TITLE PAGE

Protocol Title: A Phase 3, Open-label Study of Adjunctive Ganaxolone (GNX) Treatment in Children and Adults with Tuberous Sclerosis Complex (TSC)-related Epilepsy (TrustTSC OLE)

Protocol Number: 1042-TSC-3002

Compound: Ganaxolone

Brief Title: Open-label study of adjunctive GNX treatment in children and adults with TSC-related epilepsy

Indication: TSC-related epilepsy

Study Phase: Phase 3

Sponsor Name: Marinus Pharmaceuticals Inc.

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Regulatory Agency Identifier Numbers:

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Protocol version/date	Document Version	Approval Date
	Protocol Amendment 3; v4.0	19 Apr 2023
	Protocol Amendment 2; v3.0	08 Dec 2022
	Protocol Amendment 1; v2.0	01 Jun 2022
	Original (v1.0 [superseded])	14 Oct 2021

CONFIDENTIALITY NOTICE

Sponsor Signatory:

Protocol Number: 1042-TSC-3002

Protocol Title:
A Phase 3, Open-label Study of Adjunctive Ganaxolone (GNX) Treatment in Children and Adults with Tuberous Sclerosis Complex (TSC)-related Epilepsy (TrustTSC OLE)

I, the undersigned, have approved of the clinical trial protocol with the date of 19 Apr 2023

DocuSigned by:
[redacted]
EBD8EF65167C44A...

April 21, 2023 | 1:25 PM EDT

[redacted]
Vice President, Clinical Development

Date

Medical Monitor Name and Contact Information is provided in Section 10.2.

INVESTIGATOR AGREEMENT

Protocol Number: 1042-TSC-3002

Protocol Title:
A Phase 3, Open-label Study of Adjunctive Ganaxolone (GNX) Treatment in Children and Adults with Tuberous Sclerosis Complex (TSC)-related Epilepsy (TrustTSC OLE)

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.

_____ _____

Principal 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** **19 Apr 2023**	**Global/Country/ Site-Specific** **Global**
Rationale for the Amendment The following changes are made in this global protocol amendment from version 3.0 to version 4.0 to: • Reflect changes to the maximum overall study duration from 1 year to 3 years. • Include updated information regarding completed and ongoing clinical studies. • Add details on pregnancy testing.		
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, and Sponsor Signatory page
Applied a correction to the Protocol Title on the signatory pages; “Trial” corrected to “Study”		Sponsor Signatory page and Investigator Agreement page
The estimated duration of the study was updated from 1 year to 3 years.		Section 1.1, Section 1.3, Section 4.1.1, and Section 6.2.
Updated rationale text to clarify the completion of Study 1042-TSC-2001 and added summary text for the ongoing Study 1042-TSC-3001.		Section 1.1 and Section 2.2.2.1.1
Updated secondary objectives and endpoints to specify objectives and endpoints which are only to be assessed in Year 1.		Section 1.1, Section 3, and Section 9.2.3
Added text to clarify that seizure eDiaries will be completed in Year 1 of the study only.		Section 1.1, Section 4.1, Section 6.5, and Section 6.6.1
Added text to clarify that after Year 1, study assessments will focus on safety evaluation and that caregiver and clinician impressions of improvement will continue to ensure continued treatment benefit.		Section 1.1, and Section 4.1
Updated text to align with the Visit numbers and dates in the revised Schedule of Activities (SoA) for inclusion of Years 2 and 3, including references to the Early Termination Visit and End of Study definition.		Section 1.1, Section 4.1, Section 4.4, Section 7.1, Section 7.2, Section 8.1.2, Section 8.1.3, Section 8.2.2, Section 8.2.3, Section 8.3.1, Section 8.3.2, Section 8.3.3, Section 8.3.4, and Section 8.3.5

New exclusion criterion 8. Added: • Exposed to any other investigational drug (except for GNX in Study 1042-TSC-2001 or Study 1042-TSC-3001) or investigational device within 30 days or fewer than 5 half-lives prior to Visit 1 (first visit of the OLE). For therapies in which half-life cannot be readily established, the Sponsor's medical monitor should be consulted.	Section 1.1, and Section 5.2
Updated Study schematic diagram to reflect change to study duration.	Section 1.2
Updated SoA table to include assessments for Year 2 and Year 3.	Section 1.3, Table 1
Updated pregnancy testing information to clarify that urine pregnancy tests will be dispensed at Visit 1 for take-home pregnancy testing to occur every 4 weeks thereafter.	Section 1.3, Table 1, and Table 1 (footnotes)
Updated pregnancy assessment to include clarification for the reporting procedure in the case of a positive take home pregnancy test.	Section 1.3, Table 1 (footnotes), and Section 10.3, Table 3 (footnotes)
Deleted text describing a washout period which is not relevant to the present study.	Section 6.6
Added text to clarify that assessments conducted by travelling nurses only applies to sites located outsite of the European Union (EU).	Section 8
Updated text to clarify that an enrollment log will be maintained by the investigator for all participants from 1042-TSC-3001 and 1042-TSC-2001.	Section 8
Added a new section to describe pregnancy testing assessments.	Section 8.3.8
Deleted text describing site termination criteria which were not applicable for this study	Section 10.1.9.2
Updated sample retention requirements from 1 year to 6 months to comply with EU requirements.	Section 10.1.11
Updated plasma drug screen procedure to clarify that this will occur during the first visit of the open-label extension.	Section 10.3, Table 3 (footnotes)

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments		
Summary of Changes Since Last Version of Approved Protocol		
Amendment Number **2**	**Amendment Date** **08 Dec 2022**	**Global/Country/ Site-Specific** **Global**
Rationale for the Amendment The following changes are made in this global protocol amendment from version 2.0 to version 3.0 to: • Add a section on contraception use, including acceptable barrier methods. • Elaborate on dose adjustments and rescue medications. • Updated information of the Investigational Product (IP) background and the ganaxolone (GNX) Clinical Development Program with the most current information and to align with the current version of the Investigator's Brochure (IB). • Add a new section to include Suspected Unexpected Serious Adverse Reaction (SUSAR) language. • Update 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 exploratory research.		
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 "subjects" with "participants".		Throughout the document
Updated Protocol amendment date and version in the header.		Protocol header
Updated the list of abbreviations.		List of Abbreviations
Exploratory objective removed from Synopsis.		Section 1.1
Updated information of the IP background and the GNX Clinical Development Program with the most current information and to align with the current version of the IB.		Section 1.1, Section 2.2.2, and Section 2.2.2.1
Updated endpoints subheaders in "objectives and endpoints"		Section 1.1 and Section 3
Specified that version 2 of the Short Form 36 (SF-36) will be used during the study.		Section 1.1 (footnote), Section 1.3 (footnote), Section 3 (footnote), Section 8.2.4, and Section 10.10
Updates to inclusion criterion 2. Added: • If the participant is not qualified or able to provide written informed consent based on age, developmental stage, intellectual capacity, or other factors, parent(s)/LAR(s) must provide assent for study participation, if appropriate.		Section 1.1 and Section 5.1

Updated the first definition of seizure types that **do not count** towards the primary endpoint: Replaced: • Focal aware seizures without motor features (eg, absence or focal nonmotor seizures with or without impairment of awareness). With • 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 8.1.1.2, and Section 8.2.1
Revised contraception information throughout the protocol (inclusion criteria 5 and 6). Removed 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 10.5.1, Section 10.5.2, and Section 10.5.3
Specified in Table 3 (Laboratory tests) that a urine drug screen could be performed if a plasma sample is difficult or impossible to obtain.	Section 10.3
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 GNX dosing to manage tolerability.	Section 6.2
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 electrocardiograms (ECG) assessment to be completed by a mobile vendor.	Section 8
Added a note for Investigational Sites in the United Kingdom (UK) related to the study procedures. Added: Note for Investigational Sites in the 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
Text revised to change CKD-EPI formula to calculate estimated glomerular filtration rate (eGFR) with Cockcroft-Gault formula or pediatric GFR calculator or Bedside Schwartz. Added text related to maximum amount of blood that will be collected from participants (previously in Section 8).	Section 8.3.4
Added a new section to include Suspected Unexpected Serious Adverse Reaction (SUSAR) language.	Section 8.4.4.1

Updated ICF processes to include that minor participants must be re-consented if they reach the age of majority during the course of study and to delete any reference of separate section in the ICF for optional exploratory research. 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 any remaining specimens to be used for exploratory research. 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 10.1.11
Contact details for Marinus Project Managers updated.	Section 10.2.2.2
Minor pictures updates in Dosing Instructions.	Section 10.7

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **01 June 2022**	**Global/Country/ Site-Specific** **Global**
Rationale for the Amendment The rationale for the major changes in this protocol amendment are as follows: • The maximum study duration was changed from 2 years to 1 year and study visits updated according to 1-year duration. • 12-lead electrocardiogram (ECG) and clinical safety laboratory tests (hematology, clinical chemistry, and urinalysis) were added as they will be evaluated as part of the safety assessment in the open-label extension (OLE) study. • The ganaxolone (GNX) suspension stability was updated from 2 years to 18 months. • The dosing instructions for the oral suspension were updated to match the package insert. • The Short Form 36 (SF-36) was updated for better clarity.		
Description of Changes		**Section(s) Affected by Change**
Minor editorial updates made throughout for grammar, consistency, and clarity.		Throughout the document
Updated cross references.		Throughout the document
Replaced the term anti-epileptic drugs (AEDs) with the preferred term anti-seizure medication (ASM) per TSC Alliance.		Throughout the document
Updated definition of mTOR from “mammalian target of rapamycin” to the preferred definition “mechanistic target of rapamycin” per TSC Alliance.		Throughout the document
Protocol date and version added to the header.		Protocol header, Title Page
The Investigational New Drug (IND) number was corrected, and the EudraCT number was added.		Title Page
Protocol short name “TrustTSC OLE” added to the protocol title.		Title Page, Sponsor Signatory, Investigator Agreement, Section 1.1
Updated the List of Abbreviations.		List of Abbreviations
The Data Monitoring Committee (DMC) was eliminated.		List of Abbreviations, Section 2.3.1, Section 8.4.7, Section 10.1.6
Clarified the term children used along the document refers to the full range of pediatric participants to cover the full span of age per the International Council for Harmonisation (ICH) definition.		Section 1.1, Section 4.1
Updated the Synopsis to include the eligibility criteria from the main body of the protocol.		Section 1.1
The estimated duration of the study was updated from 2 years to 1 year.		Section 1.1, Section 1.3, Section 4.1.1, Section 6.2
Removed Study Visits at Weeks 65, 78, 91, and 104, and Safety Follow-up visit changed from Visit 10 (Week 108) to Visit 6 (Week 56).		Section 1.1, Section 1.3, Section 4.1, Section 4.4,

	Section 7.1, Section 7.2, Section 8.1.2, Section 8.1.3, Section 8.2.2, Section 8.2.3, Section 8.2.4, Section 8.3.1, Section 8.3.2, Section 8.3.5
Added and described 12-lead ECG evaluation.	Section 1.1, Section 2.3.1, Section 3, Section 8, Section 8.3.3, Section 8.4.5, Section 9.2.2, Section 9.2.5, Section 10.3 (Table 3)
Added and described clinical safety laboratory testing (hematology, clinical, chemistry, and urinalysis).	Section 1.1, Section 2.3.1, Section 3, Section 8.3.4, Section 8.4.5, Section 9.2.2, Section 9.2.5, Section 10.3 (Table 3)
Revised male contraception requirements to state these should be continued for 30 days after the last dose of investigational product (IP).	Section 1.1, Section 5.1, Section 10.5.2
Updated text to align with the most recent version of the Investigator's Brochure (December 2021).	Section 1.1, Section 2.2.2, Section 2.2.2.1, Section 2.2.2.1.1, Section 2.2.2.2, Section 2.3.1
Indicated the duration of OLE long-term GNX treatment and maintenance period (52 weeks) for better clarity.	Section 1.2
Central ASM level collection was eliminated.	Section 1.3, Section 8.3.6, Section 10.3 (Table 3)
The schedule of activities (SOA) was amended to: • Specify type of study visits (in person or phone visits). • Indicate visits for 12-lead ECG. • Indicate visits for clinical laboratory test (hematology, clinical chemistry, and urinalysis). • Add concomitant medication review visits. • Update and reorganize table footnotes. • Update table abbreviations.	Section 1.3
Number of study sites participating in the OLE study was updated from 60 to 75.	Section 4.1.3
Updated in scientific rationale for study design from "patient populations being pursued for development" to "patient populations that may benefit from GNX treatment".	Section 4.2
Updated GNX suspension stability from "at least 2 years" to "at least 18 months". Included the recommendation of using the suspension within 30 days after opening.	Section 6.1 (Table 2)
Indicated pediatric blood volumes collection should be minimized as much as possible.	Section 8

Eliminated statement related to GNX concentration that may unblind the study since it is not applicable to the OLE study.	Section 8.6.1
Updated criteria of study termination to describe reasons for study termination.	Section 10.1.9.2
Updated back-up Sponsor Project Managers.	Section 10.2.2.2
Included vital signs (blood pressure [BP], heart rate [HR], respiratory rate [RR], and body temperature) in Table 3.	Section 10.3 (Table 3)
Eliminated the statement “Data collection laws in France prohibit the collection of data on race and ethnicity” as the laws of this country allows these data collection.	Section 10.6
Updated dosing instructions for the oral suspension to match the package insert.	Section 10.7
Updated SF-36 to a more comprehensible format for participants.	Section 10.10

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LIST OF TABLES

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LIST OF ABBREVIATIONS

ACTH	adrenocorticotropic hormone
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
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
CIOMS	Council for International Organizations of Medical Sciences
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CSA	Controlled Substances Act
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DEA	Drug Enforcement Agency
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic seizure diary
eGFR	estimated glomerular filtration rate
FXS	Fragile X syndrome
GABA	γ-aminobutyric acid
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GNX	ganaxolone
GTP	guanosine triphosphate
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 spasms
ITT	intent-to-treat
LAR	legally authorized representative
mTOR	mechanistic target of rapamycin
mTORC1	mechanistic target of rapamycin complex 1
NHS	National Health Service
OL	open-label
OLE	open-label extension
PCDH	protocadherin
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PPD	postpartum depression
PRN	pro re nata (as needed)
PTSD	posttraumatic stress disorder
QTL	quality tolerance limit
Rheb	Ras homolog enriched in brain
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SE	status epilepticus
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SF-36	Short Form 36
SIB	suicidal ideation and behavior
SIF/DRF	Seizure Identification Form/Diagnostic Review Form
SOA	schedule of activities
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
THP	tetrahydroprogesterone
tid	3 times a day
TQT	thorough QT

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, Open-label Study of Adjunctive Ganaxolone (GNX) Treatment in Children and Adults with Tuberous Sclerosis Complex (TSC)-related Epilepsy (TrustTSC OLE).

Brief Title:
Open-label study of adjunctive GNX treatment 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 hamartin (TSC1) and tuberin (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 Ras homolog enriched in brain (Rheb) (Krueger and Northrup, 2013). Everolimus (Afinitor®), a mechanistic target of rapamycin (mTORC1) 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 (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). 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 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 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 for this study was completed on 08 Mar 2023.

In the double-blind Phase 3 Study 1042-TSC-3001, the primary objective is to assess the safety and efficacy of GNX compared to placebo as adjunctive therapy for seizures associated with TSC-related epilepsy in participants aged 1 through 65 years. The study consists of a 4-week

baseline followed by a 16-week treatment phase, consisting of a 4-week titration and 12-week maintenance period. Study 1042-TSC-3001 began enrolling in 2022 and is ongoing. Study 1042-TSC-2001 and Study 1042-TSC-3001 are parent studies for this open-label extension (OLE).

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 long-term safety and tolerability of GNX as adjunctive therapy for seizures associated with TSC in children and adults.
Secondary Objectives
• For the first year, to determine the percentage of change from baseline[a] in 28-day seizure[b] frequency during open-label treatment. • For the first year, to assess the change in frequency of countable focal seizures frequency from baseline[a] during open-label treatment. • For the first year, to assess changes in mood, behavior, and quality of life using SF-36. • To assess overall clinical outcome using 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.
Endpoints
Primary Endpoints
The primary endpoints are the following safety endpoints: • Incidence and severity of AEs, SAEs and withdrawals and dose-reductions due to AEs. • Vital sign measurements including blood pressure, heart rate, respiratory rate, body temperature, height, and body weight. • Physical, neurological, and developmental examination. • 12-lead ECG. • Clinical laboratory tests. • C-SSRS.
Secondary Endpoints
• Percentage change from baseline[a] in 28-day seizure[b] frequency during open-label treatment (first year only). • Percentage change from baseline[a] in 28-day seizure[b] frequency during the long-term treatment (first year only). • Number (%) of participants considered treatment responders[c] (first year only). • CGI-I at the last scheduled study visit. • Change from baseline in the quality-of-life scale SF-36 (first year only).

- Change from baseline[a] in the percentage of seizure-free days during treatment, based on seizure type[b] (first year only).
- Change from baseline of CGI-CSID.

AE = adverse event; CGI-CSID = Clinical Global Impression of Change in Seizure Intensity/Duration; CGI-I = Clinical Global Impression of Improvement; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; GNX = ganaxolone; PK = pharmacokinetic(s); SAE = serious adverse events; SF-36 = Short Form 36 (version 2); SQS = Sleep Quality Scale; TSC = Tuberous Sclerosis Complex

a Baseline for efficacy assessments is defined as based on the participant's prior study as follows:
- Study 1042-TSC-2001 – the original baseline is considered to be Visit 2 for participants continuing in Study 1042-TSC-3002.
- Study 1042-TSC-3001 – the original baseline is considered to be Visit 2 for participants previously randomized to GNX.

Note: For other assessments, the baseline is considered to be Visit 1, the first visit of the open-label extension (OLE).

b 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 efficacy endpoints 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 seizure frequency during open-label treatment.

Overall Design:
This is a Phase 3, global, OLE study of adjunctive GNX treatment in children and adults with TSC who previously participated in either Study 1042-TSC-3001 or Study 1042-TSC-2001. For this protocol, the term children will refer to the full range of pediatric participants.

For all participants who enter the OLE, the last visit in the parent Study 1042-TSC-3001 or Study 1042-TSC-2001 will be the same as the First Visit in this OLE study and visit activities will not be duplicated.

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

Participants or their parent(s)/caregiver(s) or LAR(s) are expected to complete electronic seizure diary (eDiary) entries to document the number and type(s) of seizures daily throughout the first year of the study. After the first year, study assessments will focus on safety evaluation. Caregiver and clinician global impressions of improvement will continue to be assessed to ensure that participants are continuing to receive benefit from treatment. A variety of clinician and caregiver administered instruments will be used to assess efficacy at the study visits including:

- Clinical Global Impression of Improvement (CGI-I) by parent(s)/caregiver(s) and clinician.
- Caregiver Global Impression of Change in Seizure Intensity/Duration (CGI-CSID).

- Short Form 36 (SF-36) (first year of the study only).

Safety monitoring and assessments will be conducted throughout the study.

The maximum dose for all participants is 1800 mg/day.

Participants who discontinue the investigational product (IP) should undergo a 2-week taper period. The taper period may be shortened, if necessary, for participant safety. Participants who discontinue the IP before the scheduled completion of the study will have an Early Termination Visit, as per Visit 13 (Week 156), and return to the site 2 weeks after the end of the taper period to complete the safety follow-up assessments.

The study design is presented in Figure 1.

Disclosure Statement:
This is an open-label, single arm study with no blinding as all participants will receive adjunctive GNX.

Number of Participants:
It is planned that approximately 169 participants from Study 1042-TSC-3001 and Study 1042-TSC-2001 will be enrolled in this OLE study and continue treatment with GNX.

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 do not participate in the study, 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. Completion of Study 1042-TSC-3001 or participants who continue to meet study requirements in Study 1042-TSC-2001.
2. Participant/parent(s)/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 or able to provide written informed consent based on age, developmental stage, intellectual capacity, or other factors, parent(s)/LAR(s) must provide assent for study participation, if appropriate.
3. Parents/caregivers is (are) willing and able to maintain an accurate and complete daily seizure diary for the duration of the study.
4. Willling and able to take IP (suspension) as directed with food 3 times a day (tid).
5. 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 visit. 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 Visit 1 [first visit of the OLE]), 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.

6. 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.

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

1. Pregnant or breastfeeding.
2. An active central nervous system (CNS) infection, demyelinating disease, or degenerative neurological disease.
3. History of psychogenic nonepileptic seizures.
4. Any disease or condition (other than TSC) at the initial visit that could 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.
5. Unwillingness to avoid excessive alcohol use or cannabis use throughout the study.
6. Have active suicidal plan/intent or have had active suicidal thoughts in the past 6 months or a suicide attempt in the past 6 months.
7. Known sensitivity or allergy to any component in the IP(s), progesterone, or other related steroid compounds.
8. Exposed to any other investigational drug (except for GNX in Study 1042-TSC-2001 or Study 1042-TSC-3001) or investigational device within 30 days or fewer than 5 half-lives prior to Visit 1 (first visit of the OLE). For therapies in which half-life cannot be readily established, the Sponsor's medical monitor should be consulted.

Intervention Groups and Duration:

This is an OLE study and all participants will receive treatment with GNX after completing Study 1042-TSC-3001 (in this study participants previously randomized to placebo will be titrated to GNX under double-blind conditions prior to study completion) or Study 1042-TSC-2001.

In both parent studies, GNX is to be titrated to a maximum dose of 1800 mg/day and given as an oral suspension (50 mg/mL) with food. Participants will continue the GNX dose determined in Study 1042-TSC-3001 or Study 1042-TSC-2001 in this OLE unless a dose change is clinically indicated.

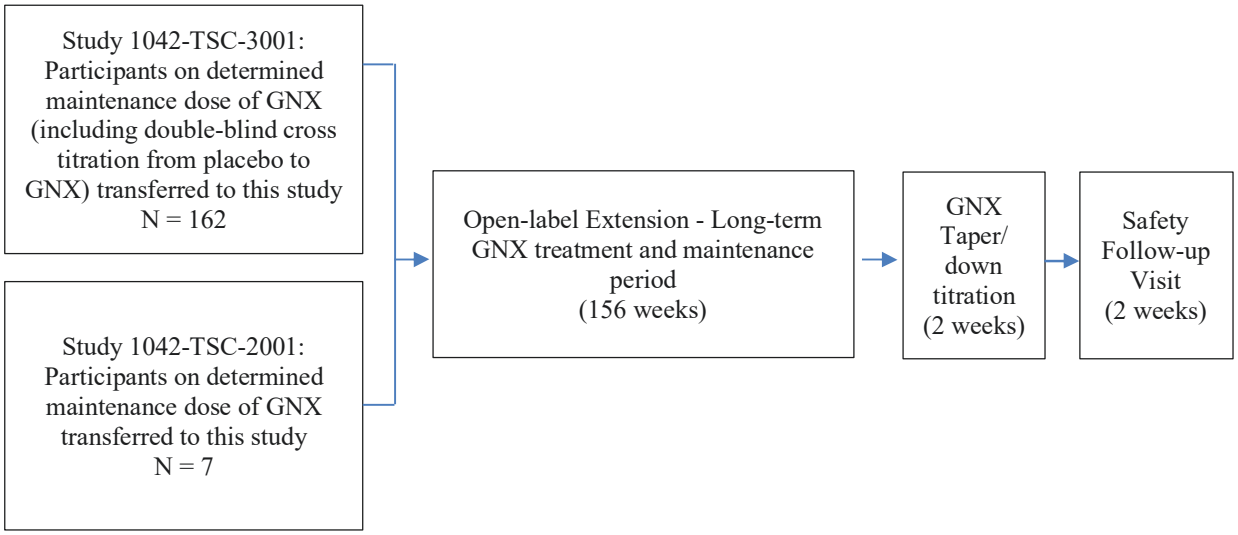
Participants who discontinue the IP should undergo a 2-week taper period, which may be shortened, if necessary, for patient safety. Participants who discontinue the IP before the scheduled completion of the study will have an Early Termination Visit, as per Visit 13 (Week 156), and return to the site 2 weeks after the end of the taper period to complete the safety follow-up assessments.

It is estimated that the maximum duration of participation in this study will be approximately 3 years.

Interim Analysis:
No formal interim analysis is planned.

1.2 Schema

Figure 1. Study Schematic Diagram



GNX = ganaxolone; TSC = Tuberous Sclerosis Complex.

1.3 Schedule of Activities

Table 1. Schedule of Activities for Open-Label Phase

		Open-Label Maintenance												Safety Follow-up
Week (All dates are relative to the first OLE dose on Day 1)		**Year 1**				**Year 2**				**Year 3[b]**				
	0	**13**	**26**	**39**	**52**	**65**	**78**	**91**	**104**	**117**	**130**	**143**	**156**	**160**
Visit and Visit Windows (Telehealth permitted where it is accepted as the standard of care)	**First Visit of the OLE[a] V1**	**All windows for these visits are ± 14 days**												**± 3 days**
		V2 Phone	**V3**	**V4 Phone**	**V5**	**V6 Phone**	**V7**	**V8 Phone**	**V9**	**V10 Phone**	**V11**	**V12 Phone**	**V13 or ET[c]**	**V14**
Screening and Diagnosis														
Informed Consent/Assent	X													
Inclusion/Exclusion Criteria	X													
Demographics and Medical History Review[d]	X													
Safety Assessments														
Vital signs (BP, HR, RR, body temperature, height, weight)	X		X		X		X		X		X		X	X
Physical/Neurological/Developmental Examination	X		X		X		X		X		X		X	X
12-lead ECG	X		X											X
Clinical Laboratory Tests[e]	X		X		X		X		X		X		X	
Pregnancy Test (and dispense pregnancy test for monthly home testing; WOCBP)[f]	X													
Investigational Product PK[g]	X		X		X									
Concomitant ASM Level Review (if collected per standard of care)[h]	X		X		X		X		X		X		X	
Adverse Events	X	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	X
C-SSRS (since previous visit)[i]	X		X		X		X		X		X		X	X

		Open-Label Maintenance												Safety Follow-up
Week (All dates are relative to the first OLE dose on Day 1)		**Year 1**				**Year 2**				**Year 3[b]**				
	0	**13**	**26**	**39**	**52**	**65**	**78**	**91**	**104**	**117**	**130**	**143**	**156**	**160**
Visit and Visit Windows (Telehealth permitted where it is accepted as the standard of care)	**First Visit of the OLE[a] V1**	**All windows for these visits are ± 14 days**												**± 3 days**
		V2 Phone	**V3**	**V4 Phone**	**V5**	**V6 Phone**	**V7**	**V8 Phone**	**V9**	**V10 Phone**	**V11**	**V12 Phone**	**V13 or ET[c]**	**V14**
Efficacy Assessments														
Seizure eDiary review	X	X	X	X	X									
CGI-CSID	X		X		X		X		X		X		X	
CGI-I by parents/ caregiver(s)/LAR(s) and clinician	X		X		X		X		X		X		X	
SF-36	X		X		X									
Investigational Product														
Dispense IP	X		X		X		X		X		X		X	

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; C-SSRS = Columbia-Suicide Severity Rating Scale; eCRF = electronic case report form; ECG = electrocardiogram; ET = early termination; HR = heart rate; IP = investigational product; LAR = legally authorized representative; OLE = open-label extension; PK = pharmacokinetic; QOL = quality of life; RR = respiratory rate; SF-36 = Short Form 36 (version 2); WOCBP = women of childbearing potential.

a Any data collected at the final visit of the parent study will be carried over to Study 1042-TSC-3002. Any procedures not performed at the final visit of the parent study will be conducted at Visit 1 on Day 1 of this study.

b It is estimated that the maximum duration of participation in this OLE study will be approximately 3 years.

c For participants who discontinue treatment, either early, or at Visit 13 (Week 156) and prior to down-titration unless medically indicated.

d Demographics and medical history will be reviewed to confirm there are no changes from the parent study.

e Hematology, clinical chemistry, and urinalysis (see Section 8.3.4).

f A serum pregnancy test is required for all WOCBP at Visit 1 on Day 1 of this OLE study. Urine pregnancy testing will then be performed every 4 weeks throughout the OLE using take-home pregnancy tests. Any positive home pregnany test will be followed up with a confirmatory serum pregnancy test.

g Population PK will be conducted at Visit 3 and Visit 5 and the PK sample can be drawn when convenient during the specified study visit.

h If the levels of ASM co-administered with the IP are measured routinely, this information will be recorded in the eCRF.

i Only for participants ≥ 11 years of age, if appropriate, otherwise, clinical judgment will be used.

2 INTRODUCTION

Ganaxolone (GNX) is a small molecule being developed for use as an anti-seizure medication (ASM) in rare pediatric seizure disorders including cyclin-dependent kinase-like 5 deficiency disorder (CDD),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 mechanistic target of rapamycin complex 1 (mTORC1), an important intracellular regulator of growth and

metabolism via its inhibition of the small GTPase Ras homolog enriched in brain (Rheb) (Krueger and Northrup, 2013). Everolimus (Afinitor®), a mechanistic target of rapamycin (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 spasms (IS) are 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 participants without tubers (Jülich and Sahin, 2014).

2.2.2 Investigational Product Background: 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 cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients 2 years of age and older. GNX is a Schedule V controlled substance.

Ganaxolone is being further evaluated for use as an ASM in adolescents and adults with status epilepticus (SE) and paediatric and adult patients with seizures associated with tuberous sclerosis complex (TSC).

The completed GNX clinical program comprises Phase 1 studies conducted in healthy participants, adults with migraine, and adults with renal impairment and Phase 2/3 studies were conducted in adults with epilepsy, infants and children with seizure disorders, children with fragile X syndrome (FXS), adults with posttraumatic stress disorder (PTSD), women with postpartum depression (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

Study 1042-TSC-2001 and Study 1042-TSC-3001 are parent studies for this OLE.

- In the single arm Phase 2 Study 1042-TSC-2001, 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 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 the study was completed on 08 Mar 2023.

- In the double-blind Phase 3 Study 1042-TSC-3001, the primary objective is to assess the safety and efficacy of GNX compared to placebo as adjunctive therapy for seizures associated with TSC-related epilepsy in participants aged 1 through 65 years. The study consists of a 4-week baseline followed by a 16-week treatment phase, consisting of a 4-week titration and 12-week maintenance period.
  - Study 1042-TSC-3001 began enrolling in 2022 and is ongoing.

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 (23.84% 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, infantile spasms, 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 TSC population. Of the 24 participants screened, 4 discontinued the study due to adverse events (AEs), with somnolence, sedation, and fatigue being the most common treatment-emergent AEs. Additionally, 1 treatment-related SAE of seizure was reported.

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, sedation, and gait disturbance) 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, fatigue, sedation, and gait disturbance. Of the AEs present at frequency > 1% and 2 times the frequency of placebo in the aggregate AE data, all 12 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. However, in Study 1042-SE-2001, 2 SAEs of sedation were reported and led to early discontinuation and revision of the reference safety information.

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

2.3.2 Benefit Assessment

This is an OLE study to evaluate long-term safety and efficacy of adjunctive GNX therapy for seizures associated with TSC in children and adults. This patient population may benefit from the development of GNX as participants will receive GNX treatment that may help control their epilepsy.

2.3.3 Overall Benefit: Risk Conclusion

Taking into account the measures to minimize risk to participants participating in this study, the potential risks identified in association with GNX are justified by the anticipated benefits to participants with TSC-related epilepsy.

3 OBJECTIVES AND ENDPOINTS

Objectives
Primary Objective
• To assess the long-term safety and tolerability of GNX as adjunctive therapy for seizures associated with TSC in children and adults.
Secondary Objectives
• For the first year, to determine the percentage of change from baseline[a] in 28-day seizure[b] frequency during open-label treatment. • For the first year, to assess the change in frequency of countable focal seizures frequency from baseline[a] during open-label treatment. • For the first year, to assess changes in mood, behavior, and quality of life using SF-36. • To assess overall clinical outcome using 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
• To evaluate the long-term effects of GNX as add-on therapy to antiepileptic medications.
Endpoints
Primary Endpoints
The primary endpoints are the following safety endpoints: • Incidence and severity of AEs, SAEs and withdrawals and dose-reductions due to AEs. • Vital sign measurements including blood pressure, heart rate, respiratory rate, body temperature, height, and body weight. • Physical, neurological, and developmental examination. • 12-lead ECG. • Clinical laboratory tests. • C-SSRS.
Secondary Endpoints
• Percentage change from baseline[a] in 28-day seizure[b] frequency during open-label treatment (first year only). • Percentage change from baseline[a] in 28-day seizure[b] frequency during the long-term treatment (first year only). • Number (%) of participants considered treatment responders[c] (first year only). • CGI-I at the last scheduled study visit. • Change from baseline in the quality-of-life scale SF-36 (first year only). • Change from baseline[a] in the percentage of seizure-free days during treatment, based on seizure type[b] (first year only). • Change from baseline of CGI-CSID.

AE = adverse event; CGI-CSID = Clinical Global Impression of Change in Seizure Intensity/Duration; CGI-I = Clinical Global Impression of Improvement; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; GNX = ganaxolone; PK = pharmacokinetic(s); SAE = serious adverse events; SF-36 = Short Form 36 (version 2); SQS = Sleep Quality Scale; TSC = Tuberous Sclerosis Complex.

a Baseline for efficacy assessments is defined as based on the participant's prior study as follows:
- Study 1042-TSC-2001 – the original baseline is considered to be Visit 2 for participants continuing in Study 1042-TSC-3002.
- Study 1042-TSC-3001 – the original baseline is considered to be Visit 2 for participants previously randomized to GNX.

Note: For other assessments, the baseline is considered to be Visit 1, the first visit of the OLE.

b 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 efficacy endpoints 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 seizure frequency during open-label treatment.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 3, global, OLE study of adjunctive GNX treatment in children and adults with TSC-related epilepsy who previously participated in either Study 1042-TSC-3001 or Study 1042-TSC-2001. For this protocol, the term children will refer to the full range of pediatric participants.

For all participants who enter the OLE, the last visit in the parent Study 1042-TSC-3001 or Study 1042-TSC-2001 will be the same as the First Visit in this OLE study and visit activities will not be duplicated.

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

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 first year of the study. After the first year, study assessments will focus on safety evaluation. Caregiver and clinician global impressions of improvement will continue to be assessed to ensure that participants are continuing to receive benefit from treatment. A variety of clinician and caregiver administered outcome measures will be used at the study visits to assess efficacy. These include:

- Clinical Global Impression of Improvement (CGI-I) by parent(s)/caregiver(s) and clinician.
- Caregiver Global Impression of Change in Seizure Intensity/Duration (CGI-CSID).

- Short Form 36 (SF-36) (first year of the study only).

Safety monitoring assessments will be conducted throughout the study.

The maximum dose for all participants is 1800 mg/day.

Participants who discontinue the investigational product (IP) should undergo a 2-week taper period. The taper period may be shortened, if necessary, for participant safety. Participants who discontinue the IP before the scheduled completion of the study will have an Early Termination Visit, as per Visit 13 (Week 156), and return to the site 2 weeks after the end of the taper period to complete the safety follow-up assessments.

The study design is presented in Figure 1.

4.1.1 Study Duration for Participation

It is estimated that the maximum duration of participation in this study will be approximately 3 years.

4.1.2 Number of Participants

It is planned that approximately 169 participants from Study 1042-TSC-3001 and Study 1042-TSC-2001 will be enrolled in this OLE and continue treatment with GNX.

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 do not participate in the study, 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 75 sites (US and ex-US).

4.2 Scientific Rationale for Study Design

This is a Phase 3, OLE 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 patient populations that may benefit from GNX treatment. The eligibility criteria allow for the selection of participants comparable to the expected type of patient seen in clinical practice.

All eligible participants will have the option to receive treatment with GNX in this study after participating in Study 1042-TSC-3001 or Study 1042-TSC-2001.

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; Laxer et al, 2000; Kerrigan et al, 2000; Pieribone et al, 2007).

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.

In both parent studies (Study 1042-TSC-3001 and Study 1042-TSC-2001), GNX is to be titrated to a maximum target dose of 1800 mg/day and given as an oral suspension (50 mg/mL) with food, eg, shortly after a meal or snack.

Participants will continue the GNX dose determined in Study 1042-TSC-3001 or Study 1042-TSC-2001 in this OLE unless a dose change is clinically indicated.
Additional dosing information can be found in Section 6.2.

4.4 End of Study Definition

End of Study (Individual Patient): A participant is considered to have completed the study if they have completed all study visits up to and including Visit 14 (Week 160) (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 (Section 10.1.3) before any procedures specified in the protocol are performed.

5.1 Inclusion Criteria

1. Completion of Study 1042-TSC-3001 or participants who continue to meet study requirements in Study 1042-TSC-2001.
2. Participant/parent(s)/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 or able to provide written informed consent based on age, developmental stage, intellectual capacity, or other factors, parent(s)/LAR(s) must provide assent for study participation, if appropriate.

3. Parent(s)/caregiver(s) is(are) willing and able to maintain an accurate and complete daily seizure diary for the duration of the study.
4. Willing and able to take IP (suspension) as directed with food 3 times a day (tid).
5. 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 visit. 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 Visit 1 [first visit of the OLE]), 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.
6. 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).

5.2 Exclusion Criteria

1. Pregnant or breastfeeding.
2. An active CNS infection, demyelinating disease, or degenerative neurological disease.
3. History of psychogenic nonepileptic seizures.
4. Any disease or condition (other than TSC) at the initial visit that could 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.
5. Unwillingness to avoid excessive alcohol use or cannabis use throughout the study.
6. Have active suicidal plan/intent or have had active suicidal thoughts in the past 6 months or a suicide attempt in the past 6 months.
7. Known sensitivity or allergy to any component in the IP(s), progesterone, or other related steroid compounds.
8. Exposed to any other investigational drug (except for GNX in Study 1042-TSC-2001 or Study 1042-TSC-3001) or investigational device within 30 days or fewer than 5 half-lives prior to Visit 1 (first visit of the OLE). For therapies in which half-life cannot be readily established, the Sponsor's medical monitor should be consulted.

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 consumption grapefruit or grapefruit juice, Seville oranges, or starfruits during the study, or excessive consumption of alcohol during the study.

During each visit when PK samples are collected, participants should 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.

5.4 Screen Failures

There is no screening period in this OLE study and hence no screen failures. Participants enrolled into this study will continue to take the dose of GNX assigned to them in the parent Study 1042-TSC-3001 or Study 1042-TSC-2001.

6 STUDY INTERVENTION(S) 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 (Table 2).

Table 2. Study Intervention(s) Administered

Intervention Label	
Intervention Name	GNX.
Intervention Description	GNX oral suspension, tid.
Dose Formulation	Suspension in 4 fl oz bottles.
Unit Dose Strength(s)	50 mg/mL suspension containing 110 mL GNX.
Dosage Level(s)	Participants in the OLE will take the starting dose as determined in Study 1042-TSC-3001 or Study 1042-TSC-2001. The IP, GNX, is to be administered tid with food, eg, after a meal or snack. See Section 6.2 for details of permitted dose modifications.
Route of Administration	Oral.
Use	ASM in TSC-related epilepsy.
IMP and NIMP/AxMP	GNX.
Sourcing	Provided centrally by the sponsor.
Packaging and Labeling	Ganaxolone is a Schedule V Controlled Substance in the US. The GNX (50 mg/mL) 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. 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; HDPE = high density polyethylene; IP = investigational product; OLE = open label extension; tid = 3 times a day; TSC = tuberous sclerosis complex; US = United States.

6.2 Dose Modification

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

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 rechallenge 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 up to 1800 mg/day. It is estimated that the maximum duration of participation in this OLE study will be approximately 3 years.

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 (CSA) and Drug Enforcement Administration (DEA) 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 IP storage area, such as fumigation of a storage room, that could affect the integrity of the product(s).

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. IP 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 IP 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

This is an open-label study; all participants will be treated with GNX and there is no randomization or blinding of the IP.

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 during the first year. 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 for the OLE 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.

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

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.

Use of dietary supplements or herbal preparations are permitted if the participant has been using them consistently for more than 6 months prior to entry into the OLE and does not plan on changing the dose for the duration of the maintenance period. Use of St. John's Wort and Chinese medicine therapies is not permitted (Section 6.6.2).

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 the 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 allowed 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.

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 during the first year. The medication name, dose, start and stop dates, and frequency of dosing will also be recorded in the clinical database during the second and third year.

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 adrenocorticotropic hormone (ACTH), prednisone or other glucocorticoid is not permitted, nor use of the strong inducers of cytochrome P450 3A4 (CYP3A4) (except approved ASMs: carbamazepine, phenytoin derivatives, phenobarbital, or primidone), rifampin, St. John's Wort, and Chinese medicine therapies.

Note: Concomitant intranasal or pro re nata (PRN) topical steroids for dermatologic reactions and allergic rhinitis are allowed.

Products containing tetrahydrocannabinol (THC) or non-approved CBD are excluded during treatment. THC or non-approved CBD should be washed out for at least 4 weeks prior to the initial visit. Participants with a positive result on THC or CBD laboratory tests during the parent study, and who do not have an explanatory Epidiolex®/Epidyolex® prescription, will not be eligible to participate in this OLE.

6.7 Intervention After the End of the Study

Treatment can continue until the sponsor terminates this study.

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 such, as drug-induced rash. If the participant discontinues the IP, evaluations listed for the Early Termination Visit (Visit 13 [Week 156]; as shown in the SOA [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 IP, and total amount of IP taken must be recorded in the eCRF and source documents. Discontinuation of 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.

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:
  - Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT) or alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT) > 3 × upper limit of normal (ULN).
  - Total bilirubin levels > 1.5 × ULN.
  - Estimated glomerular filtration rate (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.

At the time of discontinuing from the study, if possible, an Early Termination Visit (Visit 13 [Week 156]) should be conducted as shown in the SOA (Table 1). 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 10.1.9.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SOA (Section 1.3). Study dates will be based on the date of the first dose of IP in this OLE and not the date of 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 by the site staff using 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 evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain an enrollment log to record details of all participants from 1042-TSC-3001 and 1042-TSC-2001 studies who enter this OLE and to confirm eligibility or record reasons for participant exclusion, as applicable.

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

8.1 General Study Periods

8.1.1 Screening, Enrollment, Randomization, and Baseline

There is no screening period in this OLE study. Participants from Study 1042-TSC-3001 and Study 1042-TSC-2001 will be enrolled in this OLE if eligible and continue maintenance treatment with GNX.

Note for Investigational Sites in the United Kingdom (UK): 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 assessments (Section 10.1.3 for the informed consent procedure). This will occur at the end of the double-blind treatment period in Study 1042-TSC-3001 and before any dose adjustments are made or prior to entry into the OLE for participants in Study 1042-TSC-2001.

8.1.1.1 Demographics and Medical History

Demographics including age, gender, ethnicity, and race, as allowed according to local regulations, will be collected in the parent study. 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 in the parent study as will the participant's developmental history. This will include the grade level of schoolwork 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.

Details of prior medications include all treatment, including but not limited to herbal treatments, vitamins, surgical implants (such as vagal nerve stimulator [VNS]), and prescribed medications, will be collected.

Demographics and Medical History will be reviewed at the end of the parent(s)/LAR(s) study/Visit 1 (First Visit of the OLE).

8.1.1.2 Seizure Identification and Diagnostic Review

Per the inclusion criteria of the parent study, enrollment will be based on the presence and frequency of the seizure types defined as follows:

- 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 efficacy endpoints 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.

To standardize seizure identification and classification in the study, a Seizure Identification Form/Diagnostic Review Form (SIF/DRF) will be submitted and reviewed by the Epilepsy Study Consortium prior to the participant's entry into the parent study and this information will be used in this OLE.

8.1.2 Open-label Treatment Phase

Open-label treatment with the IP, at the dose determined in the parent study, will continue in this OLE. All dates during the open-label phase will be based off the date of the first dose of IP in the OLE.

Participants who discontinue the study prematurely before Visit 13 (Week 156) 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 for Visit 13 should then be performed (Table 1).

8.1.3 Safety Follow-up

A safety follow-up visit will be conducted at Visit 14 (Week 160), which will be 2 weeks after the end of the 2-week taper for participants who are not continuing commercially available GNX (Table 1). This will be the end of study visit for these participants.

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 diary. Days in which no seizures occur will also be noted. Changes in seizure intensity/duration, CGI-I, as well as changes in behavior and neuropsychiatric symptoms will be assessed by a variety of clinician and caregiver administered instruments.

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

8.2.1 Seizure Type and Frequency

The Epilepsy Study Consortium will review participant seizure data and assign the seizure type for each participant in the parent study.

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

Seizure types that count towards the efficacy endpoints 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 efficacy endpoints 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 during the first year. 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 – 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 IP relative to baseline (prior to treatment with 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 (Section 10.8).

Clinical Global Impression – Improvement (parent/caregiver/LAR and clinician) will be assessed at Visit 1 (First Visit of the OLE), Visit 3 (Week 26), Visit 5 (Week 52), Visit 7 (Week 78), Visit 9 (Week 104), Visit 11 (Week 130), and Visit 13 (Week 156).

8.2.3 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 investigational product relative to baseline (prior to treatment with investigational product). The scale ranges from 1- very much improved, 2- much improved, 3- minimally improved, 4- no change, 5- minimally worse, 6- much worse, and 7- very much worse (Section 10.9).

CGI-CSID will be assessed at Visit 1 (First Visit of the OLE), Visit 3 (Week 26), Visit 5 (Week 52), Visit 7 (Week 78), Visit 9 (Week 104), Visit 11 (Week 130), and Visit 13 (Week 156).

8.2.4 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 (Section 10.10).

The SF-36 will be conducted at Visit 1 (First Visit of the OLE), Visit 3 (Week 26), and Visit 5 (Week 52).

8.3 Safety Assessments

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

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 questions using an identifiable sound, single word, multiple word, or 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 at Visit 1 (First Visit of the OLE), Visit 3 (Week 26), Visit 5 (Week 52), Visit 7 (Week 78), Visit 9 (Week 104), Visit 11 (Week 130), Visit 13 (Week 156), and Visit 14 (Week 160).

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 BP, pulse, and RR. Three readings of BP 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 collected at Visit 1 (First Visit of the OLE), Visit 3 (Week 26), Visit 5 (Week 52), Visit 7 (Week 78), Visit 9 (Week 104), Visit 11 (Week 130), Visit 13 (Week 156), and Visit 14 (Week 160).

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 heart rate and measures PR, QRS, QT, and QTc intervals.

12-lead ECGs will be performed at Visit 1 (First Visit of the OLE), Visit 3 (Week 26), and Visit 14 (Week 160).

8.3.4 Clinical Safety Laboratory Tests

Laboratory safety assessments will be collected to monitor participant safety. Clinical laboratory tests are listed in Section 10.3 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 as serum pregnancy test for all WOCBP. 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 glomerular filtration rate [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.

Blood samples will be collected for clinical laboratory tests at Visit 1 (First Visit for the OLE), Visit 3 (Week 26), Visit 5 (Week 52), Visit 7 (Week 78), Visit 9 (Week 104), Visit 11 (Week 130), and Visit 13 (Week 156).

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 25 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. In the pediatric population, the blood volumes collected should be minimized as much as possible.

In addition, urinalysis will be conducted at Visit 1 (First Visit for the OLE), Visit 3 (Week 26), Visit 5 (Week 52), Visit 7 (Week 78), Visit 9 (Week 104), Visit 11 (Week 130), and Visit 13 (Week 156) for all participants.

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 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 suicidal ideation and behavior and to report such symptoms immediately to the study investigator.

The 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) (Section 10.11). 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 will be completed at Visit 1 (First Visit of the OLE) (and compared with data collected in the parent study), and then 6-monthly at Visit 3 (Week 26), Visit 5 (Week 52), Visit 7 (Week 78), Visit 9 (Week 104), Visit 11 (Week 130), Visit 13 (Week 156), and Visit 14 (Week 160) (and compared with data collected in the previous visit).

8.3.6 Concomitant Anti-seizure Medicine Levels

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

Further details are provided in the SOA (Table 1).

8.3.7 Investigational Product Pharmacokinetics

Please refer to Section 8.6 for additional details regarding PK assessments.

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

8.3.8 Pregnancy Testing

A serum pregnancy test is required for all WOCBP at Visit 1 on Day 1 of this OLE study. Urine pregnancy testing will then be performed every 4 weeks throughout the OLE using take-home pregnancy tests. Any positive home pregnany test will be followed up with a confirmatory serum pregnancy test.

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/caregiver/LAR) throughout the study (Table 1).

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 (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 of the first dose of the IP in the OLE until the defined follow-up period at the timepoints specified in the SOA (Section 1.3). Any AE that begins in a parent study and is ongoing at the time of the first dose of IP in the OLE will be included as an AE in the OLE. This includes events occurring during the initial visit in the study, regardless of whether or not the IP has been administered. All AEs reported after the initiation of IP will be considered treatment-emergent AEs. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed

individually. All AEs should be captured on the appropriate AE pages in the eCRF and in source documents. In addition to untoward AEs, unexpected benefits outside the IP indication should also be captured on the AE eCRF page.

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.

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)/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 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 (SUSARs) 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 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 vital signs, physical, neurological, and developmental examinations, 12-lead ECG parameters, or clinical laboratory values 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 treatment period, there are abnormal vital signs, physical, neurological, and developmental, 12-lead ECG, or clinical laboratory 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 the change 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 on a routine basis.

Note: However, if either of the following 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 event of special interest (AESI) includes any non-serious conduction 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 the 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 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 (900 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

8.6.1 Pharmacokinetics

Whole blood samples of approximately 2 mL will be collected for measurement of the plasma concentrations of GNX as specified in the SOA (Section 1.3).

There is no specified time window for collection of the blood sample for PK analyses.

The time of the participants' last dose of the IP and the time of their next dose of the IP should be specified in relation to the time of the PK draw.

The actual date and time (24-hour clock time) each sample is collected must be accurately recorded in the source document and appropriate eCRF.

Instructions for the collection and handling of biological samples will be provided by the sponsor. Please refer to the laboratory manual for processing instructions.

Samples will be used to evaluate the PK of GNX. Each sample will be divided into 2 aliquots (1 for PK, 1 as a backup). Samples collected for analyses of GNX concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Additional samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

8.6.2 Pharmacodynamics

PD parameters are not evaluated in this study.

8.7 Genetics

Genetic parameters are not evaluated in this study.

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 Analysis Sets

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

Participant Analysis Set	Description
Intent-to-treat (ITT) set	All participants who receive at least 1 dose of the IP. Participants will be summarized overall and by the treatment group to which they were randomized in the parent study (placebo or GNX). This population will be used for efficacy analyses.
Safety analysis set	All participants who receive at least 1 dose of the IP. This population will be used for the safety analyses.

GNX = ganaxolone; IP = investigational product/GNX.

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 efficacy analyses will be performed within the ITT population.

9.2 Statistical Analyses

9.2.1 General Considerations

The results of the primary, secondary, and exploratory endpoints will be summarized separately. The results will be summarized by the treatment received by participants in the parent study. Participant demographics, characteristics, and medical history at randomization or the start of the parent study will be summarized using descriptive statistics.

9.2.2 Primary Endpoints

The primary endpoints are the following safety endpoints:

- Incidence and severity of AEs, SAEs and withdrawals and dose-reductions due to AEs.
- Vital sign measurements including BP, HR, RR, body temperature, height, and body weight.
- Physical, neurological, and developmental examination.
- 12-lead ECG.
- Clinical laboratory tests.
- C-SSRS.

Further details are provided in Section 9.2.5.

9.2.3 Secondary Endpoints Analysis

The secondary endpoints are:

- Percentage change from baseline in 28-day seizure frequency during open-label treatment (first year only).
- Percentage change from baseline in 28-day seizure frequency during the long-term treatment (first year only).
- Number (%) of participants considered treatment responders (first year only).
- CGI-I at the last scheduled study visit.
- Change from baseline in the quality-of-life scale SF-36 (first year only).
- Change from baseline in the percentage of seizure-free days during treatment, based on seizure type (first year only).
- Change from baseline of CGI-CSID.

All the endpoints will be included in data listings.

9.2.4 Pharmacokinetic Analysis

A population PK approach addressing the relationship between GNX PK parameters and individual characteristics will be implemented as follows:

- Visit 3 (Week 26).
- Visit 5 (Week 52).

For PK assays there is no specified time to draw the PK sample and these can be drawn whenever convenient during the specified study visits.

Exact time of sample withdrawal and drug intake will be recorded in the eCRF.

9.2.5 Safety Analyses

All safety analyses will be performed in the Safety Population. The results will be summarized overall and by the treatment received in the parent study (placebo or GNX).

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

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

Safety assessments include:

- AEs.
- Vital signs including BP, HR, RR, body temperature, height, and body weight.
- Physical, neurological, and developmental examinations.
- 12-lead ECG.
- Clinical laboratory tests.
- Concomitant ASM levels (as detailed in Section 8.3.6).
- C-SSRS.

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

9.2.6 Subgroup Analysis

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

- Gender (Female vs Male).
- Age groups (1 to 6 years; 7 to 12 years; 13 to 17 years; and 18 years and above).

All the analyses will follow the rules:

- The results will be presented overall, for participants previously enrolled in Study 1042-TSC-2001, and for participants previously enrolled in Study 1042-TSC-3001 results will also be classified according to the double-blind treatment received by participants in Study 1042-TSC-3001.
- The seizure endpoints will be derived starting from the first dosing day of OLE treatment.
- No per protocol analyses will be performed

9.3 Interim Analysis

No formal interim analysis is planned.

9.4 Sample Size Determination

Approximately 169 participants will be enrolled, which is a combination of participants who completed Study 1042-TSC-3001 or Study 1042-TSC-2001. The total sample size is not powered for the primary and secondary endpoints.

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 sub-investigators 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)/LAR(s) and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants/parents(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.

Participant/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/caregiver(s) or LAR(s).

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 investigator's 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 will also 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 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.

10.1.7 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 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)/caregiver(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.

10.1.8 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.

10.1.9 Study and Site Start and Closure

10.1.9.1 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.

10.1.9.2 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 investigational product 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

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IRBs/IECs, 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.

10.1.10 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.

10.1.11 Sample Storage and Destruction

Any blood including PK samples collected according to the SOA (Section 1.3) 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 6 months 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 an SAE, the investigator must notify the sponsor by email or fax the Marinus Clinical Study Serious Adverse Event Form within 24 hours to Marinus' drug safety vendor at:

- Email: safetyTSC3001@marinuspharma.com
- Fax: +1 484-679-2138

10.2.2 Sponsor Contacts

10.2.2.1 Sponsor Medical Monitor

[redacted]
Consultant Medical Monitor
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]
VP, Clinical Development
Mobile Telephone: [redacted]
Email: [redacted] (primary contact method)

10.2.2.2 Sponsor Project Managers

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

Back-up:

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

10.3 Appendix 3: Clinical Laboratory Safety 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 such as hematology, clinical chemistry, or urinalysis 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[a]	• Quantitative serum β-HCG serum pregnancy
Other tests	• Drug screen[b] • Follicle-stimulating hormone and estradiol (as needed in women of nonchildbearing potential only) • Vital signs (BP, HR, RR, and body temperature) • 12-lead ECG

AST = aspartate aminotransferase; β-HCG = β-human chorionic growth hormone; BP = blood pressure; BUN = blood urea nitrogen; CBD = cannabidiol; eGFR = estimated glomerular filtration rate; ECG = electrocardiogram; HR = heart rate; RR = respiratory rate; SGOT = serum glutamic oxaloacetic transaminase; THC = tetrahydrocannabinol.

a Any positive home pregnany test will be followed up with a confirmatory serum pregnancy test.

b 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 during the first visit of the OLE.

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 [ICH] 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) who has signed 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(s)/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 ECG, radiological scans, 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:
Results in death
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.
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.
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.
Is a congenital anomaly/birth defect
Is a suspected transmission of any infectious agent via an authorized medicinal product
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 of the first dose of IP in the OLE.
- 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 reporting forms.
- 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 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 visit. 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, 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.

10.6 Appendix 6: Country-specific Requirements

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

10.7 Appendix 7: Dosing Instructions for Oral Suspension

GANAXOLONE 1042-TSC-3002 STUDY
DOSING INSTRUCTIONS FOR ORAL SUSPENSION

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 kg).

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

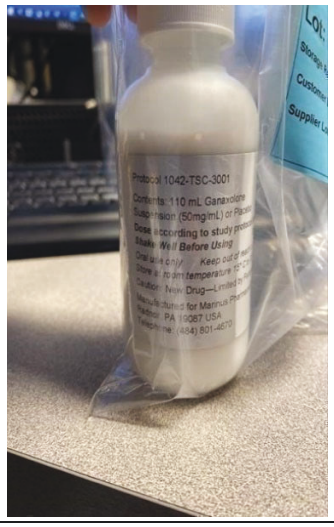
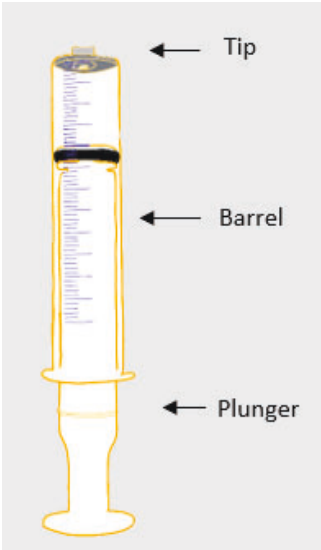
GANAXOLONE 1042-TSC-3002 STUDY
DOSING INSTRUCTIONS FOR ORAL SUSPENSION

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

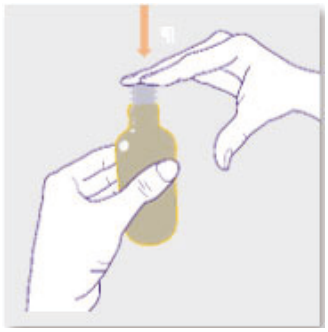
Important:

- Follow your study doctor's instructions for the dose of study drug to take or give. Study drug must 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:

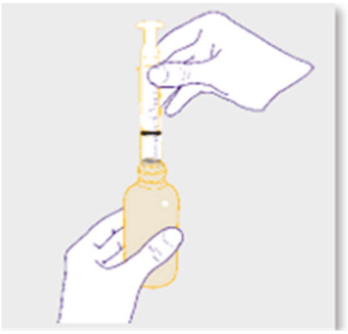
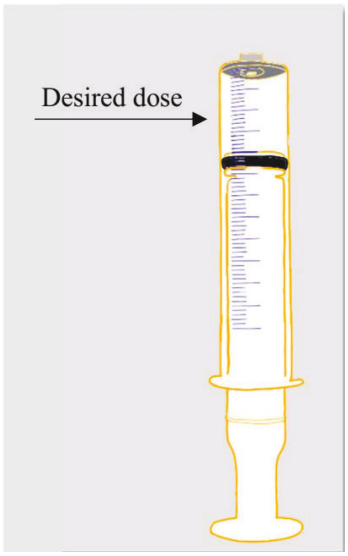
Child-resistant cap:	
Press-in bottle adapter:	
Bottle of study drug:	
Reusable oral syringe to take or give the dose of study drug: **Note:** If you lose or damage an oral syringe, or cannot read the markings, use a new syringe. Contact your study doctor for extra syringes if you run out.	

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 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 medication. This helps you measure the correct amount of medicine. **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 adaptor is fully inserted. If not fully inserted, small parts such as the bottle adaptor 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.

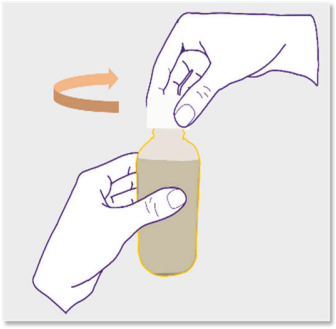
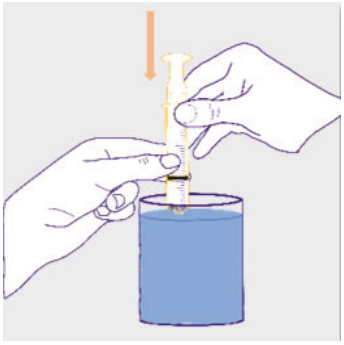
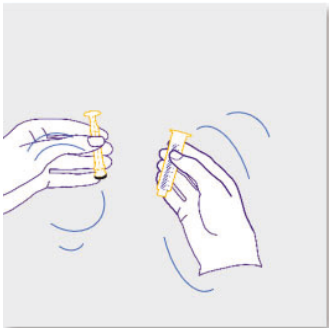
5. Gather the oral syringe, push the plunger all the way down and insert the tip of the oral syringe fully into the press-in bottle adapter. With the syringe in place, turn the bottle upside down.	 
6. Slowly pull the plunger of the oral syringe to withdraw the dose of study drug needed. Line up the 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 press-in 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.

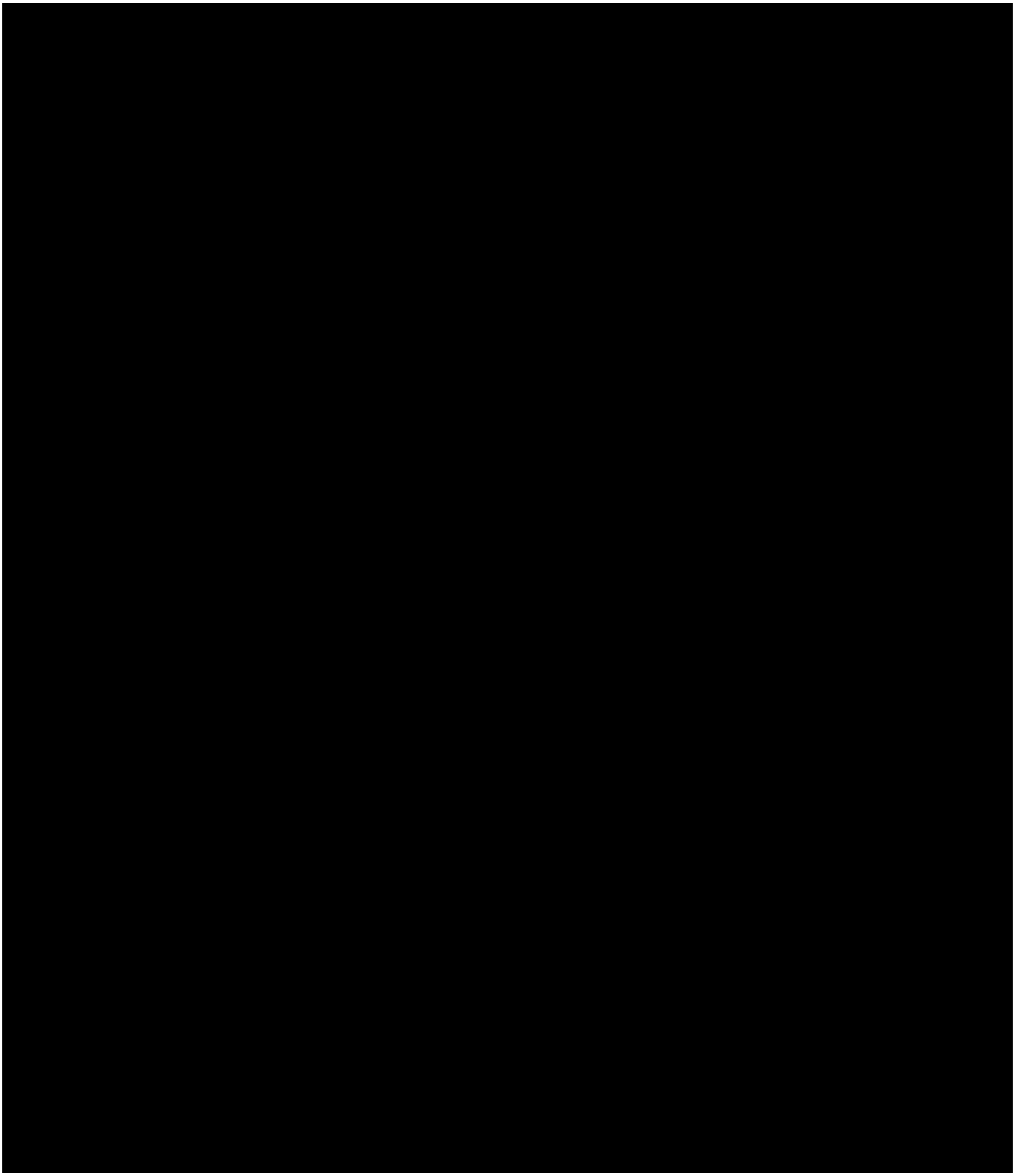
Frequently asked Questions:

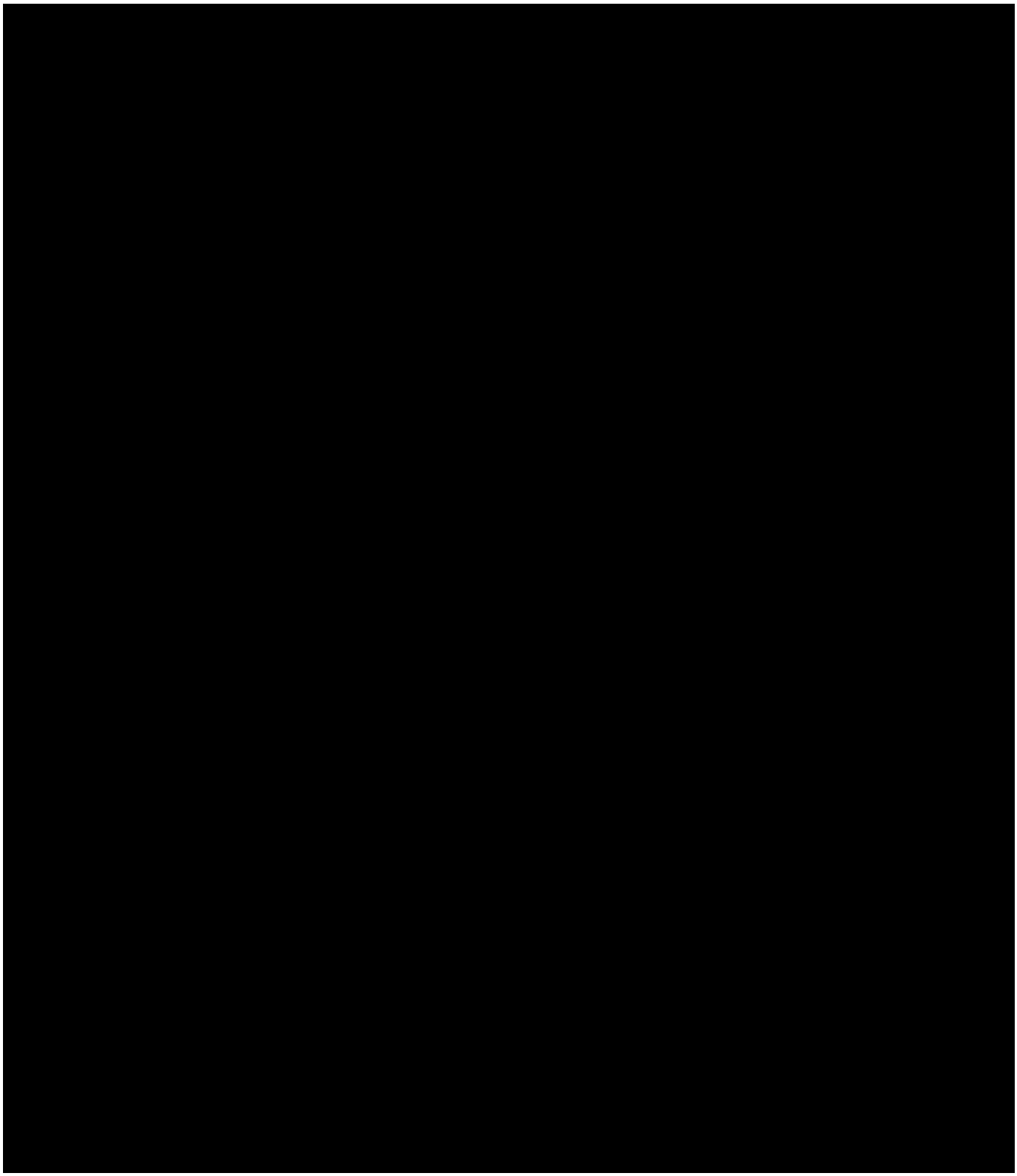
Q: What if there are air bubbles in the oral syringe?

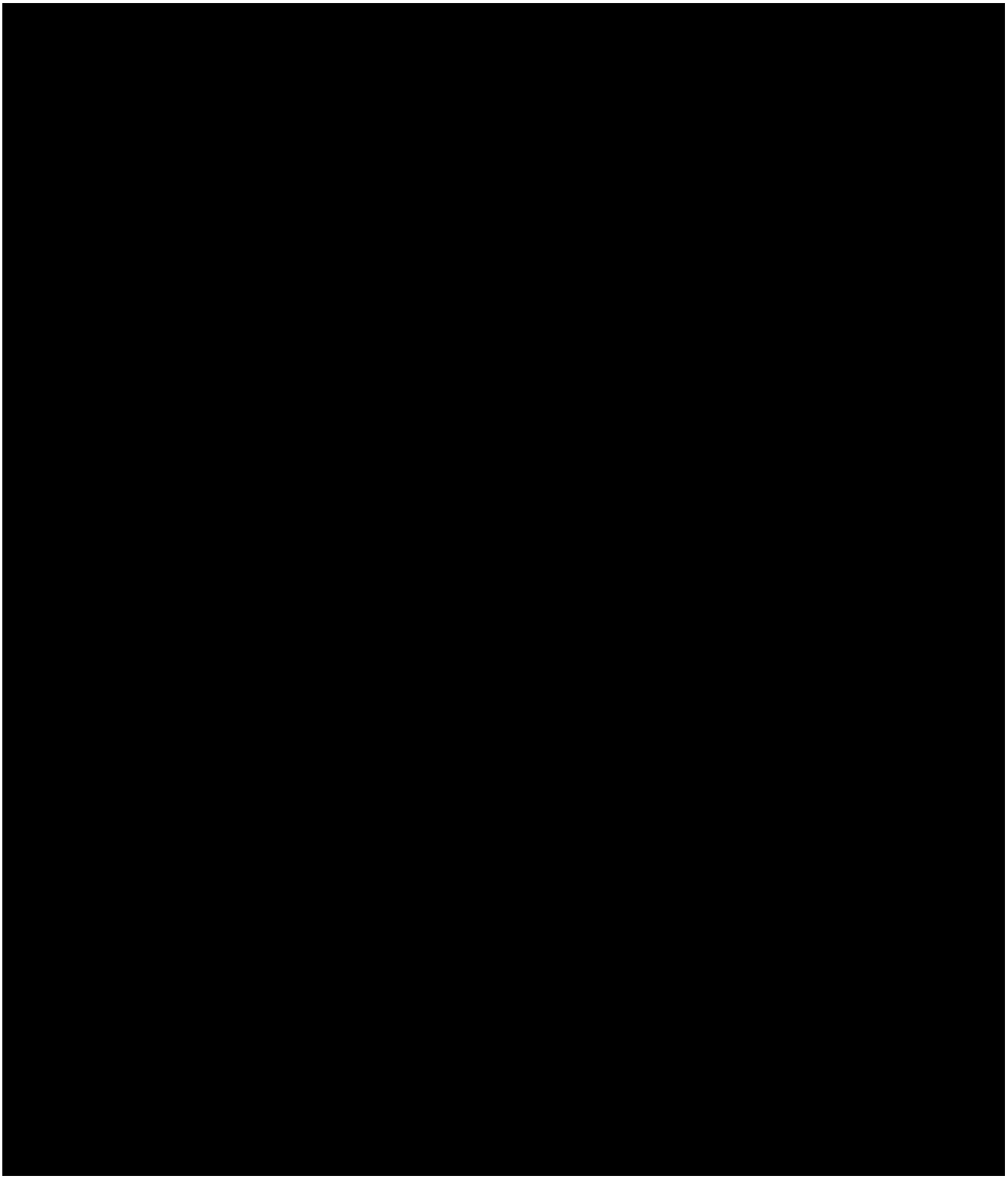
A: Slowly push the liquid back into the bottle and repeat step 6 until the air bubbles are gone.

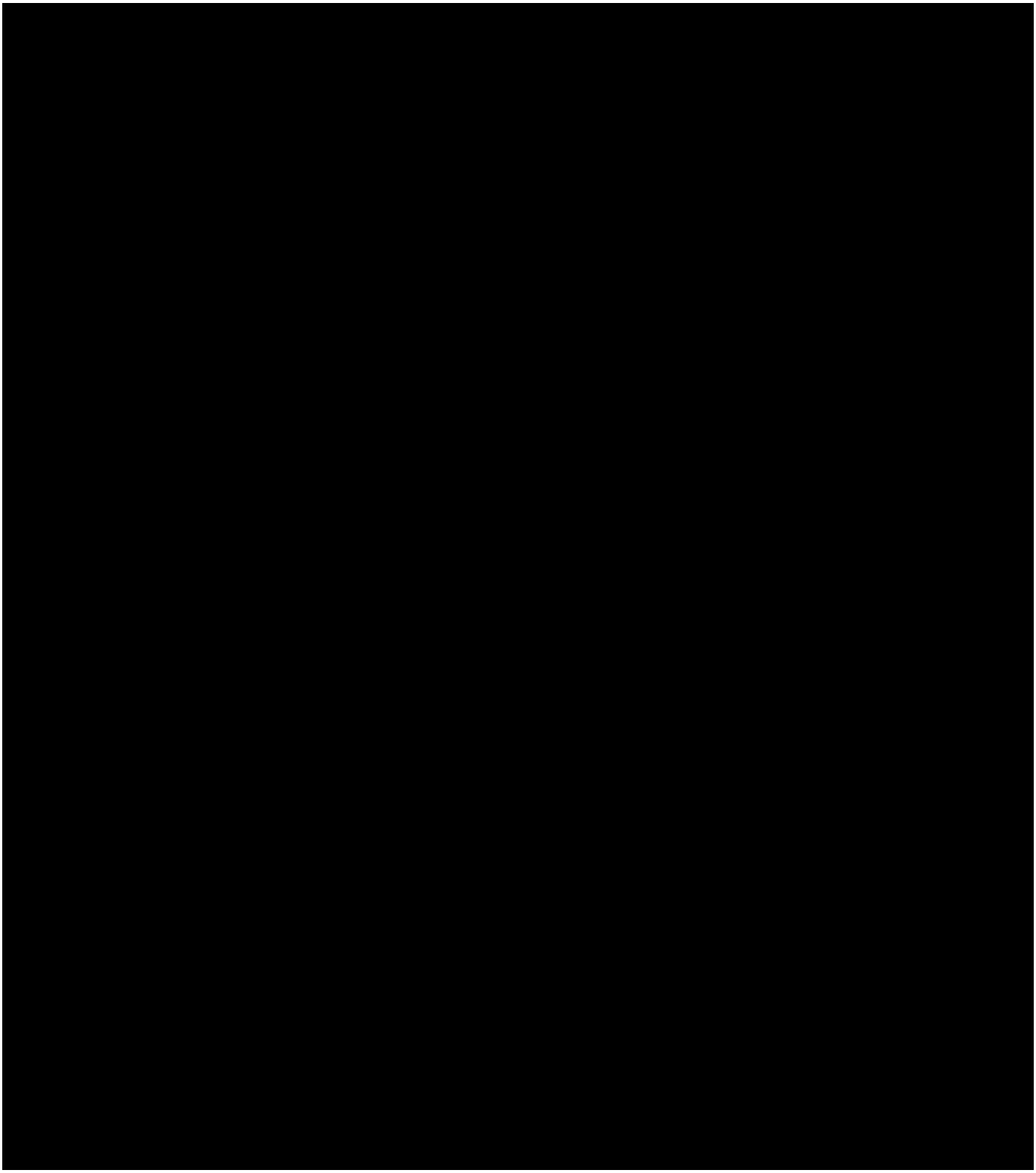
Q: What should I do if the oral syringe is not completely dry before use?

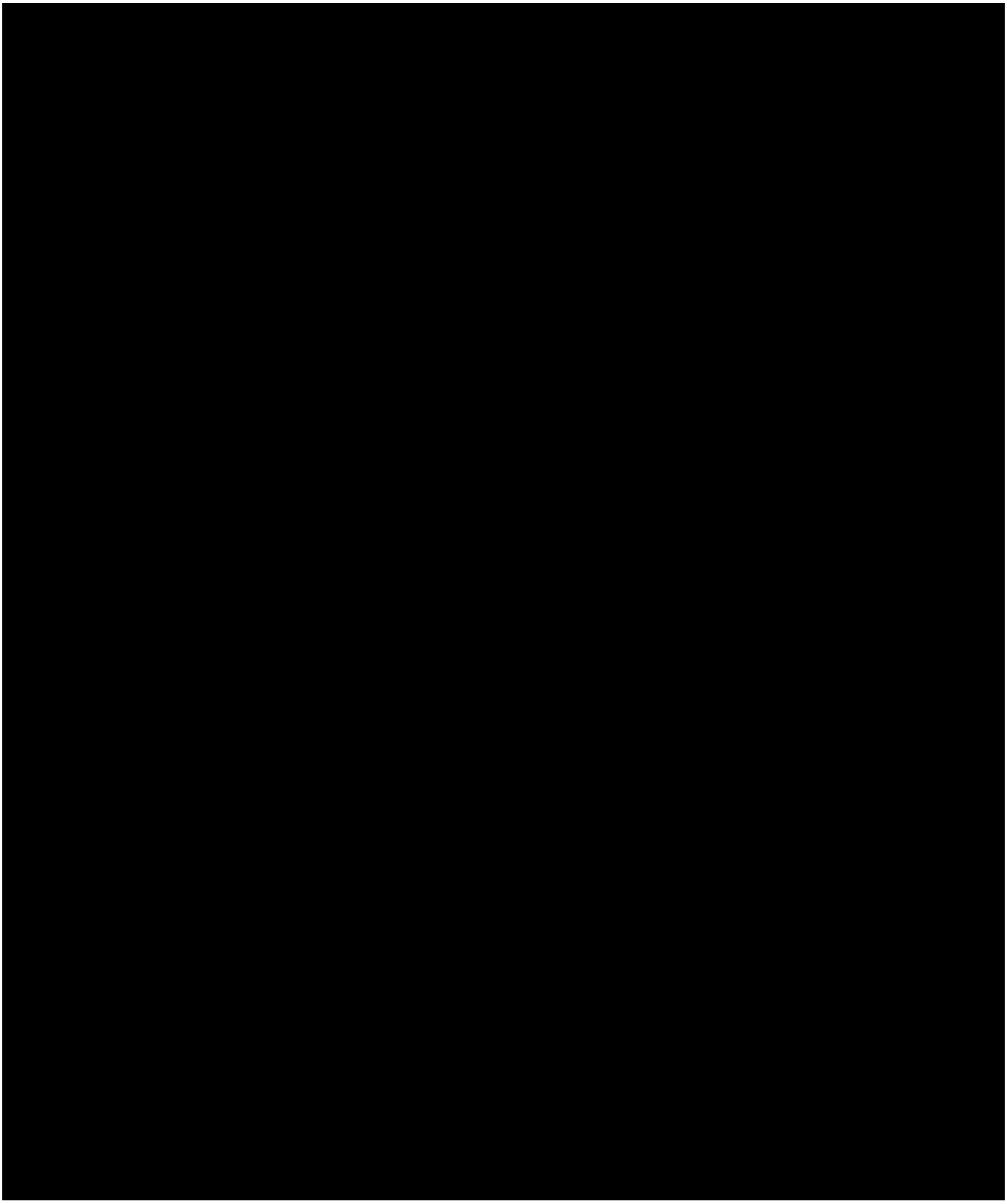
A: If the oral syringe is not completely dry, use a spare syringe provided by your study doctor.

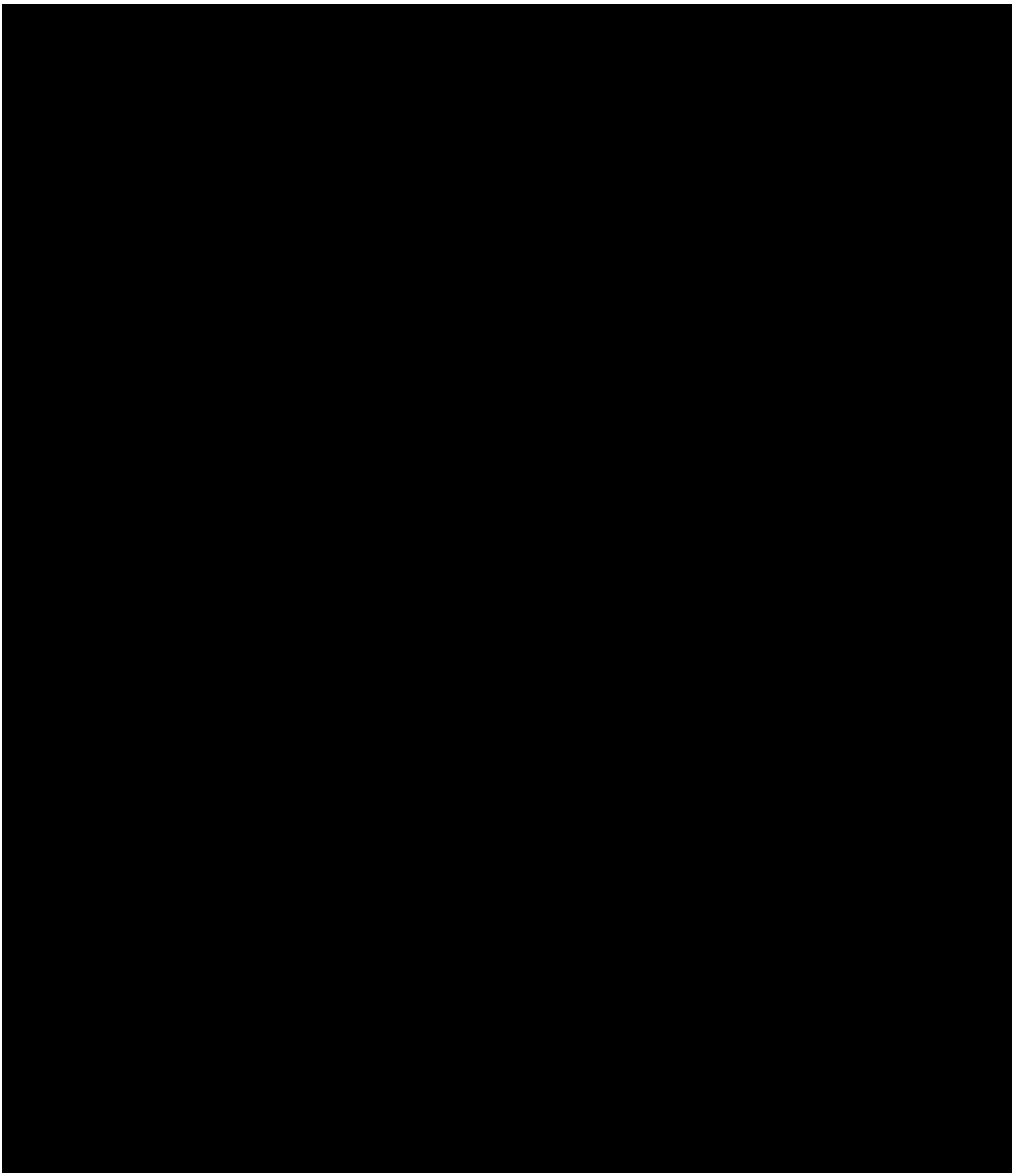


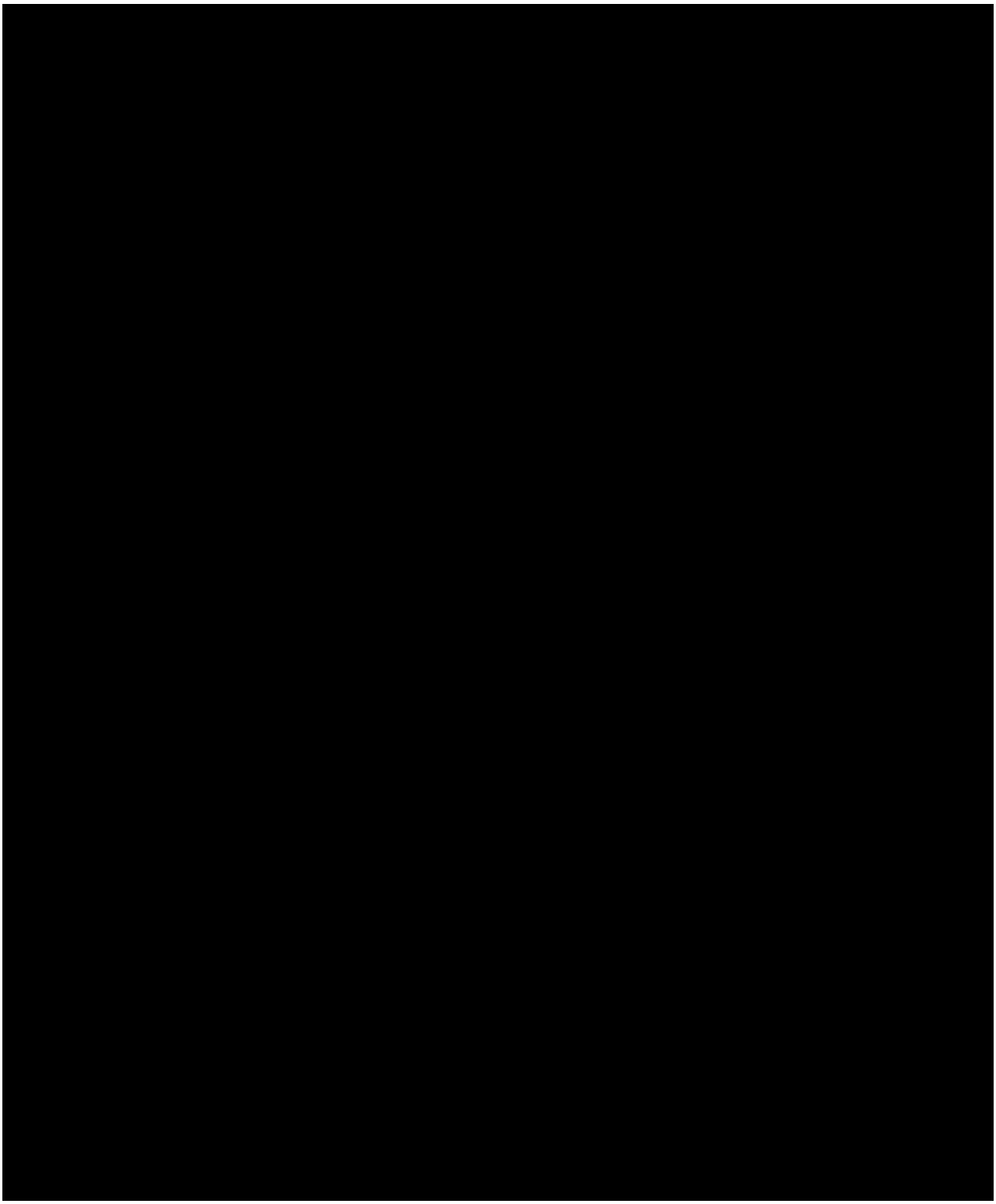


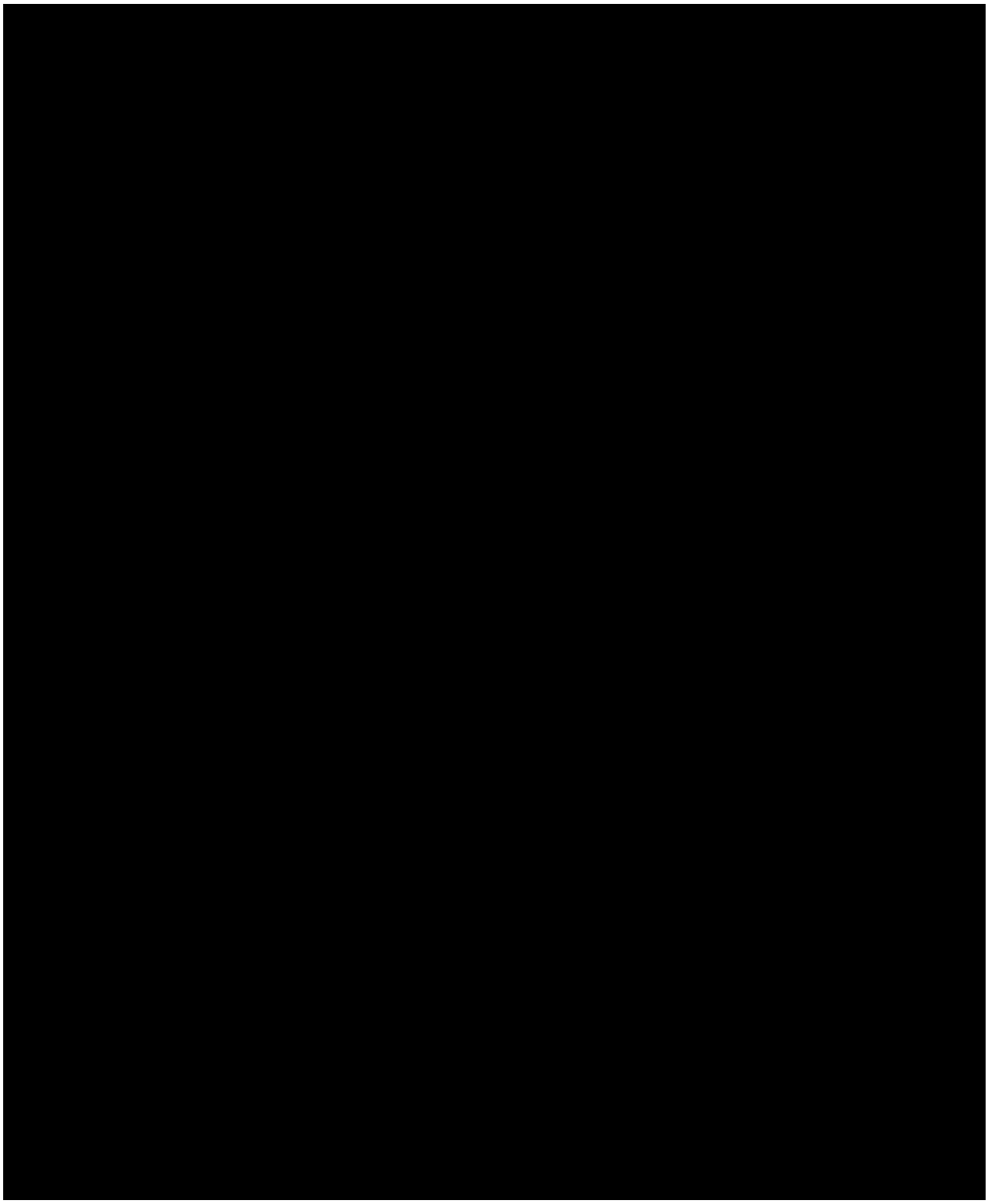












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