclude the participants from the study, unless the participant is taking prescribed Epidiolex®.
i. Serum pregnancy test is required for all WOCBP at Visits 1 and 2. At Visits 4, 8, 9, 12, and 13A, the investigator may choose to do either a serum or urine pregnancy test.
j. PK samples will be collected at these visits; Visit 8 (Week 5): between 1 to 5 hours since last IP dosing, Visit 9 (Week 9): between 4 to 8 hours since the last IP dosing, and Visit 12 (Week 16) where there is no specified time window relative to dosing).
k. Concomitant ASMs or their dose must be stable for 4 weeks prior to screening and should not be changed at any time prior to Visit 12. Concomitant ASM levels at Visit 1 (Screening), Visit 8, and on study completion will be obtained centrally for the following if the participant is prescribed these medications: cannabidiol, clobazam (which requires clobazam and desmethylclobazam levels), any mTOR inhibitor (including everolimus, sirolimus, etc.), and/or valproate.
l. If the levels of any ASM co-administered with the IP are measured routinely per standard of care, this information will be recorded in the eCRF.
m. Only for participants ≥ 11 years of age, if appropriate, otherwise, clinical judgment will be used.
n. For participants aged 4 to 12 years of age, if appropriate (Section 8.2.5).
o. For participants ≥ 13 years of age, if appropriate.
p. For parent(s)/caregiver(s)/LAR(s) of the participant to complete, if appropriate. Peds-QL-FIM for past 1 month at baseline visit and Peds-QL-FIM for past 7 days at on-study visits (see Section 8.2.7).

Table 1 Schedule of Assessments Continued - Part B for Participants who Continue in the OLE[a]

Part B (For Participants who Continue in the OLE)						
	Last Visit in Period	**Double-blind Phase (Titration) (4 Weeks)**				**End of Study Visit/ET /First Visit of the OLE**
WEEK (All dates are relative to the first dose)	**Wk 16**	**Wk 16(3 Days Post-V12)**	**Wk 17**	**Wk 18**	**Wk 19**	**Wk 20**
Visit and Visit Window (visits are either in person or telehealth)	**± 3 days**	**± 1 day**	**All windows for these visits are ± 3 days**			**± 3 days**
VISIT	**V12**	**V13B Phone**	**V14 Phone**	**V15**	**V16 Phone**	**V17**
Screening and Diagnosis						
Informed Consent for OLE entry[b]						X
Inclusion/Exclusion Criteria for OLE	X					X
Safety Assessments						
Vital signs (BP, HR, and RR), Body temperature, Height, and Weight	X			X		X
Physical/Neurological/ Developmental Exam Follow-up	X					X
12-Lead ECG	X			X		X
Clinical Laboratory Tests[c]	X					X
Urinalysis	X					X
Drug Screen						X
Pregnancy Test (WOCBP)[d]	X					X
Tanner Staging						X
Investigational Product PK[e]	X			X		X

Part B (For Participants who Continue in the OLE)						
	Last Visit in Period	**Double-blind Phase (Titration) (4 Weeks)**				**End of Study Visit/ET /First Visit of the OLE**
WEEK (All dates are relative to the first dose)	**Wk 16**	**Wk 16(3 Days Post-V12)**	**Wk 17**	**Wk 18**	**Wk 19**	**Wk 20**
Visit and Visit Window (visits are either in person or telehealth)	**± 3 days**	**± 1 day**	**All windows for these visits are ± 3 days**			**± 3 days**
VISIT	**V12**	**V13B Phone**	**V14 Phone**	**V15**	**V16 Phone**	**V17**
Concomitant ASM Levels[f]	X					X
Concomitant ASM Level Review (if collected per standard of care)	X			X		X
Adverse Events	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X
C-SSRS (since previous visit)[g]	X			X		X
Efficacy Assessments						
Seizure eDiary Review	X	X	X	X	X	X
CGI-I by Parent(s)/Caregiver(s)/LAR(s) and Clinician	X			X		X
CGI-CSID	X			X		X
Exploratory Assessments						
[redacted]						
ADAMS	X			X		X
Peds-QL-FIM[j]	X			X		X
ELDQOL	X			X		X

Part B (For Participants who Continue in the OLE)						
	Last Visit in Period	**Double-blind Phase (Titration) (4 Weeks)**				**End of Study Visit/ET /First Visit of the OLE**
WEEK (All dates are relative to the first dose)	**Wk 16**	**Wk 16(3 Days Post-V12)**	**Wk 17**	**Wk 18**	**Wk 19**	**Wk 20**
Visit and Visit Window (visits are either in person or telehealth)	**± 3 days**	**± 1 day**	**All windows for these visits are ± 3 days**			**± 3 days**
VISIT	**V12**	**V13B Phone**	**V14 Phone**	**V15**	**V16 Phone**	**V17**
SF-36	X			X		X
Investigational Product						
Dispense Investigational Product[k]	X					X

ADAMS = Anxiety, Depression, and Mood Scale; ASM = anti-seizure medication; BP = blood pressure; CGI-CSID = Caregiver Global Impression of Change in Seizure Intensity/Duration; CGI-I = Clinical Global Impression of Improvement; [redacted]C-SSRS = Columbia-Suicide Severity Rating Scale; D/C = discontinuation; ECG = electrocardiogram; eDiary = electronic seizure diary; ELDQOL = Epilepsy and Learning Disabilities Quality of Life; ET = early termination; HR = heart rate; IWRS = interactive web-based response system; OLE = open-label extension; LAR = legally authorized representative; Peds-QL-FIM = Pediatric Quality of Life – Family Impact Module; PK = pharmacokinetic; QOL = quality of life; SF-36 = Short Form 36 (version 2); SQS = Sleep Quality Scale; RR = respiratory rate; WOCBP = women of childbearing potential.

a. For participants continuing into the OLE, relevant data from the 1042-TSC-3001 study database will be shared with the 1042-TSC-3002 study database.
b. The timing of consent for the 1042-TSC-3002 OLE study should occur at or before Visit 17.
c. Chemistry and Hematology (Section 8.4.5).
d. The investigator may choose to do either a serum or urine pregnancy test for all WOCP at Visit 12. At Visit 17, serum pregnancy test is required for all WOCBP.
e. Population PK will be conducted at these visits: Visit 12 (Week 16), Visit 15 (Week 18), and Visit 17 (Week 20) where there are no specified time windows relative to dosing.
f. Concomitant ASMs or their dose must be stable for 4 weeks prior to this visit. Concomitant ASM levels will be obtained centrally for the following if the participant is prescribed these medications: cannabidiol, clobazam (which requires clobazam and desmethylclobazam levels), any mTOR inhibitor (including everolimus, sirolimus, etc.), and/or valproate.
g. Only for participants ≥ 11 years of age, if appropriate, otherwise, clinical judgment will be used.
h. For participants aged 4 to 12 years of age, if appropriate (Section 8.2.5).
i. For participants ≥ 13 years of age, if appropriate (Section 8.2.5).
j. For the parent(s)/caregiver(s)/LAR(s) of the participant to complete, if appropriate. Peds-QL-FIM for past 7 days at on-study visits (see Section 8.2.7).
k. The IP dispensation at Visit 17 is the first visit of the OLE and will occur using the 1042-TSC-3002 IWRS.

2 INTRODUCTION

Ganaxolone (GNX) is a small molecule being developed for use as an ASM in rare pediatric seizure disorders including cyclin-dependent kinase-like 5 deficiency disorder (CDD), tuberous sclerosis complex (TSC)-related epilepsy, and status epilepticus (SE).

GNX has also been investigated in adults with post-traumatic stress disorder (PTSD), migraine, postpartum depression (PPD), and children with protocadherin (PCDH)-related epilepsy, and fragile X syndrome (FXS).

2.1 Study Rationale

Gamma-aminobutyric acid (GABA) appears to play a central role in the development of TSC-related epilepsy, possibly due to altered expression of endogenous $GABA_A$ receptor modulators (Di Michele et al, 2003). The $3\alpha_5$-reduced-tetrahydroprogesterone (THP) metabolites of progesterone, including 3α, 5α-THP (allopregnanolone), are positive allosteric modulators of the $GABA_A$ receptor. In contrast, 3β5-THP acts as functional antagonists of the $GABA_A$ receptor by reducing the ability of 3α5-THP to exert a potentiating effect on the $GABA_A$ receptor. Di Michele et al (2003) have demonstrated decreases in allopregnanolone and 3α, 5β-THP relative to 3β5-THP enantiomers in patients with TSC-related epilepsy but not in patients with TSC without epilepsy, or in controls. This change in the ratio of 3α5- and 3β5-THP enantiomers could alter neuronal excitability mediated by $GABA_A$ receptors and predispose to the development of epilepsy in TSC. The role of $GABA_A$ receptor mediation is also supported by the greater efficacy of vigabatrin, a specific and irreversible inhibitor of GABA-aminotransferase leading to increased synaptic GABA levels, in seizures due to TSC relative to other epilepsies (Curatolo et al, 2001). These findings provide compelling evidence for the potential role of neuroactive steroids in the treatment of TSC-related epilepsy.

It is hypothesized that the augmentation of $GABA_A$-receptor mediated signaling with GNX treatment will reduce seizures in patients with TSC. Changes in neurobehavioral symptoms, mood, sleep, and quality of life will also be assessed.

2.2 Background

2.2.1 Disease Background

TSC is a multi-system disorder of embryonal cortical development which can affect many organs through the overgrowth of benign tumors known as hamartomas. While the disease phenotype can be extremely variable, neurologic manifestations such as epilepsy can be seen in up to 90% of TSC patients (Krueger and Northrup, 2013). The condition is caused by inherited mutations in either the *TSC1* (hamartin) gene, located on chromosome 9q34, or the *TSC2* (tuberin) 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 TSC1 and TSC2 form a regulatory complex responsible for limiting the activity of mTORC1, an important intracellular regulator of growth and metabolism via its inhibition of the small GTPase Ras homolog enriched

in brain (Krueger and Northrup, 2013). Everolimus (Afinitor®), a mechanistic target of rapamycin complex 1 (mTORC1) inhibitor, has been shown to decrease seizures (Mizuguchi et al, 2019; French et al, 2016). More recently, CBD (Epidiolex®) demonstrated seizure reduction efficacy in a randomized controlled trial (Thiele et al, 2021).

TSC is one of the most common genetic causes of epilepsy, with seizure type and characteristics that vary by age (Jülich and Sahin, 2014). Infantile spasm (IS) is the most common seizure type presenting in infancy and represents the first manifestation of epilepsy in 50% of patients. In older children and adults, focal impaired awareness seizures (previously classified as complex partial seizures) are the most common (Chu-Shore, 2010); other focal and generalized seizures may also occur. Over 30% of patients develop treatment-refractory epilepsy (Jülich and Sahin, 2014). While seizures have typically been ascribed to cortical or subcortical tubers and subependymal nodules, epilepsy in TSC can be considered multifactorial in origin as seizures can originate in other brain areas or can occur in TSC participants without tubers (Jülich and Sahin, 2014).

2.2.2 Investigational Product Background: Ganaxolone

Ganaxolone (GNX) (3α-hydroxy-3β-methyl-5α-pregnan-20-one) is a small molecule under investigation for use as an ASM in rare pediatric seizure disorders and SE. GNX is a Schedule V Controlled Substance in the United States (US). The 50 mg/mL GNX oral suspension is approved in the US for the treatment of seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients 2 years of age and older. GNX is the 3β-methylated synthetic analog of allopregnanolone, an endogenous allosteric modulator of central nervous system (CNS) $GABA_A$ receptors. GNX has potency and efficacy comparable to allopregnanolone in activating synaptic and extra-synaptic $GABA_A$ receptors at a site distinct from benzodiazepines and barbiturates (Carter et al, 1997). GNX has protective activity in diverse rodent seizure models (Reddy and Rogwski, 2012; Bialer et al, 2010). Clinical studies have demonstrated that GNX has anticonvulsant activity with an acceptable safety and tolerability profile in the dose range of 900 to 1800 mg in adults and children (Sperling et al, 2017; Pieribone et al, 2007; Kerrigan et al, 2000; Laxer et al, 2000). Further, GNX reduces seizures in children with IS and refractory pediatric epilepsy. In an open-label (OL) study, pediatric participants 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). A total of 15 participants with a history of IS completed treatment; 5 of the 15 participants 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%. There was 1 participant who became spasm-free and 1 non responder (with a decrease of < 25%) was spasm-free from Weeks 2 to 7.

In addition to its anticonvulsant activity, GNX has been shown to reduce anxiety, hyperactivity, and attention in children with FXS (Ligsay et al, 2016). Similar behavior problems occur in individuals with TSC, with rates of approximately 50% for attention deficit/hyperactivity disorder and autistic spectrum disorder (Jülich and Sahin, 2014).

2.2.2.1 Ganaxolone Clinical Development Program

In the US, GNX, under the brand name ZTALMY®, is indicated for the treatment of seizures associated with CDKL5 deficiency disorder (CDD) in patients 2 years of age and older. GNX is a Schedule V controlled substance.

GNX is being further evaluated for use as an ASM in adolescents and adults with SE and pediatric and adult patients with seizures associated with TSC.

The completed GNX clinical program comprises Phase 1 studies conducted in healthy participants, adults with migraine, and adults with renal impairment. Phase 2/3 studies were conducted in adults with epilepsy, infants and children with seizure disorders, children with FXS, adults with PTSD, women with PPD, adults with migraine, adolescents, and adults with SE, and pediatric and adult participants with seizures associated with TSC. In these studies, the efficacy, safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of GNX were evaluated with an oral dosing duration ranging from 1 day up to more than 5 years, using doses from 50 to 3200 mg/day. Additionally, intravenous (IV) bolus doses ranging from 10 to 30 mg over durations of 2 to 5 minutes, continuous infusion of 10 to 30 mg/hour for 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 participants. In participants with SE, IV infusions of up to 713 mg/day have been evaluated.

As of 10 Oct 2022, an estimated 2172 participants have received at least 1 dose of GNX across the completed studies. This includes 511 participants in Phase 1 and 1661 participants in Phase 2/3 studies. Participants who received GNX ranged in age from 4 months to 88 years.

Formulations used to date in the clinical development program are summarized and listed by study in the Investigator's Brochure (IB).

2.2.2.1.1 TSC-related Epilepsy

In TSC-related epilepsy, Study 1042-TSC-2001 is a Phase 2, single arm study with GNX. The primary objective was to assess the preliminary safety and efficacy of GNX as adjunctive therapy for the treatment of seizures in participants aged 2 to 65 years with genetically or clinically confirmed TSC-related epilepsy. The core phase of the study (Part A) consisted of a 4-week baseline followed by a treatment phase, consisting of a 4-week titration and 8-week maintenance period. The primary efficacy endpoint was the percent reduction in countable, TSC-associated seizures from the baseline through the end of Period A treatment phase. Review of data for the primary endpoint showed a median 16.6% reduction in 28-day primary endpoint seizure frequency relative to the 4-week baseline period, with 30.4% of patients achieving a 50% or more seizure reduction. The CSR for the study was completed on 08 Mar 2023.

Additional information detailing ongoing and completed clinical GNX studies may be found in the current IB.

2.2.2.2 Clinical Safety Overview

In all completed placebo-controlled studies, 63.5% (742/1168) of participants who received GNX and 51.9% (443/853) of participants who received placebo experienced at least 1 treatment-emergent adverse event (TEAE). In these studies, the most frequently reported (ie, in > 5% of participants) TEAEs in GNX-treated participants were: somnolence (23.8% GNX, 7.7% placebo), dizziness (12.2% GNX, 3.5% placebo), fatigue (11.2% GNX, 4.8% placebo), and headache (6.3% GNX, 6.9% placebo). All these events, except headache, occurred more frequently in GNX-treated participants than placebo participants. CNS-related events appeared to be dose related, with the majority of these events occurring at doses ≥ 500 mg and were non-serious, mild to moderate in severity, and did not lead to discontinuation of treatment. These TEAEs were also anticipated based on the mechanism of action of GNX.

In all completed placebo-controlled studies, the incidence of serious adverse events (SAEs) was balanced between the GNX-treated participants (33/1168 participants, 2.8%) and placebo participants (26/853 participants, 3.0%), respectively. In these studies, the only SAEs reported in more than 1 participant in the GNX treatment group were seizure and sedation.

In all completed studies, including OL, long-term follow-up studies, 5.4% (118/2172 participants) of participants who received GNX experienced at least 1 SAE. With long-term exposure, no new safety findings were identified through the review of SAEs in these studies. The most frequently reported SAEs (ie, in > 2 participants) were seizure, SE, IS, epilepsy, pneumonia, pneumonia aspiration, pyrexia, seizure cluster, , dehydration, gastro-esophageal reflux disease, rash, somnolence, and upper respiratory tract infection. In all studies, most of the SAEs were considered unrelated to treatment according to the investigator, and most resolved.

The Phase 2 study (protocol 1042-TSC-2001) showed a consistent safety profile in a pure TSC population. Of the 24 patients screened, 4 discontinued the study due to adverse events (AEs). Somnolence, sedation, and fatigue were the most common treatment emergent AEs.

Additional information describing the safety of GNX may be found in the current IB.

2.3 Benefit/Risk Assessment

Based on clinical and non-clinical data from studies with GNX, the overall benefit/risk profile favors clinical development of GNX for the treatment of TSC-related epilepsy.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of GNX may be found in the IB.

2.3.1 Risk Assessment

CNS-related effects (such as somnolence and sedation) have been identified as an important risk related to the mechanism of action of GNX. In placebo-controlled studies the most common CNS effects were somnolence, dizziness, sedation, and gait disturbance. Of the AEs present at frequency > 1% and 2 times the frequency of placebo in the aggregate AE data, 12/13 AEs are related to CNS function. The most common CNS-related AEs that led to discontinuation reported in placebo-controlled studies were dizziness (GNX 1.1%; placebo 0.4%); somnolence (GNX 0.9%; placebo 0.4%); and fatigue (GNX 0.8%; placebo 0.1%). These CNS effects were typically non-serious, mild to moderate in severity, and did not lead to discontinuation of treatment.

Unblinded safety data will be reviewed on an ongoing basis by an independent Data Monitoring Committee (DMC) who will monitor safety and safeguard the interests of study participants.

The dose titration phase included in this study will minimize risk to participants from CNS-related effects as well as other treatment-related AEs.

The safety assessments to be performed in this study including clinical laboratory tests, vital signs, 12-lead electrocardiogram (ECG), physical and neurological examinations, AE assessments, Columbia-Suicide Severity Rating Scale (C-SSRS), and Tanner staging. These are all standard evaluations to ensure participant safety in this clinical study.

2.3.2 Benefit Assessment

This study will evaluate the efficacy of GNX compared to placebo as adjunctive therapy for seizures associated with TSC in children and adults. This population may benefit from the development of GNX as participants randomized to GNX will receive treatment that may help with control of their epilepsy. These participants as well as participants randomized to placebo have the option to continue GNX treatment in the Open-label extension (OLE) study for up to an additional 3 years.

2.3.3 Overall Benefit: Risk Conclusion

Taking into account the measures to minimize risk to study participants, the potential risks associated with GNX are justified by the anticipated benefits that may be afforded to participants with TSC-related epilepsy.

3 OBJECTIVES AND ENDPOINTS

Objectives
Primary Objective
• To assess the safety and efficacy of GNX compared to placebo as adjunctive therapy for seizures associated with TSC in children and adults as assessed by the change from baseline[a] in the frequency of countable major motor and focal seizures (primary endpoint seizures[b]) during the double-blind phase.
Secondary Objectives
• To determine the percentage of change from baseline[a] in 28-day primary endpoint seizure[b] frequency during the maintenance period. • To assess the change in focal seizure frequency from baseline[a] during the double-blind phase. • To assess changes in mood, behavior, and quality of life using the following: o ADAMS. o Peds-QL-FIM. o SF-36. o ELDQOL. • To assess overall clinical outcome using the CGI-I scores by the clinician and the parent(s)/caregiver(s)/LAR(s). • To evaluate the changes in seizure intensity and duration using the CGI-CSID.
Exploratory Objectives
[redacted]
Safety Objectives
• To assess the safety and tolerability of GNX compared with placebo as adjunctive therapy.
Endpoints
Primary Endpoint
• The primary efficacy endpoint is the percentage change from baseline[a] in 28-day primary endpoint seizure[b] frequency during the double-blind phase.
Secondary Endpoints
Key Secondary Efficacy Endpoints: • Percentage change from baseline[a] in 28-day primary endpoint seizure[b] frequency during the maintenance period (FDA). For EMA this is the primary endpoint. • Number (%) of participants considered treatment responders[c] during the double-blind phase (FDA). For the EMA, this endpoint will be evaluated over the maintenance period only.

- Number (%) of participants considered treatment responders[c] during the maintenance period.
- CGI-I at the last scheduled visit in the double-blind phase.

Secondary Efficacy Endpoints (Behavior/Neuropsychiatric/Quality of life):

- Change from baseline in ADAMS total score and sub-score.
- Change from baseline in quality-of-life scales: Peds-QL-FIM, SF-36, and ELDQOL.

Secondary Efficacy Endpoints (Seizure Control):

- Change from baseline[a] in the percentage of seizure-free days during the double-blind phase, based on primary endpoint seizure[b] type (FDA). For the EMA, this endpoint will be evaluated over the maintenance period only.
- Change from baseline[a] in the CGI-CSID at the end of the double-blind phase (FDA). For the EMA, this endpoint will be evaluated over the maintenance period only.
- Participants with a ≥ 25% and ≥ 75% reduction from baseline in primary endpoint seizure[b] frequency during the double-blind phase (FDA). For the EMA, this endpoint will be evaluated over the maintenance period only.
- Participants with a ≥ 25%, ≥ 50%, and ≥ 75% reduction from baseline[a] in primary endpoint seizure[b] frequency during the maintenance period.
- Responder analysis for primary endpoint seizures[b] and all seizures during the double-blind phase using the following response categories: ≤ 0%, > 0% to < 25%, ≥ 25% to < 50%, ≥ 50% to < 75%, and ≥ 75% to 100% (FDA). For the EMA, this endpoint will be evaluated over the maintenance period only.
- Percent change in 28-day frequency of all seizures.
- Change from baseline[a] in the percentage of seizure-free days, based on all seizure types.
- Change from baseline[a] in the longest seizure-free interval, based on primary endpoint seizure type[b] and all seizure types.

Exploratory Endpoints

[redacted]

Safety Endpoints
• Incidence and severity of AEs, SAEs, and withdrawals and dose-reductions due to AEs. • Other measures of safety including physical/neurological/developmental examinations, vital sign measurements (eg, blood pressure, heart rate, respiratory rate, and body temperature), 12-lead ECGs, clinical laboratory tests, and suicidal ideation and behavior risk monitoring.

The primary and secondary endpoints (unless otherwise defined) for the United States FDA will be based on the double-blind phase (titration and maintenance period). The primary and secondary endpoints (unless otherwise defined) for the EMA will be based on the maintenance period only.

ADAMS = Anxiety, Depression, and Mood Scale; AE = adverse event; CGI-CSID = Clinical Global Impression of Change in Seizure Intensity/Duration; CGI-I = Clinical Global Impression of Improvement; [redacted]ELDQOL = Epilepsy and Learning Disabilities Quality of Life; EMA = European Medicines Agency; FDA = Food and Drug Administration; GNX = ganaxolone; LAR = legally authorized representative; Peds-QL-FIM = Pediatric Quality of Life - Family Impact Module; PK = pharmacokinetic(s); SAE = serious adverse events; SF-36 = Short Form 36 (version 2); SQS = Sleep Quality Scale; TSC = Tuberous Sclerosis Complex.

a Baseline is defined as the first 28 days following screening.

b Primary endpoint seizure types are defined as the following: focal motor seizures without impairment of consciousness or awareness, focal seizures with impairment of consciousness or awareness with motor features, focal seizures evolving to bilateral, tonic-clonic convulsive seizures, and generalized motor seizures including tonic-clonic, bilateral tonic, bilateral clonic, or atonic/drop seizures. Seizures must have a motor component sufficiently prominent and distinct to clearly establish the observed symptoms as epileptic in origin. Seizures that do not count towards the primary endpoint include: focal or generalized nonmotor seizures (eg, absence seizures or focal nonmotor seizures with or without impairment of awareness), infantile or epileptic spasms, and myoclonic seizures.

c Treatment responders are defined as those participants with a $\geq$ 50% reduction from baseline in primary endpoint seizure frequency during the double-blind or maintenance phase.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 3, global, double-blind, randomized, placebo-controlled study of adjunctive GNX treatment in children and adults with TSC-related epilepsy. The study consists of a 4-week prospective baseline phase, defined as the first 28 days following screening, followed by a double-blind phase consisting of a 4-week titration period and a 12-week maintenance period.

Participants eligible for inclusion in this double-blind study must have inadequately controlled seizures after exposure to at least 2 ASMs administered at adequate doses and for adequate durations, with approximately 8 seizures per month in the 2 months prior to screening and seizure-free periods of not more than 1 week.

Procedures specific to this protocol and not otherwise considered standard of care, will not be performed until written informed consent from the participant or their parent(s)/LAR(s), as appropriate, has been appropriately obtained.

An interactive response technology system will be used to randomize participants, dispense drug, track treatment, and maintain the blind throughout the duration of the study.

Participants or their parent(s)/caregiver(s)/LAR(s) are expected to complete electronic seizure diary (eDiary) entries to document the number and type(s) of seizures daily throughout the study. A variety of clinician and caregiver administered instruments will be used to assess efficacy, and will include:

- Clinical Global Impression — Severity (CGI-S).
- Clinical Global Impression of Improvement (CGI-I) by parent(s)/caregiver(s)/LAR(s) and clinician.
- Caregiver Global Impression of Change in Seizure Intensity/Duration (CGI-CSID).
- [redacted]
- Anxiety, Depression, and Mood Scale (ADAMS).
- Pediatric Quality of Life – Family Impact Module (Peds-QL-FIM).
- Short Form 36 (SF-36).
- Epilepsy and Learning Disabilities Quality of Life (ELDQOL).

The titration schedule is as follows:

- Start – Day 1.
- Titration 1 – Day 7.
- Titration 2 – Day 14.
- Titration 3 – Day 21.
- Final titration – Day 28.
- Maintenance begins on Day 29 (Start of Week 5).

GNX (or matching volumes of placebo suspension) will be titrated at approximately weekly intervals over 4 weeks to a maximum dose based on the participant's starting weight 63 mg/kg/day with a maximum daily dose of 1800 mg (for patients > 28 kg).

The participant may have the dose of Investigational Product (IP) temporarily or permanently decreased at any point in the maintenance period to manage tolerability. Additional dosing information can be found in Section 6.2.

Any dose adjustments that are not part of the prespecified titration schedule, including alternative dosing paradigms, should be discussed with the sponsor medical monitor prior to making the change. If it is not possible to contact the medical monitor prior to the dose adjustment, the medical monitor should be notified as soon as possible after making the change.

The maximum dose for all participants is 1800 mg/day. The total double-blind phase (titration and maintenance periods) should not exceed 16 weeks.

Participants who discontinue the IP should undergo a 2-week taper period. The taper period may be shortened at the discretion of the investigator as clinically indicated. Participants who discontinue the IP before the scheduled completion of the study will return to the site 2 weeks after the end of taper to complete the safety follow-up assessments.

Following completion of the double-blind phase, participants who are compliant with study conduct will have the option to enroll and be treated with GNX in a separate open-label extension study (OLE), 1042-TSC-3002. All participants entering the OLE will have their dose of study medication adjusted in a double-blind cross-titration over 4 weeks such that all are receiving GNX at study completion. Participants who do not continue in the OLE will undergo a 2- to 4-weeks double-blind down-titration and taper if discontinuing IP (See Figure 1).

4.1.1 Study Duration for Participation

Eligible participants will collect 4 weeks of prospective baseline seizure data prior to starting treatment. Participants will be randomized (1:1) to double-blind treatment with GNX or placebo. GNX is to be titrated to target dose over 4 weeks. The total double-blind phase (titration and maintenance period) should not exceed 16 weeks.

Following completion of the treatment period, participants who are compliant with study conduct will have the option to enroll and be treated with GNX in a separate OLE study, 1042-TSC-3002. All participants entering the OLE will have their dose of study medication adjusted in a double-blind cross-titration over 4 weeks such that all are receiving GNX at study completion. Participants who do not continue in the OLE will undergo a 2- to 4-week double-blind down-titration and taper if discontinuing IP.

4.1.2 Number of Participants

Approximately 200 participants with TSC will be screened with the aim of randomizing approximately 128 participants (64 per arm), aged 1 to 65 years (2 – 65 for EU, MENA, and OC) (inclusive). Participants will be randomized (1:1) to either GNX or placebo as adjunctive therapy with their standard anti-seizure medication (ASMs).

Note: Enrolled means the participant, or their LAR(s), has agreed to participate in the study following completion of the informed consent process and screening. Potential participants who are screened for the purpose of determining eligibility for the study, but who subsequently are not eligible for study entry, are not considered enrolled, unless otherwise specified by the protocol.

4.1.3 Number of Sites

This global, multicenter study will be conducted at approximately 80-85 sites (US and ex-US).

4.2 Scientific Rationale for Study Design

This is a Phase 3, double-blind, randomized, placebo-controlled study of adjunctive GNX treatment in children and adults with TSC-related epilepsy. Children and adults with TSC-related epilepsy are included in the study as this is one of the populations being pursued for development. The eligibility criteria allow for the selection of participants comparable to the patients seen in clinical practice.

Randomization will be used in this study to avoid bias in the assignment of participants to treatment, to prevent introducing bias into the study evaluations and statistical analyses, and to ensure participant characteristics are balanced between the GNX and placebo arms. In order to facilitate subgroup analysis, randomization will be stratified with respect to whether the participant is taking concomitant CBD or not.

All the efficacy and safety assessments included in this study are standard measures used in clinical studies in general and epilepsy trials in particular.

4.3 Justification for Dose

A minimum GNX dose of 33 mg/kg/day or 900 mg/day is generally required for assessment of efficacy during the study. Clinical studies have demonstrated that GNX has anticonvulsant activity with an acceptable safety and tolerability profile in the dose range of 900 to 1800 mg in adults and children (Sperling et al, 2017; Pieribone et al, 2007; Kerrigan et al, 2000; Laxer et al, 2000).

Dosing will be based on doses that have been shown to be safe in children and adults in multiple studies with healthy volunteers and individuals with epilepsy.

GNX is to be given as an oral suspension (50 mg/mL) with food, eg, shortly after a meal or snack.

This study plans to enroll participants as young as 1 year of age. Based on the known clearance pathway of GNX (which is primarily CYP3A4/5) and CYP3A4 maturation by the age of 1 month, the dosing strategy for pediatric participants 1 to 2 years was guided by a recently completed population PK analysis which incorporated allometric principles. The similarity of model maximum plasma concentration (C_{max}) and the area under the plasma concentration-time curve (AUC) with the proposed dosing regimen across a range of doses administered in previous clinical trials in participants 2 years of age and older coupled with the known maturation of CYP3A4 indicates that a similar exposure will be achieved in participants 1 to 2 years of age with the proposed dosing regimen.

GNX (or matching volumes of placebo suspension) will be titrated at approximately weekly intervals over 4 weeks to a maximum dose based on the participant's starting weight 63 mg/kg/day with a maximum daily dose of 1800 mg (for patients > 28 kg).

In the Phase 2 data for GNX in TSC there was the suggestion of a possible interaction with CBD. In the trial of 23 treated patients, approximately half were on cannabidiol, and there was an association between higher CBD doses and increased somnolence. Given the small sample size, more definitive conclusions were not possible. As a result, patients taking concomitant CBD (Epidiolex®) must be monitored closely throughout this Phase 3 protocol and discussed with the medical monitor if AEs are seen (particularly those that are somnolence-related).

The maximum dose for all participants is 1800 mg/day. The total double-blind phase (titration and maintenance periods) should not exceed 16 weeks.

Additional dosing information can be found in Section 6.2.

4.4 End of Study Definition

End of Study (Individual Participant): A participant is considered to have completed the study if they have completed all study visits up to and including Week 20 (Table 1).

A participant is considered to have ended their participation when they either complete the study, or when they withdraw and complete the early termination visit.

End of Study (End of Trial): The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the Schedule of Activities (SOA; Table 1) for the last participant in the study globally.

5 STUDY POPULATION

Each participant and/or their parent(s)/LAR(s), as appropriate, must participate in the informed consent process and provide written informed consent or assent (see Section 10.1.3) before any procedures specified in the protocol are performed.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria are met:

1. Clinical or mutational diagnosis of TSC consistent with (Northrup et al, 2021):
   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 (eg, 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 principal investigator (PI) or designee must review the results of the [redacted] and confirm that the causal relationship to the epilepsy syndrome is likely.

OR

   b. Clinical diagnosis of definite TSC which includes 2 major features or 1 major feature with ≥ 2 minor features.

Major features	Minor features
Hypomelanotic macules (≥ 3, at least 5-mm diameter)	"Confetti" skin lesions
Angiofibroma (≥ 3) or fibrous cephalic plaque	Dental enamel pits (≥ 3)
Ungual fibromas (≥ 2)	Intraoral fibromas (≥ 2)
Shagreen patch	Retinal achromic patch
Multiple retinal hamartomas	Multiple renal cysts
Multiple cortical tubers and/or radial migration lines	Nonrenal hamartomas
Subependymal nodules (≥ 2)	Sclerotic bone lesions
Subependymal giant cell astrocytoma	
Cardiac rhabdomyoma	
Lymphangioleiomyomatosis (LAM)*	
Angiomyolipomas (≥ 2)*	

* A combination of the 2 major clinical features (LAM and angiomyolipomas) without other features does not meet criteria for a definite diagnosis.

The investigator must document which of the features (major or minor) fulfill the clinical diagnostic criteria.

2. Male or female participants aged 1 through 65 years, inclusive. For Europe (EU), Middle East and North Africa (MENA), and Oceania (OC) Male or Female participants aged 2 through 65 years, inclusive.
3. Participant/parent(s) or LAR(s) willing and able 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. If the participant is not qualified nor able to provide written informed consent based on age, developmental stage, intellectual capacity, or other factors, parent(s)/LAR(s) must provide consent for study participation, if appropriate.

4. Failure to control seizures despite appropriate trial of 2 or more ASMs at therapeutic doses and for adequate duration of treatment per PI judgment.
5. Participants should be on a stable regimen of ASMs (including moderate or strong inducer or inhibitor anti-seizure medications eg, carbamazepine, phenytoin, etc.) at therapeutic doses for ≥ 28 days prior to the screening visit, and without a foreseeable change in dosing for the duration of the study. (Note: Minor dose adjustment to address tolerability and safety events may be allowed on case-by-case basis and it should be discussed with the study medical monitor.)
6. A history of at least 8 countable seizures per month in the 2 months prior to screening with no more than 1 seizure free week in each month. This includes seizures of any kind.
7. Have at least 8 primary endpoint seizures in the first 28 days following the screening visit. The primary endpoint seizure types are defined as the following:
   a. Focal motor seizures without impairment of consciousness or awareness.
   b. Focal seizures with impairment of consciousness or awareness with motor features.
   c. Focal seizures evolving to bilateral, tonic-clonic seizures.
   d. Generalized motor seizures including tonic-clonic, bilateral tonic, bilateral clonic, or atonic/drop seizures.

   Seizures that **do not count** towards the primary endpoint include:
   a. Focal or generalized nonmotor seizures (eg, absence seizures or focal nonmotor seizures with or without impairment of awareness).
   b. Infantile or epileptic spasms.
   c. Myoclonic seizures.
8. Participants with surgically implanted vagal nerve stimulator (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 ≥ 6 months prior to the screening visit.
   b. The settings must have remained constant for 3 months prior to the screening visit and are expected to remain constant throughout the study.
   c. The battery is expected to last for the duration of the study.
9. Parent(s)/caregiver(s)/LAR(s) or the participant, as appropriate, is (are) willing and able to maintain an accurate and complete daily seizure eDiary for the duration of the study.
10. Willing and able to take IP (suspension) as directed with food (tid).
11. Women of childbearing potential (WOCBP) 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 and baseline visits. Childbearing potential is defined as a female who is biologically capable of becoming pregnant. Medically acceptable methods of birth control include intrauterine devices (that have been in place for at least 1 month prior to the screening visit), hormonal contraceptives (eg, combined oral contraceptives, patch, vaginal ring, injectables, and implants), and surgical sterilization (such as oophorectomy or tubal ligation). When used consistently and correctly, “double-barrier” methods of contraception can be used as an effective alternative to highly effective contraception methods (see Section 10.5.3 for “double-barrier” methods). Contraceptive

measures such as Plan B™, sold for emergency use after unprotected sex, are not acceptable methods for routine use

12. Male participants must agree to use highly effective contraceptive methods during the study and for 30 days after the last dose of IP. Highly effective methods of contraception include surgical sterilization (such as a vasectomy) and adequate "double-barrier" methods (see Section 10.5.3 for "double-barrier" methods).

Note: The Epilepsy Study Consortium will review and classify all seizure types reported by the investigator, incorporating the medical history, [redacted] seizure description, and historical records (including electroencephalogram [EEG], when available). This review and classification does not need to be completed prior to study entry but should be completed in parallel, and may complete after the participant has been enrolled in the study.

5.2 Exclusion Criteria

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

1. Previous exposure to GNX.
2. Pregnant or breastfeeding.
3. Participants who have been taking felbamate for less than 1 year prior to screening.
4. Participants taking CBD preparations other than Epidiolex®.
5. A positive result on drug screen for CBD or THC at Visit 1 (screening), with the exception of results that are fully explained by prescribed Epidiolex®, which can be adjusted by the investigator in the event of any AEs.
6. Concurrent use of adrenocorticotropic hormone (ACTH), prednisone or other glucocorticoid is not permitted, nor use of the strong inducers of cytochrome P450 3A4 (CYP3A4), rifampin and St. John's Wort.

   Participants on ACTH, prednisone, or other systemically (non-inhaled or topical) administered steroids should be off the product > 28 days prior to screening.

   Rifampin and St. John's Wort must be discontinued at least 28 days before Visit 2, study drug initiation.

   Note:

   a. Use of concomitant intranasal or pro re nata (PRN) topical steroids for dermatologic reactions and allergic rhinitis are allowed during the study.
   b. This exclusion criterion does not prohibit the use of approved ASMs.
7. Changes in any chronic medications within the 4 weeks prior to the screening visit. All chronic concomitant medications must be relatively stable in dose for at least 4 weeks prior to the screening visit unless otherwise noted. Small dose adjustment to manage tolerability and safety events is permitted and should be discussed with the study medical monitor.
8. Participants who have epilepsy surgery planned during the study or who have undergone surgery for epilepsy within the 6 months prior to screening.
9. An active CNS infection, demyelinating disease, degenerative neurological disease, or CNS disease deemed progressive as evaluated by brain magnetic resonance imaging (MRI). This

includes tumor growth which in the opinion of the investigator could affect primary endpoint seizure control.

10. Any disease or condition (medical or surgical; other than TSC) at the screening visit that might compromise the hematologic, cardiovascular (including any cardiac conduction defect), 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 participant at increased risk or interfere with the assessment of safety/efficacy. This may include any illness in the past 4 weeks which in the opinion of the investigator may affect seizure frequency.
11. Hepatic impairment sufficient to affect patient safety, or 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.
12. Biliary impairment sufficient to affect patient safety, or total bilirubin levels > 1.5 × ULN at screening or baseline visit and confirmed by a repeat test. In cases of Gilbert's Syndrome, resulting in stable levels of total bilirubin greater than ULN, the medical monitor can determine if a protocol exception can be made.
13. Renal impairment sufficient to affect patient safety, or estimated glomerular filtration rate (eGFR) < 30 mL/min (calculated using the Cockcroft-Gault formula or Pediatric glomerular filtration rate [GFR] calculator or Bedside Schwartz), will be excluded from study entry or will be discontinued if the criterion is met post baseline (Levey et al, 2006). Cases of temporary renal insufficiency should be discussed with the medical monitor to determine the participant's study continuation.
14. Exposed to any other investigational drug or investigational device within 30 days or fewer than 5 half-lives prior to the screening visit. For therapies in which half-life cannot be readily established, the Sponsor's medical monitor should be consulted.
15. Unwillingness to avoid excessive alcohol use throughout the study.
16. Have active suicidal plan/intent, active suicidal thoughts or a suicide attempt in the past 6 months.
17. Known sensitivity or allergy to any component in the IP(s), progesterone, or other related steroid compounds.
18. Participants deprived of their liberty by a judicial or administrative decision, or for psychiatric treatment, or participants admitted to a health or social services facility for purposes other than research.
19. Participants receiving traditional Chinese medicine therapies within the prior 28 days of the screening.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Participants are requested to take the IP tid with food , eg, shortly after a meal or snack.

In addition, participants should refrain from grapefruit or grapefruit juice, Seville oranges, starfruits¸ or excessive consumption of alcohol during the study.

During each visit when PK samples are collected, participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for approximately 24 hours before dosing until after collection of the PK sample such that these items are ingested the morning before the study visit and not consumed again until after the PK samples are collected.

5.3.2 Contraception Use and Donation of Sperm and Ova

WOCBP must be using a medically acceptable form of birth control and have a negative quantitative serum β-HCG test collected at the initial screening and baseline visits.

Pregnancy testing will be performed at all in-person visits for all WOCBP to monitor participant safety throughout the duration of participation in the trial.

WOCBP and male participants must be advised to use a medically acceptable, highly effective method of birth control throughout the study period and for 30 days after the last dose of IP.

Participants should not donate sperm or ova during the study and for 30 days after the last dose.

See Appendix 10.5 for further details on what constitutes a medically acceptable, highly effective method of birth control.

5.4 Screen Failures

A screen failure occurs when a participant for whom informed consent/assent has been obtained is not randomized into the study and does not receive IP, regardless of reason.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes date of informed consent/assent, screen failure date and details, demography, eligibility criteria, and any SAE.

Participant rescreening is allowed as agreed by the sponsor and the investigator unless there is a general concern for participant safety or an inability for the participant to become eligible (eg, GNX allergy, sensitivity, or exposure, non-TSC and/or other ineligible epilepsy, chronic prohibited medical condition, or treatment). Rescreened participants should be assigned a new participant number for every screening/rescreening event. The medical monitor should be contacted for subsequent rescreening.

6 STUDY INTERVENTION AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Refer to the Pharmacy Manual for more detailed information regarding the storage, preparation, destruction, and administration of each treatment.

6.1 Study Intervention(s) Administered

The IP for this study is GNX and the control drug is placebo (see Table 2).

Table 2. Study Intervention(s) Administered

<table>
<tr><td>Intervention Label</td><td colspan="2"></td></tr>
<tr><td>Intervention Name</td><td>GNX</td><td>Placebo</td></tr>
<tr><td>Intervention Description</td><td>GNX oral suspension, tid</td><td>Identical to GNX suspension, tid</td></tr>
<tr><td>Dose Formulation</td><td>Suspension in 4 fl oz bottles</td><td>Matched suspension in 4 fl oz bottles</td></tr>
<tr><td>Unit Dose Strength(s)</td><td>50 mg/mL suspension containing 110 mL GNX</td><td>Not applicable</td></tr>
<tr><td>Dosage Level(s)</td><td colspan="2">GNX (or matching volumes of placebo suspension) will be administered tid with food, eg, shortly after a meal or snack, and titrated at approximately weekly intervals over 4 weeks based on the participant’s starting weight. The titration will start on Day 1 and end on Day 28 (see table below), with maintenance beginning on Day 29 at the start of Week 5.
<table>
<tr><th colspan="4">28 kg (62 pounds) or less</th></tr>
<tr><th>Day</th><th>Per dose (mg/kg)</th><th>Per day (mg/kg)</th><th>% target (63 mg/kg/day)</th></tr>
<tr><td>1</td><td>2</td><td>6</td><td>10</td></tr>
<tr><td>7</td><td>4</td><td>12</td><td>19</td></tr>
<tr><td>14</td><td>8</td><td>24</td><td>38</td></tr>
<tr><td>21</td><td>14</td><td>42</td><td>67</td></tr>
<tr><td>28</td><td>21</td><td>63</td><td>100</td></tr>
<tr><th colspan="4">Greater than 28 kg (62 pounds)</th></tr>
<tr><th>Day</th><th>Per dose (mg)</th><th>Per day (mg)</th><th>% target (1800 mg/day)</th></tr>
<tr><td>1</td><td>50</td><td>150</td><td>8</td></tr>
<tr><td>7</td><td>100</td><td>300</td><td>17</td></tr>
<tr><td>14</td><td>200</td><td>600</td><td>33</td></tr>
<tr><td>21</td><td>400</td><td>1200</td><td>67</td></tr>
<tr><td>28</td><td>600</td><td>1800</td><td>100</td></tr>
</table>
See Section 6.2 for details of permitted dose modifications.</td></tr>
<tr><td>Route of Administration</td><td colspan="2">Oral</td></tr>
</table>

Use	ASM in TSC-related epilepsy	
IMP and NIMP/AxMP	GNX	Matched placebo
Sourcing	Provided centrally by the sponsor	
Packaging and Labeling	GNX is a Schedule V Controlled Substance in the US. The GNX (50 mg/mL) and placebo oral suspensions will be provided in HDPE bottles with a child-resistant closure. For GNX, each bottle contains 110 mL of GNX suspension, and these bottles should be stored at room temperature (20°C to 25°C [68°F to 77°F]; excursions permitted from 15°C to 30°C [59°F to 86°F]). This suspension is stable for at least 18 months at room temperature (20°C to 25°C [68°F to 77°F]; excursions permitted from 15°C to 30°C [59°F to 86°F]). After opening, suspension should be used within 30 days. A placebo suspension, identical in taste and appearance with GNX suspension, will be supplied at an equal volume. Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the sponsor. 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 to satisfy local or hospital requirements, but must not: • Contradict the clinical study label • Obscure the clinical study label • Identify the study participant by name, without consultation with the sponsor. Additional labels may not be added without the sponsor's prior full agreement.	

ASM = anti-seizure medication; GNX = ganaxolone; HPDE = high density polyethylene; IP = investigational product; tid = 3 times a day; US = United States.

6.2 Dose Modification

The protocol allows some alterations from the currently outlined dosing schedule.

GNX (or matching volumes of placebo suspension) will be titrated at approximately weekly intervals over 4 weeks to a maximum dose based on the participant's starting weight 63 mg/kg/day up to a maximum daily dose of 1800 mg (for participants > 28 kg). Any participant may have the dose of IP temporarily or permanently decreased at any point in the maintenance period to manage tolerability.

Adjustments to GNX titration or dose may be used to manage tolerability. The most common, dose-related, AEs in clinical experience to date, are somnolence, sedation, and lethargy. If a participant experiences one of these AEs during titration (or any other event which is, in the investigator's opinion dose-related), there are several potential approaches to GNX dosing to manage tolerability:

1. Maintain the dose of GNX to determine whether tolerability improves with additional time at the achieved dose.

2. Reduce the dose of GNX:

- Reduce the amount of GNX to the midpoint between the last well-tolerated dose and dose producing the adverse effect(s).
- If the intermediate dose is tolerated, after several days the participant may escalate to the dose that previously produced the adverse effect(s). If tolerability is acceptable, they may maintain at that dose or continue the titration as scheduled if not at the maximal daily dose (63 mg/kg/day or 1800 mg/day).
- If the participant does not tolerate the re-challenge with re-escalation of the dose, they may return to the highest dose that was previously well-tolerated. The investigator may maintain that dose or may attempt re-titration, based on their clinical judgment.

Any adjustment in dose should be discussed with the medical monitor in advance, if possible. Other modifications in dose or titration may be warranted based on the participant's clinical situation. Such adjustments may be instituted in consultation with the medical monitor.

If the dose is interrupted for more than 48 hours, then the investigator should speak with the medical monitor regarding whether and how to re-initiate the medication.

The maximum dose for all participants is 1800 mg/day. The total double-blind phase (titration and maintenance periods) should not exceed 16 weeks. In Part B, for participants who continue to the OLE, the total daily dose that the participant was taking at the completion of Part A will be maintained. The titration schedule in Table 2 will be followed until the target total daily dose for the participant is reached.

Participants who discontinue the IP should undergo a 2-week taper period. The taper period may be shortened at the discretion of the investigator as clinically indicated.

6.3 Preparation, Handling, Storage, and Accountability

6.3.1 Storage

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit and storage for all IP received and any discrepancies are reported and resolved before use of the IP.

The investigator has overall responsibility for ensuring that IP is stored in a secure, limited-access location in accordance with applicable requirements under the Controlled Substance Act and Drug Enforcement Administration regulations. 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. Details on how to store the IP can be found in the Pharmacy Manual.

All study drugs will be transported, received, stored, and handled strictly in accordance with the container, study drug label, instructions provided to the pharmacy and applicable regulations.

The IP must be stored in accordance with labeled storage conditions; the GNX oral suspension (50 mg/mL) should be stored at room temperature (20°C to 25°C [68°F to 77°F]; excursions permitted from 15°C to 30°C [59°F to 86°F]. 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 (ie, 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 participants 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.

6.3.2 Investigational Product Accountability

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study IP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Investigators will be provided with sufficient amounts of the IP to carry out this protocol for the agreed number of participants. 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 (eg, 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 participants included in this study following the procedures set out in the study protocol. Each participant will be given only the IP carrying his or her treatment assignment. All administered and/or dispensed IP will be documented on the electronic case report form (eCRFs) and/or other IP record. The investigator is responsible for ensuring the retrieval of all IP and study supplies from the participant.

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

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

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

At the end of the study, or as instructed by the sponsor, all unused stock, participant-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 product 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 contract research organization [CRO]). Shipment return forms, when used, will be signed prior to shipment from the site. Returned IP 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, participant-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 IP 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 IP delivered with those used and returned. All IPs must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.

Further guidance and information for the final disposition of unused study IP are provided in the Pharmacy Manual.

6.4 Measures to Minimize Bias

6.4.1 Randomization

Randomization procedures to minimize bias in this randomized, double-blind study are shown below.

6.4.1.1 Study using IWRS

All participants will be centrally assigned to randomized study intervention using an Interactive Web Response System (IWRS). Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site. An IWRS will be utilized for the following IP tasks:

- Randomization, stratified for current CBD use.
- Supply management.
- Inventory management and supply ordering.
- Expiration date tracking.
- Emergency unblinding.

An IWRS will centrally randomize participants. The randomization schedule (comprised of a kit list and randomization list) will be generated using standard, validated methods, and maintained by the respective supplier and IWRS vendor. The investigator will be instructed by the IWRS, which numbered bottle to use to dose a participant. The investigator and research staff will be aware of the ascending dose design of the clinical investigation; however, the investigator, the research staff, and the participants will be blinded with respect to who is receiving active drug versus placebo. The maximum placebo period is 18 weeks.

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

Study medication will be dispensed at the study visits as summarized in the SOA (Section 1.3).

Returned study medication should not be redispensed to the participants.

6.4.1.2 Participant Numbering

During the screening visit, each participant will be assigned a unique 6-digit participant number. The participant number will consist of a 3-digit clinical investigational site number assigned by the sponsor, followed by a 3-digit participant number (eg, 001) assigned by the electronic data

capture system. This participant number will also serve as the screening number. The unique 6-digit participant number will serve as the participant ID and be used to track the participant throughout the study.

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

6.4.2 Blinding

6.4.2.1 Blinded Investigational Product

This is a double-blind study in which study staff as well as study participant and caregiver(s) are blinded to study intervention. The contents of each bottle will be blinded using labels with unique bottle numbers.

Only the IP supplier and the sponsor's IP manager will be unblinded as to the contents of each bottle of IP.

6.4.2.2 Blind Break (IWRS)

The IWRS will be programmed with blind-breaking functionality. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination.

If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.

6.5 Study Intervention Compliance

When participants are dosed at the site, they will receive the IP directly from the investigator or designee, under medical supervision. The dose of the IP and study participant identification at this time will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When participants administer the IP at home, compliance with the IP will be assessed at each visit. Compliance will be assessed by inspecting the eDiary entries and returned supplies, with queries as necessary, during the site visits. Parent(s)/caregiver(s)/LAR(s) are to record daily seizure events in addition to study medication and non-study ASM administration in the eDiary device daily. Parent(s)/caregiver(s)/LAR(s) will be re-educated on the importance of adhering to daily seizure, IP and non-study ASM recording as needed. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of bottles of the IP dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and

stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the eCRF.

6.6 Concomitant Therapy

Concomitant medications refer to all treatment taken between the date of informed consent/assent and the date of the last dose of the IP.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives of the respective drug, if known (whichever is longer), before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Paracetamol/acetaminophen, at doses of ≤ 2 g/day, is permitted for use any time during the study. Other concomitant medication may be considered case-by-case by the investigator in consultation with the medical monitor.

Concomitant topical and intranasal steroids for dermatologic reactions and allergic rhinitis are allowed as needed and do not warrant exclusion from study. If the participant is currently taking an excluded medication at the time of the screening visit, then the participant must undergo a washout period equivalent to 5 half-lives of the drug before they may enter the prospective 4-week baseline phase.

Use of dietary supplements or herbal preparations are permitted if participant 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 5.2).

Concomitant treatment information must be recorded on the appropriate eCRF page. If the participant starts a new medication during the study, details of that medication including the dose and date and time of first administration, should be added to that participant's list of concomitant medications, and recorded in the eCRF as appropriate.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.1 Rescue Medicine

The use of rescue medication is allowable at any time during the study for prolonged, severe or repetitive seizures (seizure clusters). Rescue medication should be delayed for 1 hour following administration of IP unless it unsafe to wait due to the severity of the seizure(s).

Permitted rescue medications include:

- Alprazolam.
- Clobazam.
- Clonazepam.
- Diazepam.
- Lorazepam.
- Levetiracetam.
- Phenobarbital
- Midazolam.

Other rescue medications may be used if approved by the medical monitor.

Participants are expected to record rescue medications, dose levels, date, and time of administration on the eDiary. The medication name, dose, start and stop dates, and frequency of dosing will also be recorded in the clinical database.

The study site will not supply rescue medication that can be obtained locally.

6.6.2 Excluded Medications

Excluded medications include all steroid medications, other IPs, as well as ketoconazole, St. John's wort and Chinese medicine therapies.

Concurrent use of ACTH, prednisone or other glucocorticoid is not permitted, nor use of the strong inducers of CYP3A4 (except approved ASMs: carbamazepine, phenytoin derivatives, phenobarbital, or primidone), rifampin and St. John's Wort. Participants on ACTH, prednisone, or other systemically (non-inhaled or topical) administered steroids should be off the product > 28 days prior to screening. Rifampin and St John's Wort must be discontinued at least 28 days before Visit 2, study drug initiation. Chinese medicine therapies must be discontinued at least > 28 days prior to screening.

Note: Concomitant intranasal or PRN topical steroids for dermatologic reactions and allergic rhinitis are allowed.

Products containing THC or non-approved CBD are excluded during treatment. Tetrahydrocannabinol or non-approved CBD should be washed out for at least 4 weeks prior to screening. Participants with a positive result on THC or CBD laboratory tests, and who do not

have an explanatory Epidiolex®/Epidyolex® prescription, will be excluded or withdrawn from the study.

6.7 Intervention After the End of the Study

Participants may be eligible for continued treatment with GNX in an OLE. In the OLE, treatment can continue until the sponsor terminates the development of the IP in TSC or GNX has been approved and marketed in the participants' respective country.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If the IP is discontinued at any time, participants should follow the 2-week taper schedule unless otherwise medically indicated. If the participant discontinues during the maintenance period, evaluations listed for the Early Termination Visit (Visit 12; Table 1) are to be performed as completely as possible along with the end of study and safety follow-up assessment, as appropriate. Comments (spontaneous or elicited) or complaints made by the participant must be recorded in the source documents. The reason for termination, date of stopping the IP, and total amount of the IP taken must be recorded in the eCRF and source documents. Discontinuation of the IP due to AEs must also be reflected on the AE eCRF page. Participants who discontinue IP should undergo a 2-week or shorter taper period, as clinically indicated. These participants will have a visit 2 weeks after the end of taper to complete the safety follow-up assessments.

See the SOA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

The reason for early discontinuation of the IP must be determined by the investigator and recorded in the participant's source documents and on the eCRF. If a participant 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 (including pregnancy).
- Protocol violation/protocol deviation.
- Withdrawal by participant or parent(s)/LAR(s).
- Lost to follow-up.
- Lack of efficacy.
- Death.
- Investigator decision.

7.2 Discontinuation/Withdrawal From the Study

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

- Participant is found to have entered the study in violation of the protocol.
- Participant requires the use of a disallowed concomitant medication.
- Participant's condition changes after entering the clinical investigation so that the participant no longer meets the inclusion criteria or develops any of the exclusion criteria.
- Participant or parent(s)/LAR(s) withdraws consent or assent to participate in the study.
- Participant is noncompliant with the procedures set forth in the protocol.
- Participant experiences an AE/SAE that warrants withdrawal from the study.
- Any laboratory, medical, or clinical finding for which clinical intervention should take precedence over study participation. This includes:
  - AST/SGOT or ALT/SGPT > 3 × ULN.
  - Total bilirubin levels > 1.5 × ULN.
  - eGFR < 30 mL/min.
- It is the investigator's opinion that it is not in the participant'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 participant's discontinuation. Participants who discontinue the IP during the maintenance period will continue to record daily seizure frequency at minimum until the completion of the maintenance period.

At the time of discontinuing from the study, if possible, an Early Termination Visit (Visit 12) should be conducted as shown in the SOA (Section 1.3). At this visit, participants will start a 2-week taper and then return to the site 2 weeks later for safety follow-up assessments.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits without stating an intention to withdraw consent and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant. A minimum of 3 documented attempts must be made to contact any participant 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 participant'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 participant refuses or is unable to return to the site for the early termination and final safety follow-up visit, it should be documented in the eCRF.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled in Section 10.1.10.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SOA (see Section 1.3). Study dates will be based on the date of the first dose of IP and not the date of screening or baseline visits.

Study assessments can be conducted at the institution of the site investigator or remotely at the participant's home. All assessments can be conducted remotely with the use of telemedicine video tools; and for sites located outside of the European Union only, by providing traveling nurses to take vital signs, draw blood samples, and collect specimens.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SOA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the informed consent form (ICF) may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SOA.

Safety, laboratory, and analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded. Exceptions to this are if there is an urgent medical need (Section 6.4.2).

8.1 General Study Periods

8.1.1 Screening, Enrollment, Randomization, and Baseline

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

The process of identification of participants is performed by the investigator. If an investigator is seeing a patient with TSC in their clinic who is having 8 or more seizures per month, they will make a judgment regarding whether the benefits of clinical trial participation may outweigh the risks of clinical trial participation (with any alternative treatments taken into consideration). If the clinician feels that they do, then they will explain the study to the participant (or LAR). If the participant/LAR is fully informed and provides consent, then this will be documented, and the screening activities can begin.

Note for Investigational Sites in the United Kingdom (UK): National Health Services (NHS) sites in the UK will be aware of the study by virtue of the investigators participating in the site initiation visit, and being trained on the study design, conduct, and participant protection policies.

Informed consent/assent will be obtained after the study has been fully explained to the participant/parent(s)/LAR(s) and before the conduct of any screening procedures or assessments (see Section 10.1.3 for the informed consent procedure). This includes the collection of historical seizure frequency data, or if this information is not available from medical records, the participants will be asked to provide this information for the 8 weeks prior to the Screening Visit based on their own recall/records. This Screening Visit will occur 4 weeks before baseline (Week 0).

At screening, informed consent will be confirmed and the participants eligibility checked. Demographics and Medical history including prior treatment information (Section 8.1.1.1), historical seizure calendar review (Section 8.1.1.2), and a seizure identification and diagnostic review (Section 8.1.1.3) will be performed as well as other study specific procedures as outlined in the SOA (Table 1).

Randomization will occur approximately 4 weeks after screening at baseline and all participants will be centrally assigned to randomized study intervention (stratified for current CBD use) using an IWRS. Details are provided in Section 6.4.1.

8.1.1.1 Demographics and Medical History

Demographics including age, gender, ethnicity, and race will be collected, as allowed according to local regulations. 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 participant's developmental history will also be assessed. This will include the grade level of school work that the participant has completed (for individuals who are chronologically school age), as well as the investigator's estimate of the participant's developmental age. Prior medications include all treatment, including but not limited to herbal treatments, vitamins, surgical implants (such as VNS), and prescribed medications received within 30 days (or PK equivalent of 5 half-lives, whichever is longer) of the date prior to screening.

Demographics and Medical History will be reviewed and collected at the Visit 1 (screening). A review of the participant's Medical History will be performed again at Visit 2 (baseline). All findings on the medical history will be recorded on the eCRF. Prior treatment information (therapy name, start and stop date), if available, must be recorded on the appropriate eCRF page.

8.1.1.2 Historical Seizure Calendar Review

A 2-month (8-week) daily historical seizure calendar will be reviewed at the screening visit to determine eligibility per inclusion/exclusion criteria. Acceptable daily historical seizure calendars will need to denote seizure types (or sufficient description), frequency, and days that no seizures occurred.

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

8.1.1.3 Seizure Identification and Diagnostic Review

Per the inclusion criteria, enrollment into the study will be based on the presence and frequency of the primary endpoint seizure types.

Primary endpoint seizure types are defined as the following: focal motor seizures without impairment of consciousness or awareness, focal seizures with impairment of consciousness or awareness with motor features, focal seizures evolving to bilateral, tonic-clonic convulsive seizures, and generalized motor seizures including tonic-clonic, bilateral tonic, bilateral clonic, or atonic/drop seizures. Seizures must have a motor component sufficiently prominent and distinct to clearly establish the observed symptoms as epileptic in origin. Seizures that do not count towards the primary endpoint include: focal or generalized nonmotor seizures (eg, absence seizures or focal nonmotor seizures with or without impairment of awareness), infantile or epileptic spasms, and myoclonic seizures.

To standardize seizure identification and classification in the study, a SIF/DRF will be submitted and reviewed by the Epilepsy Study Consortium. The Epilepsy Study Consortium will review participant seizure data and assign the seizure type for each participant. This categorization of seizure type by the Epilepsy Study Consortium should not delay the participant's entry into the study as this will be determined by the investigator's assessment of eligibility.

Final confirmation and approval of a participant's seizure type is required prior to dispensing the IP.

Instructions for completion of the Seizure Identification and Diagnostic Review Form (SIF/DRF) can be found in the Investigator Site File.

8.1.2 Double-blind Phase

Double-blind treatment with the IP will begin after baseline assessment at Visit 2. All dates during the double-blind phase will be based off the date of randomization and the first dose of the IP. The double-blind phase will include a 4-week titration period (Day 1 to Day 28 inclusive), and a 12-week maintenance period starting on Day 29 to Visit 12 (Week 16).

Participants who discontinue the study prematurely before Visit 12 (Week 16) are required to taper their IP for 2 weeks or shorter, unless otherwise medically indicated. Participants should also complete the eDiary during this time. The end of study assessments, as detailed in the SOA Part A for Visit 13A (Table 1), should then be performed.

Participants who are not continuing in the OLE will then begin a double-blind taper period where the IP will be withdrawn from Visit 12 (Week 16) as shown in the SOA for Part A as shown in Table 1. This taper period will last for 2 weeks but may be shortened at the discretion of the investigator.

All participants entering the OLE will have their dose of study medication adjusted in a double-blind cross-titration over 4 weeks after Visit 12 (Week 16) as shown in Table 2. This will be performed under blinded conditions and participants previously treated with GNX will complete a dummy titration period.

8.1.3 Safety Follow-up

A safety follow-up visit will be conducted at Visit 13A (Week 20) after a 2- to 4-week down titration for participants who are not continuing in the OLE as shown in the SOA for Part A (Table 1). This will be the end of study visit for these participants.

For participants who plan to continue in the OLE, additional visits will be conducted as shown in in the SOA for Part B (Table 1).

8.2 Efficacy Assessments

Efficacy as determined by a reduction in seizures will be evaluated by collecting daily seizure type, duration, and frequency in a seizure eDiary. Days in which no seizures occur will also be noted. CGI-CSID and CGI-I, as well as changes in behavior and neuropsychiatric symptoms will be assessed by a variety of clinician and caregiver administered instruments.

Planned timepoints for all efficacy assessments are provided in the SOA (see Section 1.3).

8.2.1 Seizure Type and Frequency

The Epilepsy Study Consortium will review participant seizure data and assign the seizure type for each participant. This categorization of seizure type by the Epilepsy Study Consortium should not delay the participant's entry into the study as this will be determined by the investigator's assessment of eligibility.

Parent(s)/caregiver(s)/LAR(s) will record daily seizures denoting vernacular name for the seizure type, duration, and frequency in an eDiary.

Primary endpoint seizure types will be counted towards the primary endpoint. These are defined as the following:

- Focal motor seizures without impairment of consciousness or awareness.
- Focal seizures with impairment of consciousness or awareness with motor features.
- Focal seizures evolving to bilateral, tonic-clonic convulsive seizures.
- Generalized motor seizures including tonic-clonic, bilateral tonic, bilateral clonic, or atonic/drop seizures.

Seizures must have a motor component sufficiently prominent and distinct to clearly establish the observed symptoms as epileptic in origin.

Seizures that **do not count** towards the primary endpoint include:

- Focal or generalized nonmotor seizures (eg, absence seizures or focal nonmotor seizures with or without impairment of awareness).
- Infantile or epileptic spasms.
- Myoclonic seizures.

Note: Every seizure reported by the family will be fully described in the study outputs, and each description will include the vernacular name used by the participant or parent(s)/caregiver(s)/LAR(s), as appropriate, to refer to that seizure event as well as the medical seizure type as adjudicated by the Epilepsy Study Consortium. If the parent uses a medically incorrect term to refer to a specific seizure (such as calling a focal seizure with impaired

awareness "absence") it will be permitted as long as they use the term *consistently* for a single seizure type.

Participants or parent(s)/caregiver(s)/LAR(s) are to record administration of the IP and background ASMs in the eDiary. Compliance with the IP treatment will be assessed by inspecting the participants' eDiary and returned supplies with queries, as necessary.

8.2.2 Clinical Global Impression – Severity

The CGI-S is a 7-point Likert scale that will be completed by the clinician to rate the severity of illness in the participant at baseline, relative to other individuals with TSC. This should take into account overall seizure control, behavior, safety, tolerability of medications, and any involvement of non-neurological organ systems. The participant will be rated as follows: 1 – Normal, not at all a problem, 2 – Borderline problem, 3 – Mild problem, 4 – Moderate problem, 5 – Marked problem, 6 – Severe problem, 7 – Very severe problem (see Section 10.9).

CGI-S will be assessed at the baseline (Visit 2).

8.2.3 Clinical Global Impression – Improvement

The CGI-I is a 7-point Likert scale that the parent(s)/caregiver(s)/LAR(s) and clinician uses to rate the change in overall seizure control, behavior, safety, and tolerability after initiation of the IP relative to baseline (prior to treatment with the IP). The participant 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 (See Section 10.10).

CGI-I (parent[s]/caregiver[s]/LAR[s] and clinician) will be assessed at Visit 4 (Week 1), Visit 8 (Week 5), Visit 9 (Week 9), and Visit 12 (Week 16).

Participants who continue in the OLE will also have the CGI-I conducted at Visit 15 (Week 18) and Visit 17 (Week 20).

8.2.4 Caregiver Global Impression of Change in Seizure Intensity/Duration

The CGI-CSID is a 7-point Likert scale in which the parent(s)/caregiver(s)/LAR(s) assesses change in seizure intensity and/or duration after initiation of IP relative to baseline (prior to treatment with 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 (See Section 10.11).

CGI-CSID will be assessed at Visit 4 (Week 1), Visit 8 (Week 5), Visit 9 (Week 9), and Visit 12 (Week 16).

Participants who continue in the OLE will also have the CGI-CSID conducted at Visit 15 (Week 18) and Visit 17 (Week 20).

8.2.6 Anxiety, Depression, and Mood Scale

The ADAMS is a rating scale designed to screen for anxiety and depression in individuals with intellectual disability (Esbensen et al, 2003). The 28-question scale is filled out by the parent(s)/caregiver(s)/LAR(s) and is based on the participant's behavior. Each question will be rated on 4-point Likert scale as follows: 0- behavior has not occurred or is not a problem; 1- behavior occurs occasionally or is a mild problem; 2- behavior occurs quite often or is a moderate problem; and 3- behavior occurs a lot or is a severe problem (see Section 10.13).

The ADAMS will be conducted at Visit 2 (baseline), Visit 4 (Week 1), Visit 8 (Week 5), Visit 9 (Week 9), and Visit 12 (Week 16).

Participants who continue in the OLE will also have the ADAMS conducted at Visit 15 (Week 18) and Visit 17 (Week 20).

8.2.7 Pediatric Quality of Life Inventory - Family Impact Module

Peds-QL-FIM is designed to measure the impact of pediatric chronic health conditions on parents and the family. The Peds-QL-FIM measures parent self-reported physical, emotional, social, and cognitive functioning, communication, and worry. The module also measures parent-reported family daily activities and family relationships (see Section 10.14).

The Peds-QL-FIM will be conducted at Visit 2 (baseline), Visit 8 (Week 5), Visit 9 (Week 9), and Visit 12 (Week 16). Peds-QL-FIM for past 1 month will be conducted at baseline visit and Peds-QL-FIM for past 7 days will be conducted at on-study visits (see Section 10.14).

Participants who continue in the OLE will also have the Peds-QL-FIM conducted at Visit 15 (Week 18) and Visit 17 (Week 20).

8.2.8 Short Form 36

The SF-36 is a multi-purpose survey designed to capture participant or parent(s)/caregiver(s)/LAR(s) perceptions of own health and well-being. The SF-36 has 36 items grouped in 8 dimensions: physical functioning, physical and emotional limitations, social functioning, bodily pain, general, and mental health. Version 2 of SF-36 will be used for this study (see Section 10.15).

The SF-36 will be conducted at Visit 2 (baseline), Visit 4 (Week 1), Visit 8 (Week 5), Visit 9 (Week 9), and Visit 12 (Week 16).

Participants who continue in the OLE will also have the SF-36 conducted at Visit 15 (Week 18) and Visit 17 (Week 20).

8.2.9 Epilepsy and Learning Disabilities Quality of Life Scale

The ELDQOL is a 70-item parent/caregiver/LAR-reported measure that examines seizure severity, seizure related injury, ASM side effects, behavior, mood, physical status, cognitive and social functioning, communication, overall health and quality of life, and family concerns. The higher the score, the poorer the participant's quality of life, see Section 10.16.

The ELDQOL will be conducted at Visit 2 (baseline), Visit 4 (Week 1), Visit 8 (Week 5), Visit 9 (Week 9), and Visit 12 (Week 16).

Participants who continue in the OLE will also have the ELDQOL conducted at Visit 15 (Week 18) and Visit 17 (Week 20).

8.3 Safety Assessments

Planned timepoints for all safety assessments are provided in the SOA (Table 1).

8.3.1 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 participants 1 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.

The physical/neurological/developmental examinations will be conducted during Visit 1 (screening).

The physical/neurological/developmental follow-up examinations will be conducted during Visit 2 (baseline), Visit 4 (Week 1), Visit 8 (Week 5), Visit 9 (Week 9), and Visit 12 (Week 16).

Participants who continue in the OLE will also have the physical/neurological/developmental follow-up examinations conducted at Visit 17 (Week 20).

8.3.2 Vital Signs

Vital signs including heart rate (HR) (bpm), respiratory rate (RR [breaths/minute]), body temperature measured orally or on the skin, and blood pressure (BP) (mmHg) will be collected at every in-clinic visit.

BP and pulse measurements will be assessed in a sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.

BP and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

Vital signs will be measured in a sitting position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse, and RR. Three readings of blood pressure and pulse will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded.

Vital signs, body temperature, height and weight will be assessed during Visit 1 (screening), Visit 2 (baseline), Visit 4 (Week 1), Visit 8 (Week 5), Visit 9 (Week 9), and Visit 12 (Week 16).

Participants who do not continue in the OLE will have vital signs, body temperature, height and weight assessed at their end of study visit, Visit 13A, on Week 20.

Participants who continue in the OLE will also have vital signs, body temperature, height and weight assessed at Visit 15 (Week 18) and Visit 17 (Week 20).

Note: Length will be measured if height cannot be obtained.

8.3.3 Electrocardiograms

12-lead ECGs 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 participant is enrolled in the study.

12-lead ECGs will be obtained as outlined in the SOA (see Section 1.3) using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals.

12-lead ECGs will be performed at Visit 1 (screening), Visit 2 (baseline), Visit 4 (Week 1), and Visit 8 (Week 5), and Visit 12 (Week 16).

Participants who continue in the OLE will also have 12-lead ECGs conducted at Visit 15 (Week 18) and Visit 17 (Week 20).

8.3.4 Clinical Safety Laboratory Tests

Laboratory safety assessments will be collected to monitor participant safety. Clinical laboratory tests are listed in Section 10.2 and will be collected per the schedule listed in SOA (see Section 1.3). The laboratory reports must be filed with the source documents.

These clinical laboratory assessments will include complete blood count with automated differential, creatinine, blood urea nitrogen, and eGFR calculation (mL/min), comprehensive metabolic panel, as well serum pregnancy test for all WOCBP (at Visits 1 and 2 in the double-blind phase and Visit 17 for participants continuing in OLE). A central laboratory will be utilized by the sites.

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

- If AST (SGOT) or ALT (SGPT) increases > 3 times ULN during the study, participant should be followed with weekly laboratory repeat testing and continue in study if levels trending down. Participant will be discontinued if levels do not decline to under 3 × ULN.
- If total bilirubin increases to 1.5 × ULN or more during study, the participant will be discontinued.
- Participants with significant renal insufficiency, eGFR < 30 mL/min (calculated using the Cockcroft-Gault formula or pediatric GFR calculator or Bedside Schwartz), will be discontinued if the criterion is met post baseline.
- If any of the criteria above are deemed clinically significant by the investigator, then the sponsor's medical monitor should be contacted.
- If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
- If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or Common Terminology Criteria for Adverse Events [CTCAE] Grade 3 laboratory test), then the results must be recorded and discussed with the medical monitor.

Samples will be collected for clinical laboratory tests at Visit 1 (screening), Visit 2 (baseline), Visit 4 (Week 1), Visit 8 (Week 5), Visit 9 (Week 9), and Visit 12 (Week 16).

In addition, urinalysis will be conducted at Visit 1 (screening) or Visit 2 (baseline), Visit 4 (Week 1), and Visit 12 (Week 16) for all participants.

Participants who continue in the OLE will also have clinical laboratory tests and urinalysis conducted at Visit 17 (Week 20).

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 60 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples, which may increase the total volume drawn.

Note: For participants < 15 kg, the maximum blood volume taken during a single day or during a 4-week period may exceed recommendations; therefore, for all participants < 15 kg, the medical monitor should be consulted regarding which labs can be omitted. For all participants, regardless of weight, if additional labs are required, the medical monitor should be consulted to ensure that recommended blood volume limits are not unnecessarily exceeded.

8.3.5 Suicidal Ideation and Behavior Risk Monitoring (Columbia-Suicide Severity Rating Scale)

GNX is considered to be a CNS-active intervention. GNX is related to products with an increased risk of suicidal ideation or behavior. Participants with TSC may occasionally develop suicidal ideation or behavior.

Participants being treated with GNX should be monitored appropriately and observed closely for suicidal ideation and behavior (SIB) or any other unusual changes in behavior, especially at the beginning and end of the course of intervention, or at the time of dose changes, either increases or decreases. Participants who experience signs of SIB should undergo a risk assessment. All factors contributing to SIB should be evaluated and consideration should be given to discontinuation of the study intervention.

When informed consent or assent has been given, participants or parents/caregivers/LARs of participants being treated with GNX should be alerted about the need to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of SIB and to report such symptoms immediately to the study investigator.

C-SSRS will be used to rate the participant's degree of suicidal ideation on a scale ranging from "no suicidal ideation" to "active suicidal ideation with specific plan and intent" (Posner et al, 2011) (See Section 10.17). The C-SSRS will be assessed in all participants ≥ 11 years of age, if appropriate, otherwise, clinical judgment will be used.

If the participant has a positive result for C-SSRS, the medical monitor should be contacted within 24 hours and the medical monitor will determine if the individual should discontinue the trial.

The C-SSRS (baseline form) will be completed at Visit 2 (baseline), while the C-SSRS (since previous visit) will be completed at Visit 4 (Week 1), Visit 8 (Week 5), Visit 9 (Week 9), and Visit 12 (Week 16). Participants who do not continue in the OLE will have their final C-SSRS assessment at their end of study visit, Visit 13A, on Week 20.

Participants who continue in the OLE will also have the C-SSRS conducted at Visit 15 (Week 18) and Visit 17 (Week 20).

8.3.6 Concomitant Anti-epileptic Drug Levels

Concomitant ASM levels at Visit 1 (Screening), Visit 8 (end of titration), and Visit 12 (study completion) will be obtained centrally for the following if the participant is prescribed these medications:

- CBD.
- Clobazam (in which case clobazam and desmethylclobazam levels should be obtained).
- mTOR inhibitors (including everolimus, sirolimus, etc.).
- Valproate.

Participants who continue in the OLE will also have the above concomitant ASM levels collected at Visit 17 (Week 20).

If the ASM levels cannot be performed centrally local testing is permitted.

If the levels of any ASM co-administered with the IP are measured routinely per standard of care, this information will be recorded in the eCRF during the study.

Further details are provided in the SOA (Section 1.3).

8.3.7 Drug Screen

A plasma drug screen 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 test for CBD or THC will exclude the participant from the study, unless the result is fully explained by an Epidiolex® prescription, which is provided and managed by the investigator.

The plasma drug screen can be performed at any time during the study per the investigator's discretion. Concomitant use of THC and non-approved CBD is not permitted on study and will result in participant withdrawal from the study.

8.3.8 Pregnancy Testing

Pregnancy testing will be performed at all in-person visits for all WOCBP to monitor participant safety throughout the duration of participation in the trial.

Pregnancy tests are listed in Section 10.3 and will be collected per the schedule listed in SOA (see Section 10.3). Test results must be filed with the source documents.

A serum pregnancy test will occur at Visits 1 and 2. Participants who continue in the OLE will also have a serum pregnancy test at Visit 17. At Visits 4, 8, 9, 12, and 13A, the investigator may choose to do either a serum or urine pregnancy test.

8.3.9 Tanner Staging

The Tanner Staging (also known as the Tanner Scales) 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. Participants 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) for all participants. Participants who do not continue in the OLE will have Tanner staging at their end of study visit, Visit 13A, on Week 20.

Participants who continue in the OLE will also have Tanner staging conducted at Visit 17 (Week 20).

8.3.10 Investigational Product Pharmacokinetics

Please refer to Section 8.5 for additional details regarding PK assessments.

The results, date, and time of last ASM dose will be recorded in the eCRF.

8.4 Adverse Events and Serious Adverse Events

The definitions of unsolicited and solicited AEs and SAEs can be found in Section 10.4.

AEs will be reported by the participant (or, when appropriate, by parent[s]/caregiver[s]/LAR[s]).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs OR AEs that are serious, considered related to the study, or that caused the participant to discontinue the IP and the study (see Section 7).

The reference for safety information for this study is the GNX IB, which the sponsor has provided under separate cover to all investigators. For additional details, please consult the most current IB.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.4.

All initial and follow-up SAE reports must be reported by the investigator to Marinus' drug safety vendor 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 Marinus' drug safety vendor or its delegate.

8.4.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All AEs are collected from the time the informed consent/assent is signed until the defined follow-up period at the timepoints specified in the SOA (Section 10.3). 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 the IP will be considered TEAEs. 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 participant's health has returned to baseline status or all variables have returned to normal), regardless of whether the participant 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.

All SAEs (regardless of relationship to study) are collected from the time the participant/parent(s)/caregiver(s)/LAR(s) signs the informed consent/assent until the defined follow-up period stated and must be reported to Marinus' drug safety vendor 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' drug safety vendor within 24 hours of the first awareness of the event.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.4.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and non-serious AEs of special interest (as defined in Section 8.4.8) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.4.

8.4.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board/Independent Ethics Committee (IRB/IEC), and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.4.1 Suspected Unexpected Serious Adverse Reaction

A SUSAR is defined as an SAE that meets both the following criteria with respect to IP:

Suspected — is assessed as related to IP

Unexpected — compared to the IP-related AEs described in the IB, Reference Safety Information, the event meets any of the following criteria:

- The event has not been previously described.
- The event is now characterized as more severe.
- The event is now characterized more specifically (eg, an event of “interstitial nephritis” in a participant receiving an agent previously described as associated with “acute renal failure”).

In clinical trials involving ill participants, events considered related to the natural history of the disease under study or to lack of efficacy (that is, the event is considered more likely related to those factors than to other factors, including study drug) are not considered “unexpected”.

Requirements for Expedited and Periodic Reporting of Adverse Events:
SUSARs are required to be reported rapidly to regulatory authorities and to IRBs/IECs (within 7 days of initial notification for fatal or life-threatening SUSARs; within 15 days for all other SUSARs). Therefore, as with all SAEs, the site must report the event to the Marinus' drug safety vendor within 24 hours of being made aware of the event. The Sponsor and the Investigator will work together to meet these reporting requirements.

8.4.5 Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory, vital sign, 12-lead 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 double-blind treatment phase, there are abnormal clinical laboratory, vital sign, or 12-lead ECG values that were not present in the pretreatment findings observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease) is found for the abnormal values.

The investigator should decide, based on the above criteria and the clinical condition of a participant, whether a change in a clinical laboratory, vital sign, or the 12-lead ECG parameter is clinically significant and therefore, represents an AE.

8.4.6 Death Events

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

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

8.4.7 Disease-related Events and/or Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

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. This includes seizures

typical for that participant unless the seizures are changed in character, frequency, or duration. Significant worsening of the symptoms should be recorded as an AE.

The following disease-related events are common in participants with epilepsy and can be serious/life threatening:

- Seizures.
- SE.
- Falls/trauma/accidents.

As these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of an SAE. These events will be recorded within 5 business days of when they are reported to the site. These disease-related events will be monitored by the DMC on a routine basis. See Section 10.1.6.

Note: However, if either of the following conditions applies, then the event must be recorded and reported as an AE/SAE (instead of a disease-related event):

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant, or
- The investigator considers that there is a reasonable possibility that the event was related to study intervention.

8.4.8 Adverse Events of Special Interest

An adverse events of special interest (AESI) includes any non-serious condition that falls under the system organ class (SOC) of 'Breast and Reproductive disorders'. These AESIs will be submitted to Marinus' drug safety vendor using the study specific AESI reporting form.

8.4.9 Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants are to be reported from the time informed consent is signed until the defined follow-up period.

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

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

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported as outlined in Section 10.4 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.

Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. While the investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE to Marinus' drug safety vendor or delegate as outlined in Section 10.4 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.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study.

8.4.10 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error should not be reported per the SAE reporting procedure. Only a resulting AE, if it occurs, should be reported according to the procedures as described in Section 10.4. All IP provided to pediatric participants should be supervised by the parent(s)/caregiver(s)/LAR(s).

The definitions below are not mutually exclusive; an event can meet more than 1 category.

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

8.5 Treatment of Overdose

For this study, any dose of GNX greater than up to 63 mg/kg/day or over the maximum of 1800 mg/day within a 24-hour time period will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose, but participants should be closely monitored and receive supportive care.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and provide any appropriate supportive medical management.
- Obtain a plasma sample for PK analysis within 1 day from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

8.6 Pharmacokinetics and Pharmacodynamics

[redacted]

8.6.2 Pharmacodynamics

PD parameters are not evaluated in this study.

[redacted]

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

8.10 Health Economics

Health economics are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

The statistical analysis plan (SAP) will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

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

9.1 Statistical Hypotheses

Hypothesis testing will be performed for the primary endpoint: the percentage change in 28-day primary endpoint seizure frequency during the double-blind phase relative to the baseline, based on the primary endpoint seizure types. Summary statistics including confidence intervals for the treatment differences will be used to summarize the results. The hypothesis testing is:

$$H_o: \theta_{PBO} = \theta_{GNX} \qquad H_a: \theta_{PBO} \neq \theta_{GNX}$$

where θ_{GNX} is the percentage change of seizure frequency relative to the baseline for participants who treated with GNX and θ_{PBO} is similarly defined for participants receiving placebo.

9.1.1 Multiplicity Adjustment

All endpoints will be assessed descriptively, by the treatment to which the participants are randomized, with point estimates and 95% confidence intervals. The primary and secondary endpoints will be assessed in an inferential manner. Multiplicity control will be used for the primary and secondary endpoints. A gate keeping approach will be used to control the study wide Type-I error rate. There is a single primary efficacy endpoint, and formal hypothesis testing will be performed for this endpoint first. If the null hypothesis is rejected for the primary efficacy endpoint at the 2-sided α-level allocated to the final analysis of the primary endpoint, then statistical hypothesis testing will be performed on the 4 key secondary endpoints. The testing will stop if the result is non-statistically significant. All other non-key secondary and [redacted]

9.2 Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Intent-to-treat (ITT) set	All randomized participants. Participants will be summarized within the treatment group to which they were randomized. This population will be used for efficacy analyses.
Modified Intent-to-treat (mITT) set	All randomized participants who receive at least 1 dose of the IP. Participants will be summarized within the treatment group to which they were randomized. This population will be used for sensitivity analysis for efficacy.
Per-protocol (PP) set	All participants in the ITT analysis set participants who received IP for at least 6 weeks, provided at least 5 weeks of post-baseline seizure data, and without major protocol deviations that affect the efficacy endpoints (defined prior to database lock).
Safety analysis set	All randomized participants who receive at least 1 dose of the IP. Participants will be summarized within the treatment group for which they actually received treatment. This population will be used for the safety analyses.

IP = investigational product.

The Intent-to-treat (ITT) analysis set is used to analyze endpoints related to the efficacy objectives and the safety analysis set is used to analyze the endpoints and assessments related to safety. The primary analysis will be performed within the ITT population; a supportive analysis in the per-protocol (PP) and modified intent-to-treat (mITT) population will also be conducted.

9.3 Statistical Analyses

9.3.1 General Considerations

The results of the primary, secondary, and exploratory endpoints will be summarized separately. The results will be summarized by the treatment to which the participants were randomized. Participant demographics, characteristics, and medical history at randomization will be summarized using descriptive statistics.

The primary and secondary endpoints (unless otherwise defined) for the Food and Drug Administration (FDA) will be based on the double-blind phase (titration and maintenance period).

The primary and secondary endpoints (unless otherwise defined) for the European Medicines Agency (EMA) will be based on the maintenance period only.

9.3.2 Primary Endpoint(s)

The primary efficacy endpoint is the percentage change from baseline in 28-day primary endpoint seizure frequency during the double-blind phase (FDA). For the EMA, this endpoint will be evaluated over the maintenance period only.

Primary endpoint seizure types are defined as the following:

- Focal motor seizures without impairment of consciousness or awareness
- Focal seizures with impairment of consciousness or awareness with motor features
- Focal seizures evolving to bilateral, tonic-clonic convulsive seizures
- Generalized motor seizures including tonic-clonic, bilateral tonic, bilateral clonic, or atonic/drop seizures.

Seizures that do not count towards the primary endpoint include:

- Focal or generalized nonmotor seizures (eg, absence seizures or focal nonmotor seizures with or without impairment of awareness)
- Infantile or epileptic spasms
- Myoclonic seizures.

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

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

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

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

9.3.2.1 Sensitivity Analysis

There are 5 sensitivity analyses of the primary efficacy endpoint planned and these will be performed as outlined in the SAP:

- For the first sensitivity analysis, intermittent (random/sporadic) missing data during the double-blind phase and any missing data during the baseline phase will be assumed missing completely at random and the collected data will be used to calculate the 28-day seizure frequencies.
- The second sensitivity analysis is to explore the possibility that participants who stop recording their seizure counts tend to have higher counts than the other participants.
- The third sensitivity analysis will be performed on participants who achieved their maintenance dose at the start of the maintenance period. This analysis will exclude those participants who are still titrated continuously during maintenance period.
- The fourth sensitivity analysis will be performed for the primary outcome measure by using the mITT population.
- The fifth sensitivity analysis will be performed for the primary outcome measure by excluding all intercurrent events.

9.3.3 Secondary Endpoint(s) Analysis

All secondary and [redacted] will compare GNX and placebo at the end of the double-blind phase and maintenance period relative to the 4-week prospective baseline phase. The primary analyses of all secondary and [redacted] will be performed on the ITT population. All the endpoints will be included in data listings.

The key secondary endpoints are:

- Percentage change from baseline in 28-day primary endpoint seizure frequency during the maintenance period (FDA). For the EMA this is the primary endpoint.
- Number (%) of participants considered treatment responders during the double-blind phase (FDA). For the EMA, this endpoint will be evaluated over the maintenance period only. Treatment responders are defined as those participants with ≥ 50% reduction from baseline in primary endpoint seizure frequency during given period.
- Number (%) of participants considered treatment responders during the maintenance period. Treatment responders are defined as those participants with ≥ 50% reduction from baseline in primary endpoint seizure frequency during a given period.
- CGI-I at the last scheduled visit in the double-blind phase.

9.3.3.1 Secondary Efficacy: Behavioral/Neuropsychiatric/Quality of Life

Secondary efficacy endpoints in behavior, neuropsychiatric, and quality of life domains are:

- Change from baseline in ADAMS total score and sub-score.
- Change from baseline in quality-of-life scales: SF-36, Peds-QL-FIM, and ELDQOL.

9.3.3.2 Secondary Efficacy: Seizure Control

Secondary efficacy endpoints in seizure control are:

- Change from baseline in the percentage of seizure-free days during the double-blind phase, based on primary endpoint seizure types (FDA). For the EMA, this endpoint will be evaluated over the maintenance period only.
- Change from baseline in the CGI-CSID at the end of the double-blind phase (FDA). For the EMA, this endpoint will be evaluated over the maintenance period only.
- Participants with a ≥ 25% and ≥ 75% reduction from baseline in primary endpoint seizure frequency during the double-blind phase (FDA). For the EMA, this endpoint will be evaluated over the maintenance period only.
- Participants with a ≥ 25%, ≥ 50%, and ≥ 75% reduction from baseline in primary endpoint seizure frequency during the maintenance period.
- Responder analysis for primary endpoint seizures and all seizures during the double-blind phase using the following response categories: ≤ 0%, > 0% to < 25%, ≥ 25% to < 50%, ≥ 50% to < 75%, and ≥ 75% to 100% (FDA). For the EMA, this endpoint will be evaluated over the maintenance period only.
- Percent change in 28-day frequency of all seizures.
- Change from baseline in the percentage of seizure-free days, based on all seizure types.
- Change from baseline in the longest seizure-free interval, based on primary endpoint seizure types and all seizure types.

9.3.4 Exploratory Endpoint(s) Analysis

9.3.6 Safety Analyses

All safety analyses will be performed in the Safety Population. The results will be summarized by the treatment received.

The number and percentage of days that participants received IP, the highest percentage of the maximum allowable daily dose (63 mg/kg or 1800 mg) that participants received, and the total amount of IP received will be summarized.

A participant data listing will be provided with full details of the IP dispensation.

Safety assessments include:

- AEs.
- Clinical laboratory tests.
- Vital signs including BP, HR, RR, body temperature, height, and weight.
- 12-lead ECG.
- Physical, neurological, and developmental examinations.
- Concomitant ASM levels (if collected as part of standard of care by the study site).
- C-SSRS.

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

9.3.7 Subgroup Analyses

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

- Gender (Female vs Male).
- Age groups (12 months to 23 months; 2 to 11 years; 12 to 17 years; 18 to 64 years; and 65 years).

9.4 Sample Size Determination

Approximately 200 participants with TSC will be screened with the aim of randomizing approximately 128 participants into 2 treatment groups in a 1:1 ratio.

Testing of treatment effect (the actual analysis will use a Wilcoxon rank-sum test, which has approximately the same power as the Analysis of Variance [ANOVA]) for GNX vs placebo will be performed using a 5% 2-sided alpha level. A total of 64 participants per group provides at least 90% power for the primary endpoint assuming an estimate of the treatment effect difference that is at least 25% and a common standard deviation of 43% or less.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines.
- Applicable ICH GCP guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

10.1.2 Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed Consent Process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant/parent(s)/caregiver(s)/LAR(s) and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants/parent(s)/LAR(s) will be required to sign a statement of informed consent/assent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants/parent(s)/LAR(s) must be reconsented to the most current version of the ICF(s) during their participation in the study.

Minor participants must be re-consented if they reach the age of majority during the course of the study, in order to continue participating. A copy of the ICF(s) must be provided to the participant/parent(s) or LAR(s).

If a participant is rescreened, that participant/parent(s)/LAR(s) is required to sign a new ICF.

10.1.4 Data Collection

During each participant's visit to the clinic, a clinician participating in the trial will record progress notes to document all significant observations. At a minimum, these notes will contain:

- Documentation of the informed consent process, including any revisions.
- The date of the visit and the corresponding visit or day in the trial schedule.
- General participant status remarks, including any significant medical findings. The severity, frequency, duration, action taken, and outcome of any AEs and the investigators assessment of relationship to the IP must also be recorded.
- Any changes in concomitant mediations and dosages.
- A general reference to the procedures completed.
- The signature (or initials or other unique identifier) and date of each clinician (or designee) who made an entry in the progress notes.

In addition, any contact with the participant/parent(s)/caregiver(s)/LAR(s) via telephone or other means that provides significant clinical information also will be documented in the progress notes as described above. Any changes to information in the trial progress notes and other source documents will be initialed and dated on the day the change is made by a site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original data), and clearly entering the correct data (eg, ~~wrong~~

~~data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the clinician.

Information from the trial progress notes and other source documents will be data entered by investigative site personnel directly onto eCRFs in the sponsors electronic data capture system.

10.1.5 Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant/parent(s)/LAR(s) must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant/parent(s)/LAR(s) must be informed that the participant's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.6 Data Monitoring Committee Structure and Function

The DMC will review emerging study data on a periodic basis. The DMC is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the sponsor regarding the stopping of a study for safety concerns. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.

The mission of the DMC will be to safeguard the interests of study participants and to enhance the integrity and credibility of the trial. To enable the DMC to achieve their mission, the DMC will have periodic access to unblinded safety data and data regarding quality of trial conduct and will ensure the confidentiality of these data will be preserved. A DMC Charter will provide the principles and guidelines for the DMC process.

10.1.7 Dissemination of Clinical Study Data

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by local laws and regulations.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the case report form (CRF).

Guidance on completion of CRFs will be provided in the eCRF Completion Guidelines.

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 participant is screened, it is expected that site personnel will complete the eCRF entry within approximately 7 business days of the participant's visit.

The participant's parent(s)/caregiver(s)/LAR(s) must enter the information required by the protocol in the diary. A study monitor will review all seizure eDiary entries in accordance with the monitoring plan for completeness and accuracy. Discrepancies will be addressed by the participants' parent(s)/caregiver(s)/LAR(s) and qualified site personnel. When a data discrepancy warrants correction, the correction will be made by the participant's parent(s)/caregiver(s)/LAR(s) 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 participant's parent(s)/LAR(s) signs informed consent/assent, it is expected that all diary entries will be made daily and no longer than 48 hours after each day.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Quality tolerance limit(s) (QTL[s]) will be predefined in the IB to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).

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.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for a minimum of 2 years after the Sponsor's receipt of final approval of a marketing application for the drug; or, if an application is not approved for the drug, until 2 years after the shipment and delivery of the drug for investigational use is discontinued and the FDA has been notified. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

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

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.10 Study and Site Start and Closure

10.1.10.1 First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open (activated for enrollment) and will be the study start date.

10.1.10.2 Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. The decision to terminate a study may be for administrative or safety reasons. A decision to terminate for safety reasons may be driven by any data collected on the IP which negatively influences the risk/benefit assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development.

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator. Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.11 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.12 Sample Storage and Destruction

Any blood including PK samples collected according to the SOA (Section 10.3) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study participants. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

Samples can be retained for up to 1 year after the final study closure (defined as final CSR).

Since the evaluations are not expected to benefit the participant directly or to alter the treatment course, the results of pharmacogenetic, or other exploratory studies are not placed in the participant's medical record and are not to be made available to the participant, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The participant retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the participant, the investigator is to provide the sponsor with the required study and participant number so that any remaining (sample types [eg, blood, tumor]) samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by the sponsor.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the participant through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The participant has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. (See Section 10.1.4 for participant confidentiality).

10.2 Appendix 2: Emergency Contact Information

10.2.1 Serious Adverse Event Reporting

In the event of SAE, the investigator must notify the sponsor by email or fax the Marinus Clinical Study Serious Adverse Event Form within 24 hours to Marinus' [redacted] at:

- Email: [redacted]
- Fax: [redacted]

10.2.2 Sponsor Contacts

10.2.2.1 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 the back-up medical monitor:

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

10.2.2.2 Sponsor Project Managers

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

10.3 Appendix 3: Safety Laboratory Tests

The tests detailed in Table 3 will be performed by the central laboratory.

- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 3. Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters
Hematology	• Hemoglobin • Hematocrit • Erythrocytes • Leukocytes + differential • Thrombocytes (platelet count)
Clinical chemistry	• BUN • Potassium • AST/SGOT • Total bilirubin • Creatinine • Sodium • ALT/SGPT • Total protein • Fasting blood glucose • Calcium • Alkaline phosphatase • CO_2 • eGFR • Chloride
Routine urinalysis	• Specific gravity, color, clarity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)
Pregnancy testing	• Quantitative serum β-HCG serum or urine pregnancy test
ASM drug levels	• CBD, clobazam (including clobazam and desmethylclobazam), mTOR inhibitors (eg, everolimus, sirolimus, etc.), valproate
Other tests	• Drug screen[a] • Follicle-stimulating hormone and estradiol (as needed in women of nonchildbearing potential only) • Vital signs (BP, HR, RR, and body temperature) • 12-lead ECG

ALT = alanine aminotransferase; ASM = anti-seizure medication; AST = aspartate aminotransferase; β-HCG = β-human chorionic growth hormone; BP = blood pressure; BUN = blood urea nitrogen; CBD = cannabinol; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HR = heart rate; mTOR = mechanistic mammalian target of rapamycin; RR = respiratory rate; SGPT = serum glutamic pyruvic transaminase; SGOT = serum glutamic oxaloacetic transaminase; THC = tetrahydrocannabinol.

a A plasma (or urine, if plasma is difficult or impossible to obtain) drug screen will be performed to test for THC and non-approved CBD.

10.4 Appendix 4: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical investigation participant 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 Guidance E2A March 1995).
Definition of Unsolicited and Solicited AE
• An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant/participant's parent(s)/caregiver(s)/LAR(s) after signing the informed consent. Unsolicited AEs include serious and nonserious AEs. • Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participants/participant's parent(s)/caregiver(s)/LAR(s) will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant/participant's parent(s)/caregiver/LAR)(s) concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records. • Unsolicited AEs that are not medically attended nor perceived as a concern by the participant/participant's parent(s)/caregiver(s)/LAR(s) will be collected during an interview with the participant/participant's parent(s)/caregiver/LAR(s) and by review of available medical records at the next visit. • Solicited AEs are predefined local and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, 12-lead ECGs, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE. Lack of efficacy or failure of expected pharmacological action also constitutes an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.4.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
a. Results in death
b. Is life threatening The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is a suspected transmission of any infectious agent via an authorized medicinal product
g. Other situations: • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. o Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

10.4.3 Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- The monitoring period for AEs begins at the time that informed consent is obtained.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to IRB/IEC in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by IRB/IEC. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to IRB/IEC.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- Every reasonable effect will be made to follow up with participants who have AEs. Any participant who has an ongoing AE at the last study visit will be followed up, where possible, until resolution, or until the unresolved AE is judged by the investigator (or designee) to have stabilized. This will be completed at the investigator's discretion.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
- The investigator will make a determination of the relationship of the AE to the study intervention using a 2-category system according to the following guidelines:
  - Not Related: The AE is definitely or most likely caused by the participant's clinical state or the study procedure/conditions.
  - Related: The AE follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to IRB/IEC. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to IRB/IEC.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by IRB/IEC to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide IRB/IEC with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally submitted documents. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.4.4 Reporting of SAEs

SAE Reporting to IRB/IEC via Paper Data Collection Tool
• Facsimile or email transmission of the SAE paper data collection tool are the preferred methods to transmit this information to the Pharmacovigilance Team/Vendor. • In rare circumstances and in the absence of available equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting timeframes. • Contacts for SAE reporting can be found in Section 10.2 and the Study Operations Binder

10.5 Appendix 5: Contraceptive and Barrier Guidance

10.5.1 Female Contraception

WOCBP must be using a medically acceptable form of birth control and have a negative quantitative serum β-HCG test collected at the initial screening visit and baseline visits. WOCBP must be advised to use medically acceptable birth control throughout the study period and for 30 days after the last dose of IP. These include intrauterine devices (that have been in place for at least 1 month prior to the screening visit), hormonal contraceptives (eg, combined oral contraceptives, patch, vaginal ring, injectables, and implants), and surgical sterilization (such as oophorectomy or tubal ligation). When used consistently and correctly, "double barrier" methods of contraception can be used as an effective alternative to highly effective contraception methods (see Section 10.5.3 for "double-barrier methods). Contraceptive measures such as Plan B™, sold for emergency use after unprotected sex, are not acceptable methods for routine use.

10.5.2 Male Contraception

Male participants must agree to use highly effective contraceptive methods during the study and for 30 days after the last dose of IP. Highly effective methods of contraception include surgical sterilization (such as a vasectomy) and adequate "double-barrier" methods as described in Section 10.5.3. Male participants should not donate sperm during the study and for 30 days after the last dose of IP.

10.5.3 Acceptable Barrier Methods of Contraception

"Double-barrier" methods of contraception include male condom with diaphragm, or male condom with cervical cap.

10.7 Appendix 7: Country-specific Requirements

All local laws and regulatory requirements will be complied with during this study.

10.8 Appendix 8: Dosing Instructions for Oral Suspension

GANAXOLONE 1042-TSC-3001 STUDY
DOSING INSTRUCTIONSFOR ORAL SUSPENSION

PART A DOSING INSTRUCTIONS FOR ORAL SUSPENSION (DOUBLE-BLIND DOSE TITRATION, MAINTENANCE, AND TAPER)

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

Participant ID and initials: _____

Next Appointment: _____

Study Doctor (PI): _____

PI Telephone Number: _____

These are your study drug dosing instructions from now until your next visit.

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

Weight: _____ (in kgs).

Start Date	**DOSE (mL)** ***3 times/day***

PART B DOSING INSTRUCTIONS FOR ORAL SUSPENSION (DOUBLE-BLIND CROSSOVER TO OPEN-LABEL EXTENSION)

Crossover to Open-Label Extension

Participant ID and initials: _____

Next Appointment: _____

Study Doctor (PI): _____

PI Telephone Number: _____

These are your study drug dosing instructions from now until your next visit.

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

Weight: _____ (in kgs).

Type A Bottle Number(s)_____

Type B Bottle Number(s)_____

Start Date	**Type A Dose (mL)** *3 times/day*	**Type B Dose (mL)** *3 times/day*

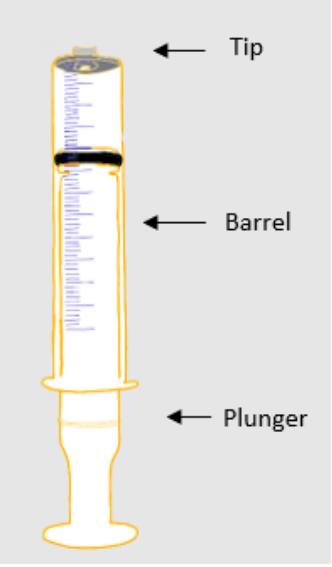
GANAXOLONE 1042-TSC-3001 STUDY
DOSING INSTRUCTIONS FOR ORAL SUSPENSION

Be sure that you read, understand, and follow these instructions carefully to ensure proper dosing of the oral suspension.

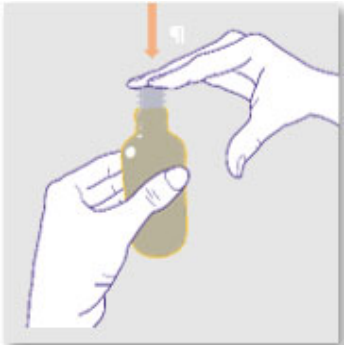
Important:

- Follow your study doctor's instructions for the dose of study drug to take or give. Study drug must always be taken or given with food and used within 30 days of opening.
- Ask your study doctor if you are not sure how to prepare, take, or give the prescribed dose of study drug.
- Always use the oral syringe provided by your study doctor with study drug to make sure you measure the right amount of study drug.
- Do not consume grapefruit or grapefruit juice, Seville oranges, starfruits¸ or excessive quantities of alcohol during the study because it could interact with the study drug.
- Each dose should be separated by at least 4 hours and not more than 12 hours. An example schedule would be 1 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 1 dose and there is less than 4 hours before the next dose, skip that dose.
- If you miss 2 days of dosing or more, call the study doctor for instructions how to restart.
- Save all empty, partially used, and unused bottles of the study drug and return the bottles at your next visit.
- Some people may report feeling dizzy or tired, or experiencing other problems after taking the study drug. These side effects usually go away after 2 or 3 days. If you experience any side effects from the study drug that interfere with your daily activities or if you have any questions, please contact your study doctor to see if a dose adjustment is necessary.

Materials provided by your study doctor:

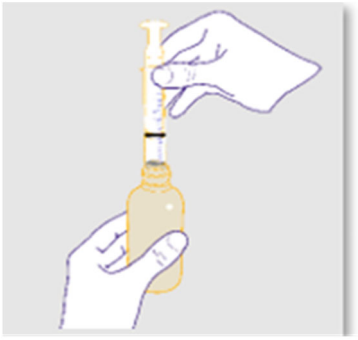
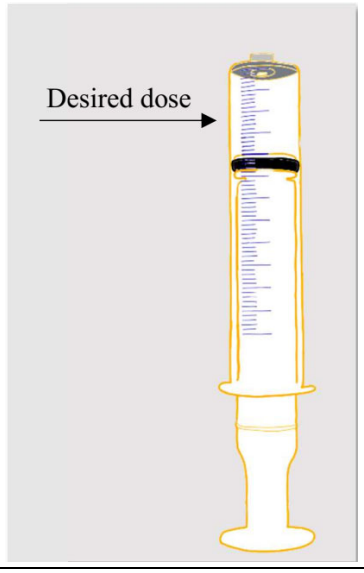
Child-resistant cap:	
Press-in bottle adapter:	
Bottle of study drug:	The picture can't be displayed.
Reusable oral syringe to take or give the dose of study drug: **Note:** If you lose or damage an oral syringe, or cannot read the markings, use a new syringe. Contact your study doctor for extra syringes if you run out.	

Prepare the bottle – to use study drug for the first time.

1. Hold the bottle in your hand and shake it up and down well for 1 minute. Always manually shake the bottle well for 1 minute and then let the bottle stand for 1 minute so that any foam built up during shaking can settle before measuring and giving **each dose** of study drug. This helps you measure the correct amount of study drug. **Note:** This step is for each dose of the study drug.	
2. Remove the child-resistant cap by pushing down while turning the cap to the left (counter-clockwise).	
3. Puncture and peel off the induction seal from the bottle. **Note:** This step is only for the first use of the bottle.	
4. Push the press-in-bottle adapter firmly into the bottle. Firmly grasp the bottle in one hand and insert the press-in bottle adapter all the way in the bottle with other hand using constant pressure. Make sure the press-in bottle adapter is fully inserted. If not fully inserted, small parts such as the press-in bottle adapter may become a choking hazard for children and pets. **Note: Do not** remove the press-in bottle adapter from the bottle after it is inserted.	

Prepare the dose

Your study doctor will tell you how much study drug to take or give.

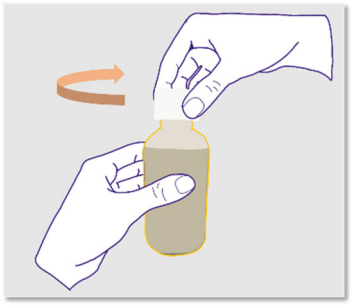
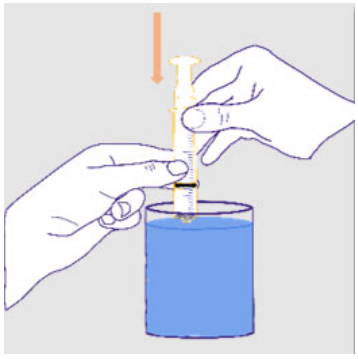
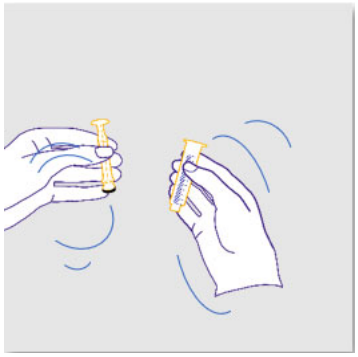
5. Gather the oral syringe, push the plunger all the way down and insert the tip of the oral syringe fully into the press-in bottle adapter. With the syringe in place, turn the bottle upside down.	 
6. Slowly pull the plunger of the oral syringe to withdraw the dose of study drug needed. Line up the end of the plunger with the marking for your dose of study drug. **What to do if you see air bubbles:** If there are air bubbles in the oral syringe, keep the bottle upside down and slowly push the plunger so that all of the liquid flows back into the bottle. Repeat step 6 until air bubbles are gone.	

7. When you have measured the correct amount of study drug, leave the oral syringe in the press-in bottle adapter and turn the bottle right side up.	 
8. Carefully remove the oral syringe from the press-in bottle adapter.	

Take or give study drug

9. Place the tip of the oral syringe against the inside of the cheek and gently push the plunger until all of the study drug in the syringe is taken or given. **Do not** forcefully push the plunger. **Do not** direct the medicine to the back of the mouth or throat. This may cause choking.	

Clean Up

10. Screw the child-resistant cap back on the press-in bottle tightly by turning the cap to the right (clockwise). Do not remove the bottle adapter. The child-resistant cap will fit over it.	
11. Fill a cup with warm soapy water and clean the oral syringe by drawing water in and out of the syringe using the plunger.	
12. Remove the plunger from the barrel of the oral syringe and rinse both parts under tap water. Do not wash the oral syringe in the dishwasher.	
13. Shake off any extra water from the plunger and oral syringe barrel and allow them to air dry until next use. Make sure the oral syringe is completely dry before the next use. A new dosing syringe should be used every day.	

How do I store study drug?

Store study drug in its original bottle in an upright position, at room temperature (20°C to 25°C [68°F to 77°F]). Keep the child-resistant cap tightly closed. Save all empty, partially used, and unused bottles of the study drug and return the bottles at your next visit.
Keep study drug out of the reach of children.

Frequently asked Questions:

Q: What if there are air bubbles in the oral syringe?

A: Slowly push the liquid back into the bottle and repeat step 6 until the air bubbles are gone.

Q: What should I do if the oral syringe is not completely dry before use?

A: If the oral syringe is not completely dry, use a spare syringe provided by your study doctor.

10.9 Appendix 9: Clinical Global Impression – Severity (CGI-S)

Clinician Completed Clinical Global Impression – Severity (CGI-S):
Baseline Interview Guide

Instructions

Clinicians should interview caregivers about the participant's current overall functioning. Specifically, consider seizure control and behavioral presentation, as listed below. Enough detail should be captured in clinical notes to enable the CGI rater to reconstruct the participant's functioning in order to rate changes at subsequent visits.

Specific example behaviors for consideration are listed here to help guide your overall description of the participant. **Please also include any additional relevant information about the participant's functioning.**

1. Seizures

Specific seizure considerations:

- Seizure type
- Seizure frequency
- Seizure intensity
- Seizure duration
- Postictal severity and duration

2. Sleep

Specific behavioral considerations:

- Difficulty falling asleep
- Nighttime wakening
- Difficulty waking in the morning

3. Communication

Specific behavioral considerations:

Receptive communication

- Responds to sound in the environment
- Responds to person's voice
- Responds to "no" or other inhibitory words
- Responds to simple instructions
- Responds to multi-step instructions
- Understands informational presentations

Expressive communication

- Produces sounds
- Social vocalizing/laughing (vocalizes or laughs in response to caregiver)
- Uses gestures
- Babbles
- Uses words

- Uses sentences
- Gives instructions with multiple steps
- Relays experiences

4. **Socialization**
   Specific behavioral considerations:
   - Responds to name/social bids
   - Shows affection
   - Seeks to share interests/enjoyment with others
   - Enjoys talking and/or playing with peers
   - Goes out with friends
   - Engages in age-appropriate leisure time activities

5. **Hyperactivity**
   Specific behavioral considerations:
   - Easily distracted
   - Difficulty sustaining attention
   - Hypermotoric (restless, constantly moving, fidgety)
   - Impulsive (acts without thinking)

6. **Irritability**
   Specific behavioral considerations:
   - Tantrums
   - Outbursts
   - Aggression
   - Agitation
   - Self-injury

Notes:_____

_____

_____

_____

_____

_____

_____

Please indicate the severity of the participant's presentation, **overall**, relative to the range of symptoms seen in Tuberous Sclerosis Complex, using the rating scale below.

CGI Severity (CGI-S)

1. Normal, not at all a problem
2. Borderline problem
3. Mild problem
4. Moderate problem
5. Marked problem
6. Severe problem
7. Very severe problem

Severity Rating: _____

10.10 Appendix 10: Clinical Global Impression – Improvement (CGI-I)

Clinical Global Impression - Improvement (CGI-I) for the Clinician/Parent/Caregiver/LAR

Date: _____ Participant No: _____

Rater Initials: _____ Participant Initials: _____

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

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

10.11 Appendix 11: Caregiver Global Impression of Change in Seizure Intensity/Duration (CGI-CSID)

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

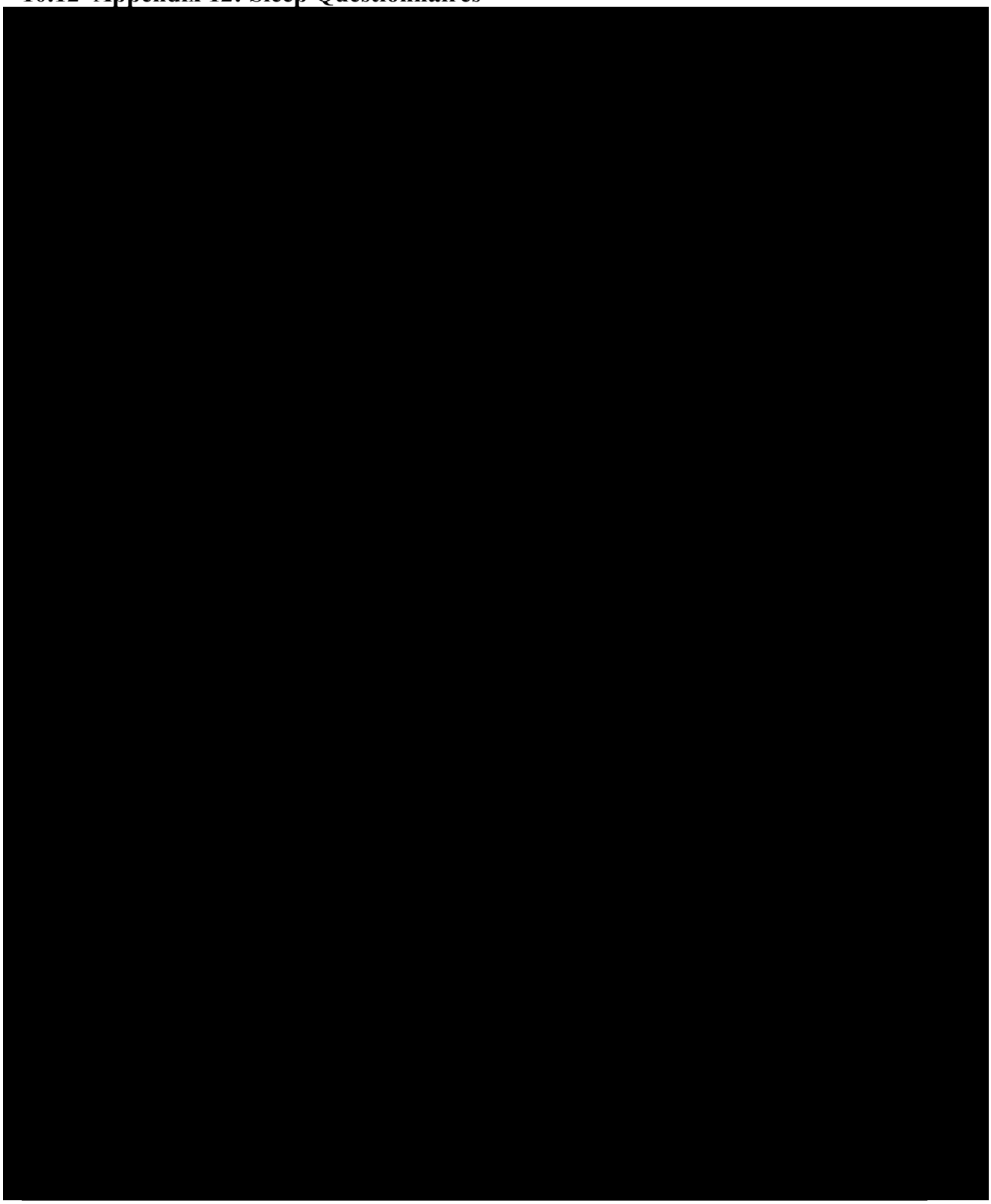
Date: _____ Participant No: _____

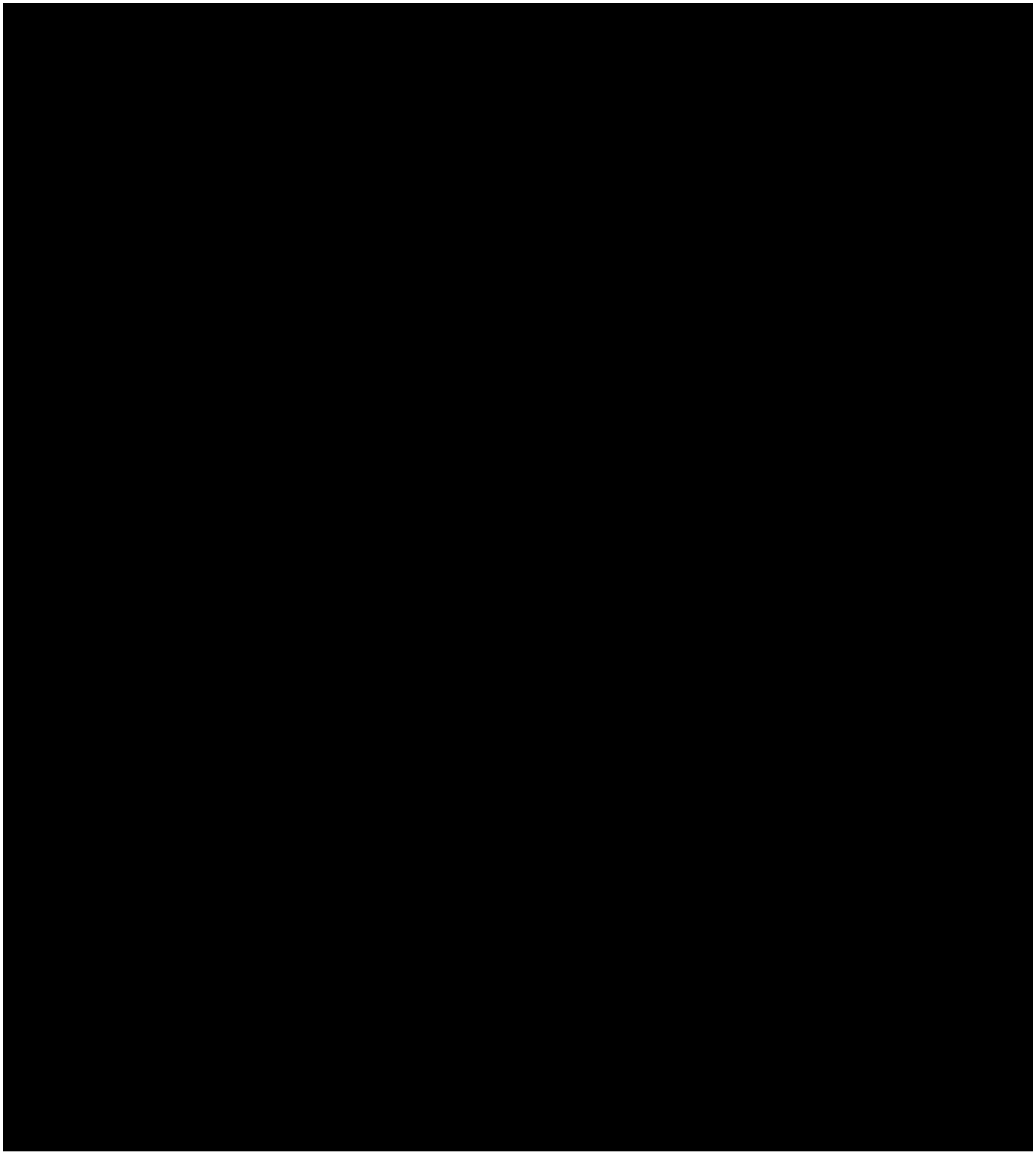
Rater Initials: _____ Participant Initials: _____

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

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

10.12 Appendix 12: Sleep Questionnaires





10.12.2 Sleep Quality Scale

Sleep Quality Scale (SQS) 85

Purpose Consisting of 28 items, the SQS evaluates six domains of sleep quality: daytime symptoms, restoration after sleep, problems initiating and maintaining sleep, difficulty waking, and sleep satisfaction. Developers hoped to create a scale that could be used as an all-inclusive assessment tool – a general, efficient measure suitable for evaluating sleep quality in a variety of patient and research populations.

Population for Testing The scale has been validated in individuals aged 18–59 years.

Administration Requiring between 5 and 10 min for administration, the scale is a simple self-report, pencil-and-paper measure.

Reliability and Validity An initial psychometric evaluation conducted by Yi and colleagues [1] found an internal consistency of .92, a test-retest reliability of .81. The SQS is strongly correlated with results obtained on the Pittsburgh Sleep Quality Index (Chap. 67). Scores achieved by the insomnia sample were significantly higher than those of controls, indicating good construct validity.

Obtaining a Copy A list of the scale's 28 items can be found in the original article published by developers [1].

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Scoring Using a four-point, Likert-type scale, respondents indicate how frequently they exhibit certain sleep behaviors (0 = "few," 1 = "sometimes," 2 = "often," and 3 = "almost always"). Scores on items belong to factors 2 and 5 (restoration after sleep and satisfaction with sleep) and are reversed before being tallied. Total scores can range from 0 to 84, with higher scores demoting more acute sleep problems.

A. Shahid et al. (eds.), *STOP, THAT and One Hundred Other Sleep Scales*,
DOI 10.1007/978-1-4419-9893-4_85, © Springer Science+Business Media, LLC 2012

The following survey is to know the quality of sleep you had for the last one month. Read the questions and check the closest answer.

Examples

Rarely: None or 1-3 times a month
Sometimes: 1-2 times a week
Often: 3-5 times a week
Almost always: 6-7 times a week

		Rarely	Sometimes	Often	Almost always
1	I have difficulty falling asleep				
2	I fall into a deep sleep				
3	I wake up while sleeping				
4	I have difficulty getting back to sleep once I wake up in the middle of the night				
5	I wake up easily because of noise				
6	I toss and turn				
7	I never go back to sleep after awaking during sleep				
8	I feel refreshed after sleep				
9	I feel unlikely to sleep after sleep				
10	Poor sleep gives me headaches				
11	Poor sleep makes me irritated				
12	I would like to sleep more after waking up				
13	My sleep hours are enough				
14	Poor sleep makes me lose my appetite				
15	Poor sleep makes it hard for me to think				
16	I feel vigorous after sleep				
17	Poor sleep makes me lose interest in work or others				
18	My fatigue is relieved after sleep				
19	Poor sleep causes me to make mistakes at work				
20	I am satisfied with my sleep				
21	Poor sleep makes me forget things more easily				
22	Poor sleep makes it hard to concentrate at work				
23	Sleepiness interferes with my daily life				
24	Poor sleep makes me lose desire in all things				
25	I have difficulty getting out of bed				
26	Poor sleep makes me easily tired at work				
27	I have a clear head after sleep				
28	Poor sleep makes my life painful				

10.13 Appendix 13: Anxiety, Depression, and Mood Scale (ADAMS)

Anxiety, Depression, and Mood Scale (ADAMS) - Baseline

Instructions

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

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

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

Anxiety, Depression, and Mood Scale (ADAMS) – Post-baseline Visits

Instructions

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

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

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

10.14 Appendix 14: Pediatric Quality of Life Inventory – Family Impact Module (Peds-QL-FIM)

ID#_____

Date:_____

PedsQL™
Family Impact Module

Version 2.0

PARENT REPORT

DIRECTIONS

Families of children sometimes have special concerns or difficulties because of the child's health. On the following page is a list of things that might be a problem for **you**. Please tell us **how much of a problem** each one has been for **you** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, as a result of your child's health, how much of a problem have **you** had with…*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel tired during the day	0	1	2	3	4
2. I feel tired when I wake up in the morning	0	1	2	3	4
3. I feel too tired to do the things I like to do	0	1	2	3	4
4. I get headaches	0	1	2	3	4
5. I feel physically weak	0	1	2	3	4
6. I feel sick to my stomach	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel anxious	0	1	2	3	4
2. I feel sad	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I feel frustrated	0	1	2	3	4
5. I feel helpless or hopeless	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel isolated from others	0	1	2	3	4
2. I have trouble getting support from others	0	1	2	3	4
3. It is hard to find time for social activities	0	1	2	3	4
4. I do not have enough energy for social activities	0	1	2	3	4

COGNITIVE FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to keep my attention on things	0	1	2	3	4
2. It is hard for me to remember what people tell me	0	1	2	3	4
3. It is hard for me to remember what I just heard	0	1	2	3	4
4. It is hard for me to think quickly	0	1	2	3	4
5. I have trouble remembering what I was just thinking	0	1	2	3	4

COMMUNICATION *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel that others do not understand my family's situation	0	1	2	3	4
2. It is hard for me to talk about my child's health with others	0	1	2	3	4
3. It is hard for me to tell doctors and nurses how I feel	0	1	2	3	4

PedsQL 3.0 - Parent Family Impact

PedsQL 3

*In the past **ONE month**, as a result of your child's health, how much of a problem have **you** had with…*

WORRY *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I worry about whether or not my child's medical treatments are working	0	1	2	3	4
2. I worry about the side effects of my child's medications/medical treatments	0	1	2	3	4
3. I worry about how others will react to my child's condition	0	1	2	3	4
4. I worry about how my child's illness is affecting other family members	0	1	2	3	4
5. I worry about my child's future	0	1	2	3	4

DIRECTIONS

Below is a list of things that might be a problem for **your family**. Please tell us **how much of a problem** each one has been for **your family** during the **past ONE month.**

*In the past **ONE month**, as a result of your child's health, how much of a problem has **your family** had with…*

DAILY ACTIVITIES *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Family activities taking more time and effort	0	1	2	3	4
2. Difficulty finding time to finish household tasks	0	1	2	3	4
3. Feeling too tired to finish household tasks	0	1	2	3	4

FAMILY RELATIONSHIPS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Lack of communication between family members	0	1	2	3	4
2. Conflicts between family members	0	1	2	3	4
3. Difficulty making decisions together as a family	0	1	2	3	4
4. Difficulty solving family problems together	0	1	2	3	4
5. Stress or tension between family members	0	1	2	3	4

ID#_____

Date:_____

PedsQL™
Family Impact Module

Version 2.0

PARENT REPORT

DIRECTIONS

Families of children sometimes have special concerns or difficulties because of the child's health. On the following page is a list of things that might be a problem for **you**. Please tell us **how much of a problem** each one has been for **you** during the **past 7 days** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **7 days**, as a result of your child's health, how much of a problem have **you** had with…*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel tired during the day	0	1	2	3	4
2. I feel tired when I wake up in the morning	0	1	2	3	4
3. I feel too tired to do the things I like to do	0	1	2	3	4
4. I get headaches	0	1	2	3	4
5. I feel physically weak	0	1	2	3	4
6. I feel sick to my stomach	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel anxious	0	1	2	3	4
2. I feel sad	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I feel frustrated	0	1	2	3	4
5. I feel helpless or hopeless	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel isolated from others	0	1	2	3	4
2. I have trouble getting support from others	0	1	2	3	4
3. It is hard to find time for social activities	0	1	2	3	4
4. I do not have enough energy for social activities	0	1	2	3	4

COGNITIVE FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to keep my attention on things	0	1	2	3	4
2. It is hard for me to remember what people tell me	0	1	2	3	4
3. It is hard for me to remember what I just heard	0	1	2	3	4
4. It is hard for me to think quickly	0	1	2	3	4
5. I have trouble remembering what I was just thinking	0	1	2	3	4

COMMUNICATION *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel that others do not understand my family's situation	0	1	2	3	4
2. It is hard for me to talk about my child's health with others	0	1	2	3	4
3. It is hard for me to tell doctors and nurses how I feel	0	1	2	3	4

PedsQL 3

*In the past **7 days**, as a result of your child's health, how much of a problem have **you** had with…*

WORRY *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I worry about whether or not my child's medical treatments are working	0	1	2	3	4
2. I worry about the side effects of my child's medications/medical treatments	0	1	2	3	4
3. I worry about how others will react to my child's condition	0	1	2	3	4
4. I worry about how my child's illness is affecting other family members	0	1	2	3	4
5. I worry about my child's future	0	1	2	3	4

DIRECTIONS

Below is a list of things that might be a problem for **your family**. Please tell us **how much of a problem** each one has been for **your family** during the **past *7 days*.**

*In the past **7 days**, as a result of your child's health, how much of a problem has **your family** had with…*

DAILY ACTIVITIES *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Family activities taking more time and effort	0	1	2	3	4
2. Difficulty finding time to finish household tasks	0	1	2	3	4
3. Feeling too tired to finish household tasks	0	1	2	3	4

FAMILY RELATIONSHIPS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Lack of communication between family members	0	1	2	3	4
2. Conflicts between family members	0	1	2	3	4
3. Difficulty making decisions together as a family	0	1	2	3	4
4. Difficulty solving family problems together	0	1	2	3	4
5. Stress or tension between family members	0	1	2	3	4

10.15 Appendix 15: Short Form 36 (version 2)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a <u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

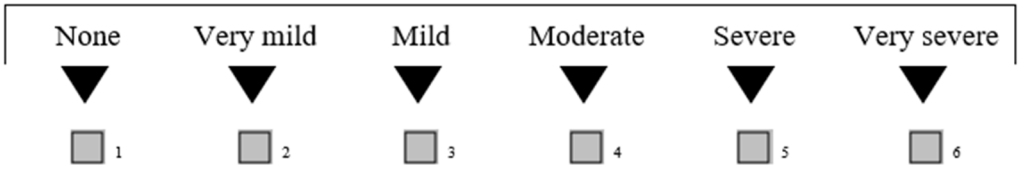
	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the <u>kind</u> of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities <u>less carefully than usual</u>	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?



8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks.

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

10.16 Appendix 16: Epilepsy and Learning Disabilities Quality of Life Scale

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Serial No. 1-3

EPILEPSY AND LEARNING DISABILITIES QUALITY OF LIFE QUESTIONNAIRE

ABOUT THESE QUESTIONS

1. These questions ask about how your child has been in the last four weeks. We are interested in how much your child's daily life and activities have been affected by his/her epilepsy and its treatment.

2. We are interested in **your views** about how things have been for your child. Your opinions are very important to us, and we hope you will take time to complete the questionnaire. We do not think it will take more than 15-20 minutes for you to do so.

3. Some people with epilepsy have more than one type of seizure. If your child experiences different types of seizures, please answer the questions as they apply to the **most severe** seizures, in your opinion, that he/she has.

4. Most of the questions can be answered simply by ringing a number next to the answer that applies to your child. Sometimes you are asked to write in a number.

5. We want to know how things have been **in the last four weeks**. If you cannot remember, do not know, or are unable to answer a particular question, please write that in.

6. Your name and address do not appear anywhere in this booklet. The information you give us will be treated as strictly confidential.

First some questions about the seizures your child has. Please answer about seizures in the last four weeks. If your child has more than one type of seizure, please think about the most severe seizures he/she has, when answering the questions. Please be sure to answer every question.

1. How severe have your child's seizures been in the last four weeks?

Very severe 1
Somewhat severe 2
Moderate 3
Mild 4
Can't say 5

4

---

2. In the last four weeks, do you think your child was aware of his/her surroundings during seizures?

Yes, during all seizures 1
Yes, during most seizures 2
Yes, during some seizures 3
No, not during any seizures 4
Can't say 5

5

---

3. In the last four weeks, did your child blank out/lose consciousness during any of his/her seizures? If yes, generally for how long?

Yes, for less than 1 minute 1
Yes, for between 1-2 minutes 2
Yes, for between 2-5 minutes 3
Yes, for more than 5 minutes 4
No, did not blank out or lose consciousness in any seizures 5
Can't say 6

6

---

4. In the last four weeks, when your child had seizures, how often did he/she fall to the ground?

Always 1
Usually 2
Sometimes/rarely 3
Never 4
Does not apply - child does not stand independently/child wheelchair bound 5
Can't say 6

7

5. In the last four weeks, was your child ever confused, disorientated or non-responsive after seizures?

Yes, always 1
Yes, often 2
Yes, sometimes/rarely 3
No, never 4
Can't say 5

8

---

6. In the last four weeks, **if** your child was confused, disorientated or non-responsive after seizures, how long did this usually last?

Usually lasted less than 1 minute 1
Usually lasted for between 1-5 minutes 2
Usually lasted for between 6 minutes - 1 hour 3
Usually lasted for more than 1 hour 4
Child never seemed confused/disorientated/non-responsive 5
Can't say 6

9

---

7. How often was your child distressed after seizures in the last four weeks?

Always 1
Usually 2
Sometimes/rarely 3
Never 4
Can't say 5

10

---

8. In the last four weeks, how often did your child wet him/herself during seizures?

Always 1
Usually 2
Sometimes/rarely 3
Never 4
Can't say - child has no control of bladder 5

11

---

9. In the last four weeks, how often did your child soil him/herself during seizures?

Always 1
Usually 2
Sometimes/rarely 3
Never 4
Can't say - child has no control of bowels 5

12

10. In the last four weeks, did your child suffer any injury to the mouth, cheek or tongue during a seizure?

Always 1
Usually 2
Sometimes/rarely 3
Never 4
Can't say 5 13

---

11. In the last four weeks, did your child suffer any injury other than to the mouth, cheek or tongue during a seizure?

Always 1
Usually 2
Sometimes/rarely 3
Never 4
Can't say 5 14

---

12. How upset was your child by the injury/injuries he/she suffered during seizures in the last four weeks?

Very upset 1
Somewhat upset 2
Not very upset 3
Not at all upset 4
Does not apply - no injuries 5
Can't say 6 15

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13. In the last four weeks, when your child recovered from his/her seizures, how often did he/she appear sleepy or subdued?

Always 1
Usually 2
Sometimes/rarely 3
Never 4
Can't say 5 16

---

14. In the last four weeks, when your child had seizures, how quickly could he/she usually return to what he/she was doing?

In less than 1 minute 1
In between 1-5 minutes 2
In between 6 minutes - 1 hour 3
In over 1 hour 4
Can't say 5 17

Now some more detailed questions about any injuries your child experienced in the last four weeks, as a result of his/her seizures.

15. In the past four weeks, how many times did your child injure him/herself during a seizure?

Not at all ..... 0 **Go to Q 17**

Number of times *(please write in)* ..... **Answer Q 16**

18

---

16. Did he/she suffer any of the following injuries as a result of having a seizure in the last four weeks?

a) An injury to his/her head which required assessment and/or treatment at hospital?

Yes 1

No 2 19

b) An injury to his/her teeth or mouth which required dental or medical treatment?

Yes 1

No 2 20

c) A fracture/broken bone?

Yes 1

No 2 21

d) Bruising or friction burns to any part of the body?

Yes 1

No 2 22

e) Cuts or grazes to any part of the body?

Yes 1

No 2 23

f) Any other injury? (*please tell us what*):

Yes 1

No 2 24

Now a few questions about the drugs your child takes for epilepsy

17. In the last four weeks, how well do you think your child's seizures have been controlled by the drugs he/she is taking?

Very well controlled 1
Fairly well controlled 2
Not very well controlled 3
Not controlled at all 4
Can't say 5 25

18. Below is a list of problems people sometimes have with the drugs they take for their epilepsy. During the last four weeks, has your child had any of the problems listed **which you think may have been caused by the drugs** he/she takes for epilepsy?

For each of the things listed, if it has always or often been a problem in the last four weeks, ring 4; if it has sometimes been a problem, ring 3, and so on. Please answer every item.

	Always a problem	Often a problem	Sometimes/rarely a problem	Never a problem	Can't say	
Unsteadiness/dizziness	1	2	3	4	5	26
Tiredness	1	2	3	4	5	
Restlessness	1	2	3	4	5	
Hyperactivity	1	2	3	4	5	
Nervousness	1	2	3	4	5	
Headache	1	2	3	4	5	
Problems with skin, e.g. rash	1	2	3	4	5	
Disturbed vision	1	2	3	4	5	
Upset stomach/nausea	1	2	3	4	5	
Difficulty paying attention	1	2	3	4	5	
Trouble with mouth or gums	1	2	3	4	5	
Shaky hands/tremor	1	2	3	4	5	
Weight gain	1	2	3	4	5	
Weight loss	1	2	3	4	5	
Sleepiness/drowsiness	1	2	3	4	5	
Memory problems	1	2	3	4	5	
Disturbed sleep	1	2	3	4	5	
Loss of appetite	1	2	3	4	5	
Behaviour problems (e.g. temper tantrums, irritability or agitation)	1	2	3	4	5	44

Any other problems (please list in the spaces below):

1 ..... 1 2 3 4
2 ..... 1 2 3 4 46

Now some questions about how your child has been generally. Please think about how your child has been over the last four weeks, compared to how he/she is normally.

19. How aware has your child been of his/her surroundings/things going on around him/her, in the last four weeks?

Very aware 1
Fairly aware 2
Not very aware 3
Not at all aware 4
Can't say 5

47

---

20. How often, in the last four weeks, did your child have problems sleeping (either difficulty falling asleep, waking during the night, or waking early)?

Always a problem 1
Often a problem 2
Sometimes/rarely a problem 3
Never a problem 4
Can't say 5

48

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21. How often was your child's appetite a problem - either eating too much or too little?

Always a problem 1
Often a problem 2
Sometimes/rarely a problem 3
Never a problem 4
Can't say 5

49

---

22. In the last four weeks, how good overall has your child's bladder control been?

Very good 1
Good 2
Poor 3
Very poor 4
Does not apply - does not have control of his/her bladder 5
Can't say 6

50

23. In the last four weeks, how good overall has your child's bowel control been?

Very good 1
Good 2
Poor 3
Very poor 4
Does not apply - does not have control of his/her bowels..... 5
Can't say 6 51

---

24. In the last four weeks, how well has your child been able to let you know what he/she wants?

Very well 1
Fairly well 2
Not very well 3
Not at all well 4
Can't say 5 52

---

25. In the last four weeks, how well has he/she been able to understand what you tell him/her?

Very well 1
Fairly well 2
Not very well 3
Not at all well 4
Can't say 5 53

---

26. In the last four weeks, how well has your child been able to pay attention to his/her favourite activities?

Very well 1
Fairly well 2
Not very well 3
Not at all well 4
Can't say 5 54

---

27. How often in the last four weeks has your child been prevented from taking part in his/her normal activities (e.g. going to school, playing, seeing friends and relatives) by his/her seizures/epilepsy?

Always 1
Often 2
Sometimes/rarely 3
Never 4
Can't say 5 55

Now some questions about your child's mood in the last four weeks

28. Here is a list of words that parents have used to describe their child's moods. In the last four weeks, has your child appeared:-

	Always	Often	Sometimes/ rarely	Never	Can't say	
Happy	1	2	3	4	5	56
Aggressive	1	2	3	4	5	
Calm	1	2	3	4	5	
Irritable	1	2	3	4	5	
Tearful	1	2	3	4	5	
Friendly	1	2	3	4	5	
Hyperactive	1	2	3	4	5	
Relaxed	1	2	3	4	5	
Sad	1	2	3	4	5	
Agitated	1	2	3	4	5	
Cheerful	1	2	3	4	5	
Restless	1	2	3	4	5	
Tantrum-prone	1	2	3	4	5	
Frustrated	1	2	3	4	5	
Withdrawn	1	2	3	4	5	
Cooperative/helpful	1	2	3	4	5	71

29. In the last four weeks, how would you say your child's general health has been overall?

Very good 1
Good 2
Fair 3
Poor 4
Very poor 5 72

---

30. How would you describe the quality of your child's life overall in the last four weeks?

Very good 1
Good 2
Fair 3
Poor 4
Very poor 5 73

---

31. In the last four weeks, how concerned have you been about your child because of his/her epilepsy?

Very concerned 1
Fairly concerned 2
Not very concerned 3
Not concerned 4 74

---

32. How severe a condition do you think his/her epilepsy is?

Very severe 1
Somewhat severe 2
Moderate 3
Mild 4
Can't say 5 75

The following questions are about yourself and your family. 2

33. During the past 4 weeks, how much emotional worry or concern did each of the following cause **you**? 4

	None at all	A little bit	Some	Quite a bit	A lot
Your child's physical health	0	1	2	3	4
Your child's emotional well-being or behaviour	0	1	2	3	4
Your child's attention or learning difficulties	0	1	2	3	4

34. During the past 4 weeks, were you limited in the amount of time **you** had for your own needs because of:

	Yes, limited a lot	Yes,limited some	Yes, limited a little	No, not limited
Your child's physical health	0	1	2	3
Your child's emotional well-being or behaviour	0	1	2	3
Your child's attention or learning difficulties	0	1	2	3

10

35. During the past 4 weeks, how often has your child's health or behaviour:

	Very often	Fairly often	Sometimes	Almost never	Never
limited the types of activities you could do as a family?	0	1	2	3	4
interrupted various everyday family activities (eating meals, watching tv)?	0	1	2	3	4
limited your ability as a family to "pick up and go" on a moment's notice?	0	1	2	3	4
caused tension or conflict in your home?	0	1	2	3	4
been a source of disagreements or arguments in your family?	0	1	2	3	4
caused you to cancel or change plans (personal or work) at the last minute?	0	1	2	3	4

36. Sometimes families may have difficulty getting along with one another. They do not always agree and they may get angry. In general, how would you rate your family's ability to get along with one another?

Excellent 1
Very good 2
Good 3
Fair 4
Poor 5

17

The next section is about your child's behaviour in the last four weeks.

37. Please read each statement and rate your child's behaviour **in the last four weeks.** For each item, decide whether the behaviour is a problem and circle the appropriate number.

18

	Not at all a problem	A slight problem	A moderately serious problem	A severe problem
Injures self on purpose	0	1	2	3
Aggressive to other children or adults (verbally or physically)	0	1	2	3
Screams inappropriately	0	1	2	3
Temper tantrums/outbursts	0	1	2	3
Irritable and whiny	0	1	2	3
Yells at inappropriate times	0	1	2	3
Depressed mood	0	1	2	3
Demands must be met immediately	0	1	2	3
Cries over minor annoyances and hurts	0	1	2	3
Mood changes quickly	0	1	2	3
Cries and screams inappropriately	0	1	2	3
Stamps feet or bangs objects or slams doors	0	1	2	3
Deliberately hurts himself/herself	0	1	2	3
Does physical violence to self	0	1	2	3
Has temper outbursts or tantrums when he/she does not get own way	0	1	2	3
Excessively active at home, school, work, or elsewhere	0	1	2	3
Boisterous (inappropriately noisy and rough)	0	1	2	3
Does not stay in seat (e.g. during lesson or training periods, meals etc)	0	1	2	3

35

The following statements are also about your child's behaviour in the last four weeks. Please circle the appropriate number.

	Not at all a problem	A slight problem	A moderately serious problem	A severe problem	
Impulsive (acts without thinking)	0	1	2	3	36
Restless, unable to sit still	0	1	2	3	
Disobedient; difficult to control	0	1	2	3	
Disturbs others	0	1	2	3	
Uncooperative	0	1	2	3	
Does not pay attention to instructions	0	1	2	3	
Disrupts group activities	0	1	2	3	
Will not sit still for any length of time	0	1	2	3	
Easily distractible	0	1	2	3	
Constantly runs or jumps around the room	0	1	2	3	
Pays no attention when spoken to	0	1	2	3	
Tends to be excessively active	0	1	2	3	
Deliberately ignores directions	0	1	2	3	48

The next few items are about your child's general ability to function with daily activities. For each item, please decide which statement best describes your child's situation and circle the appropriate number.

38. My child can walk independently for at least 100 metres 1
My child can walk independently, but for less than 100 metres..... 2
My child can walk only with support or aids 3
My child cannot walk at all but can stand..... 4
My child's mobility is limited to wheelchair use only 5 49

---

39. My child is able to move and use his/her arms and hands normally 1
My child is unable to use a pencil or a knife and fork, but can use a spoon..... 2
My child is unable to use a spoon to feed, but can feed him/herself with his/her fingers..... 3
My child is unable to feed him/herself with his/her fingers, and is fed orally by another person..... 4
My child is fed exclusively or almost exclusively by a tube..... 5

---

40. My child can dress and undress him/herself, including laces and/or buttons..... 1
My child can dress and undress him/herself, excluding laces and/or buttons..... 2
My child can only undress him/herself, alone or with assistance 3
My child can only dress him/herself, alone or with assistance 4
My child is unable to undress or dress at all..... 5

---

41. My child has normal speech..... 1
My child has some understandable speech, but it is not normal 2
My child uses only a few 2-word or 3-word phrases..... 3
My child uses only single words and no phrases..... 4
My child uses no recognisable words, but may make some sounds..... 5 52

42. Finally, please tell us your relationship to your child. Are you:

His/her mother 1
His/her father 2
Another relative 3
A formal carer 4 53

---

43. Did you find any of these questions difficult to answer? If so, please tell us which ones and why.

---

44. Are there any other comments you would like to make, either about your child and his/her epilepsy, or about this questionnaire? If so, please write in the space below.

55

Please check that you have answered **all** the questions.

Thank you for taking the time to complete this questionnaire. We are very grateful for your help.

10.17 Appendix 17: Columbia-Suicide Severity Rating Scale (C-SSRS)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Lifetime
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

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Visit Day 0: Admission
Patient No. _____
Patient Initials _____
Date _____
Time _____
Rater _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

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SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Assessment**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____
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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Assessment
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you _____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

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