CLINICAL STUDY PROTOCOL

[redacted]

An Open-Label Study to Evaluate the Long-Term Safety, Tolerability, and Efficacy of OV101 in Individuals with Angelman Syndrome (ELARA)

PROTOCOL NUMBER OV101-18-002

Sponsor:	Ovid Therapeutics Inc. [redacted]
Sponsor Contact:	[redacted]
Medical Monitor:	[redacted]
Current Protocol:	Protocol Amendment 03 (Version 04)
Date of Protocol:	13 October 2020
Previous Protocol Version and Date	Protocol Amendment 02 (Version 03): 18 November 2019 Protocol Amendment 01 (Version 02): 30 September 2019 Original Protocol (Version 01): 18 September 2018

CONFIDENTIAL

The study will be conducted according to the International Council for Harmonisation tripartite guideline E6 (R2): Good Clinical Practice.

Declaration of Investigator

I have read and understood all sections of the protocol entitled "An Open-Label Study to Evaluate the Long-Term Safety, Tolerability, and Efficacy of OV101 in Individuals with Angelman Syndrome (ELARA)" and the accompanying investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 4.0, the International Council for Harmonisation tripartite guideline E6 (R2): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with Ovid Therapeutics Inc. or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to study participants. I agree to administer study treatment only to study participants under my personal supervision or the supervision of a sub-investigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Study participant identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Ovid Therapeutics Inc.

Signature of Principal Investigator	Date

Printed Name of Principal Investigator

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Protocol Synopsis

Protocol Number:

OV101-18-002

Title:

An Open-Label Study to Evaluate the Long-Term Safety, Tolerability, and Efficacy of OV101 in Individuals with Angelman Syndrome (ELARA)

Sponsor:

Ovid Therapeutics Inc.
1460 Broadway
New York, NY 10036

Study Phase:

3

Study Sites:

Approximately 15 sites (total) in the United States, Australia, Europe, and Israel

Estimated Study Duration:

The planned duration of study participation for a study participant is approximately 3 years (from start of screening to the end-of-study visit), or until the study drug is commercially available. There are 8 scheduled clinic visits, 2 scheduled phone visits, and 5 telehealth/virtual visits.

Indication:

Angelman syndrome (AS)

Rationale:

Ovid Therapeutics Inc. (Ovid) is developing OV101 (gaboxadol) for the treatment of rare genetic disorders that are associated with severe developmental and behavioral challenges that have no approved therapies, such as AS and Fragile X syndrome. Gaboxadol was initially developed for the treatment of insomnia by H. Lundbeck A/S and Merck, but its development was discontinued in 2007 for commercial reasons. Extensive nonclinical and clinical data were generated during the initial stages of development, including data from exposure to gaboxadol in more than 4000 adult study participants (950 study participant years) with insomnia and approximately 500 adult study participants in non–insomnia-related studies.

Angelman syndrome is a severe, complex, and rare neurogenetic disorder with the prevalence of approximately 1 in every 10,000 to 24,000 live births. The condition is associated with impaired expression of the ubiquitin protein ligase E3A gene (*UBE3A*). While ubiquitin protein ligase E3A (UBE3A) is expressed bi-allelically in the cells of other tissues, in neurons the paternal allele is preferentially silenced through the epigenetic process known as imprinting. Therefore, any alteration in the maternal copy of *UBE3A* results in AS. Clinical findings range in severity and include developmental delay/intellectual disability, movement and/or balance disorder, and tremulous movement of limbs. Unique behavioral characteristics include the combination of a happy, smiling demeanor with easily provoked laughter and excitability (exhibited by hand-flapping and stereotypic movements). Individuals with AS frequently have motor dysfunction related

to gait and balance, severe disruptions in sleep, little to no speech, short attention span, anxiety, and seizures with characteristic abnormal electroencephalogram patterns.

Current treatments are aimed at managing symptoms and include antiepileptic medications for seizure control and medications for sleep and behavioral problems (e.g., anxiety). Other therapies include speech therapy, physical therapy, occupational therapy, and educational resources. Notably, current treatments do not target the underlying brain deficits.

OV101 is the first highly selective, extrasynaptic gamma-aminobutyric acid (GABA) receptor agonist that binds orthosterically to the δ-subunit of extrasynaptic GABA receptors. The mechanism of action of OV101 is unique among GABAergic agents, including benzodiazepines, zolpidem and other zolpidem-like drugs, neurosteroids, and drugs that act on GABA metabolism or uptake. Research has shown that absence (or dysfunction) of UBE3A results in an aberrant increase in the uptake of GABA, which is the main inhibitory neurotransmitter in the brain. OV101 is the first highly selective GABA receptor agonist that acts on α4δ-containing GABA A-receptors. These receptors mediate tonic inhibition and sleep maintenance. In a mouse model of AS, OV101 was shown to restore tonic inhibition in UBE3A-deficient cerebellar neurons and correct motor abnormalities in UBE3A-deficient mice. These results suggest that OV101 may alleviate the motor dysfunction observed in individuals with AS. Importantly, OV101's ability to potentiate tonic inhibition is unlike any other GABAergic agent, including benzodiazepines, zolpidem, zaleplon, zopiclone, barbiturates, neurosteroids, and drugs that act on GABA metabolism or uptake. In addition to the data on presynaptic dysfunction leading to reduced tonic inhibition, there are additional studies which speak to the potential of OV101 in AS, including modulation of sleep and cognition domains that are impaired in study participants with AS.

Phase 2 and Phase 3 studies in adult study participants with primary insomnia demonstrated that OV101 is effective in restoring classical sleep parameters (sleep induction and sleep maintenance) and slow wave sleep, resulting in an improvement in the quality and restorative effects of sleep.

A randomized, double-blind, placebo-controlled Phase 2 study (OV101-15-001, STARS; NCT02996305) evaluated the safety, tolerability, and efficacy of OV101 in adolescents and adults with AS over 12 weeks of treatment. Eighty-eight participants with AS (13 to 49 years old) were randomly assigned to 1 of 3 groups: once-daily (QD) dose of OV101 nightly (15 mg), twice-daily (BID) dose of OV101 (10 mg morning and 15 mg night), and placebo. The safety and tolerability of OV101 from Baseline to Week 12 was evaluated by comparing the frequency and severity of adverse events (AEs) and serious AEs (SAEs) in the OV101 treatment groups to those in the placebo group. OV101 was generally safe and well tolerated, with a similar incidence of AEs across all treatment groups: most AEs were mild. Treatment discontinuations due to AEs were low (placebo, 1; OV101 QD, 0; OV101 BID, 3). The most frequent AEs across all treatment groups were vomiting, somnolence, irritability, aggression, pyrexia, and upper respiratory infection. The AEs occurring in the OV101 treatment groups with greater frequency than placebo were pyrexia, rash, seizure, enuresis, myoclonic epilepsy, otitis media, and viral infection. Two study participants had an SAE of seizure: 1 study participant in the BID

group deemed "Possibly Related" and 1 study participant in the QD group deemed "Not Related."

This open-label study (OV101-18-002) will evaluate the long-term (160-week) safety and efficacy of OV101 in study participants with AS who either have completed previous Ovid studies (OV101-15-001, OV101-16-001, or OV101-19-001) or are siblings (with AS) of study participants with AS who have completed previous Ovid studies of OV101.

Objectives:

The primary objective of this study is to evaluate the long-term safety and tolerability of OV101 in individuals with AS assessed by the incidence and severity of AEs and SAEs in study participants who are at least 2 years old at the time of enrollment into this study.

The secondary objectives of this study are the following:

- To evaluate the long-term efficacy of OV101 treatment assessed by changes in behavior and sleep in study participants with AS who are at least 4 years old at the time of enrollment into this study
- To evaluate long term efficacy as assessed by clinical global impression of severity and improvement scales, VABS, CHSQ, PedsQL, and Sleep Diary in study participants with AS who are at least 4 years old at the time of enrollment into this study
- To evaluate the long-term safety and tolerability of OV101 treatment assessed by changes in suicidality assessments, vital sign measurements, laboratory assessments, physical examinations, and seizure frequency in study participants with AS who are at least 2 years old at the time of enrollment into this study.

The exploratory objective of this study is to explore the relationships among study endpoints (e.g., behavior and sleep), where appropriate.

Study Population:

Inclusion Criteria:

Each study participant must meet all the following criteria to be enrolled in this study:

1. Ovid study enrollment criteria:

- Has completed the OV101-15-001 or OV101-16-001 study up to the end of study (EOS), or
- Has completed the OV101-19-001 study up to the end of treatment (EOT), or
- Is a sibling of a study participant with AS who has completed OV101-15-001, OV10116001, or OV101-19-001

2. Has a previous diagnosis of AS with molecular confirmation.
3. Is at least 2 years old and has a body weight of at least 9 kg.
4. Has a legally acceptable representative (LAR)/caregiver capable of providing informed consent and able to attend all scheduled study visits, oversee the administration of study drug, and provide reliable, consistent feedback regarding the study participant's symptoms and performance as described in the protocol.
5. Provides assent to the protocol (to the extent possible and in accordance with local institutional review board and regulatory requirements) and has a LAR/caregiver who will provide written informed consent. Study participants providing assent must do so at the same visit as LAR/caregiver written informed consent is provided.
6. Can swallow study drug capsules with water or ingest the contents of study drug capsules after sprinkling the capsule contents onto up to 1 teaspoon of low-fat semiliquid food.
7. If a study participant is currently receiving a regimen of concomitant medications such as antiepileptic medication, gabapentin, clonidine, trazodone, melatonin, and/or a special dietary regimen, that study participant's regimen is stable for at least 4 weeks before Day 1 (first day of study drug administration) and will be maintained throughout the duration of the study (in the judgment of the investigator).
8. Has a LAR/caregiver(s) who agree not to post any of the study participant's personal medical data/condition or information related to the study on any website, message board, online support group, or social media site (e.g., Facebook, Instagram, Twitter) until notified that the study is completed.
9. Female study participants who are of childbearing potential (defined as having experienced their first menarche) must agree to use either a highly effective or acceptable form of birth control during the study and for 30 days following the last dose of the study drug. Highly effective contraceptive methods are as follows:
   - Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
     - Oral
     - Intravaginal
     - Transdermal
   - Progestogen-only hormonal contraception associated with inhibition of ovulation:
     - Oral
     - Injectable
     - Implantable
   - Intrauterine device

- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide*
- Cap, diaphragm, or sponge with spermicide*

  *A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

Exclusion Criteria:

Study participants meeting any of the following criteria will be excluded from the study:

1. Discontinued from the OV101-15-001, OV101-16-001, or OV101-19-001 study due to safety reasons causally related to OV101.
2. Has a circumstance, condition, concomitant disease (e.g., gastrointestinal, renal, hepatic, endocrine, respiratory, or cardiovascular system disease), or any clinically significant finding that could interfere with the conduct of the study or that would pose an unacceptable risk to the study participant in this study.
3. Has poorly controlled seizures defined as any of the following:
   - Weekly seizures of any frequency with a duration of more than 3 minutes each
   - Weekly seizures occurring more than 3 times per week, each with a duration of less than 3 minutes
   - Investigator assessment
4. Has any of the following laboratory abnormalities: total bilirubin >1.5 × upper limit of normal (ULN), unless known Gilbert's syndrome; alanine aminotransferase or aspartate aminotransferase >2.5 × ULN; serum creatinine >1.2 × ULN; absolute neutrophil count $<1.5 \times 10^9$/L; platelets $<80 \times 10^9$/L; hemoglobin <80 g/L; or thyroid-stimulating hormone >1.25 × ULN or <0.8 × lower limit of normal. Retesting of clinical laboratory parameters may be allowed after consultation with the medical monitor or designee.
5. Use of benzodiazepines, zolpidem, zaleplon, zopiclone, eszopiclone, barbiturates, or ramelteon for sleep, or minocycline or levodopa within the 4 weeks prior to Day 1 or during the study. Benzodiazepines administered as needed or regularly scheduled for indications other than insomnia and benzodiazepines for seizure control are permitted.
6. Is at risk of harming self and/or others (based on investigator assessment).
7. With the exception of an Ovid study of OV101, has enrolled in any clinical or used any investigational agent or device, or has participated in any investigational procedure, within the 30 days before screening or does so concurrently with this study. Observational study participation is allowed.
8. Is allergic to OV101 or any excipients of study drug.
9. The study participant or LAR/caregiver is unable to comply with study requirements (based on investigator assessment).

Study Design:

This will be an open-label, long-term safety study for evaluation of treatment with OV101 in approximately 170 study participants with AS who either have completed previous Ovid studies (OV101-15-001, OV101-16-001, or OV101-19-001) or are siblings (with AS) of study participants with AS who have completed previous Ovid studies of OV101 There will be no placebo treatment. As this study will enroll study participants who may have completed previous studies for different periods of time before entering this study (as well as study participants with AS who have not been themselves enrolled

in an Ovid study), study participants may be required to complete screening and baseline visits before receiving OV101 under this protocol.

The study will comprise a screening period of up to 30 days; a baseline visit on Day 1 for baseline assessments (at which the first dose of study drug will be taken at the site unless a patient is unable to attend a clinic visit in person due to COVID-19 restrictions, in which case the first dose of study drug to be taken at bedtime in the evening of Day 1); and clinic visits for safety and efficacy assessments over a 3-year treatment period. Baseline visits must be conducted on site and not remotely for patients who did not complete an OV101 antecedent study (eg, siblings [with AS] of study participants with AS who have completed previous Ovid studies of OV101). After the baseline visit, the clinic visits will occur at Weeks 12, 36, 64, 96, 128, and 160 (end of treatment [EOT]). If a patient cannot attend an in-person visit, a home visit may be conducted by a trained mobile healthcare professional to perform study assessments e.g. vital signs, body system assessment, clinical labs draws, review/collection of study materials.

Telehealth/virtual visits will occur at Weeks 24, 48, 80, 112, and 144. A follow-up phone safety visit at the EOS will occur approximately 14 days after the last dose of study drug (EOT) to assess safety and tolerability associated with discontinuation of treatment. A home nurse/healthcare professional visit will replace a virtual visit if the latter is not feasible. A study participant will be considered to have completed the study after completing the EOS phone visit.

The following study participants will be required to complete screening and baseline visits (and assessments) to determine eligibility before receiving OV101 under this protocol:

- Study participants who completed OV101-15-001 or OV101-16-001
- Study participants who are siblings of study participants who have completed OV101-15-001, OV101-16-001, or OV101-19-001
- Study participants who completed treatment in OV101-19-001 more than 2 weeks before completing the baseline visit under this protocol (OV101-18-002)

For study participants required to complete the screening and baseline visits, the planned duration of study participation is approximately 3 years (from the start of screening to the EOS visit), or until the study drug is commercially available.

For study participants completing the EOT visit for OV101-19-001 two weeks or less before enrolling in this OV101-18-002 protocol, the OV101-19-001 EOT visit may serve as the baseline visit for OV101-18-002. Clinical laboratory results assessed at EOT in OV101-19-001 will serve as baseline clinical laboratory results in OV101-18-002.

Study participants who meet all eligibility criteria will be enrolled on Day 1 (baseline visit) and start the study drug that evening at bedtime (not in the clinic). Each study

participant's LAR/caregiver will receive a package of study drug at the baseline visit, sufficient to last until the Week 12 visit.

Each study participant's dose of OV101 will be titrated to a maintenance dose, as tolerated by the study participant. The maximum tolerated dose (up to 15 mg at bedtime) will be maintained to the EOT. [redacted]

Phone calls to manage titration will occur on Days 6 and 11 for all study participants. [redacted]

At the Week 12, 36, 64, 96, and 128 visits, each study participant's LAR/caregiver will receive a package of study drug sufficient to last until the next scheduled visit (e.g., every 3 to 4 months) at the maximum possible dose. Unused study drug should be returned to the site at each visit.

The LAR/caregivers will complete sleep diaries on behalf of study participants over the 7-day periods immediately preceding Baseline and should be returned to the site at each visit.

The LAR/caregivers will complete seizure diaries each day during the treatment period and should be returned to the site at each visit.

Safety information will be collected during phone calls and during clinic visits. If a study participant experiences any AEs or is unable to take the study drug as prescribed, the caregiver/LAR is instructed to contact the study center. Dose adjustments are permitted for study participants who are unable to tolerate the specified dosing regimen.

At the investigator's discretion throughout the study, study participants may be evaluated at unscheduled clinic visits for reasons related to study participant safety. At unscheduled visits, study participants will be queried about AEs, changes in concomitant medications, and suicidality, and safety laboratory assessments may be conducted. Periodic interim review of safety data will be performed as part of routine pharmacovigilance activities and to support regulatory submission.

Assessments:

Safety assessments related to the study objectives of evaluating safety and tolerability of OV101 will include frequency, severity, and causality of AEs (including SAEs and AEs leading to study discontinuation), vital sign measurements, laboratory assessments, physical examinations, suicidality assessments, and seizure diary.

Efficacy assessments will include the Children's Sleep Habits Questionnaire; 7-day sleep diaries; the Pediatric Quality of Life Inventory; the Vineland Adaptive Behavior Scale, 3rd Edition; and Clinical Global Impressions (Severity and Improvement) scales. Note that efficacy assessments are only to be conducted in study participants who are at least 4

years old at study entry. If a study participant is 2 to 3 years old at study entry and turns 4 years old during the course of the study, only safety assessments are to be continued.

Study Drug, Dosage, and Route of Administration:

OV101 will be supplied as capsules containing 5-mg, 2-mg, or 0.5-mg of study drug.

Each study participant will be titrated to his/her maximum tolerated daily dose, up to a maximum daily dose of 15 mg (see **Study Design**, above).

Study participants will take all doses orally (assisted by a LAR/caregiver, if necessary), in the evening at bedtime. Capsules may be opened, with the contents sprinkled onto up to 1 teaspoon of low-fat semiliquid food (e.g., applesauce, yogurt, pudding) for ingestion, but this approach must be followed consistently throughout the study.

Sample Size:

Approximately 170 study participants will be enrolled.

Statistical Methods:

Analysis sets include the enrolled analysis set (study participants enrolled in the extension study), the safety analysis set (all study participants who receive at least 1 dose of study drug), and the full-analysis set (all study participants who receive at least 1 dose of study drug and have at least 1 post baseline efficacy assessment).

Descriptive statistics (number of study participants, mean, SD, median, minimum, and maximum) will be presented for continuous variables and frequency and percentage will be presented for categorical and ordinal variables. If there are missing values, the number missing will be presented, but without a percentage. All data collected will be included in by-study participant data listings. Two-sided 95% CIs will be provided where appropriate. Graphical displays will be utilized to investigate trends over time overall and by relevant subgroups as needed.

Separate analyses of selected endpoints, including but not limited to Clinical Global Impressions-Improvement-Angelman syndrome, Clinical Global Impressions-Severity-Angelman syndrome, and seizure diary data, will be performed for the study participants who have participated in STARS and the study participants who have participated in the NEPTUNE study (Study OV101-19-001).

All safety analyses will be performed on the safety analysis set. Treatment-emergent adverse events (TEAEs) are defined as AEs that start or increase in severity after the first dose of study drug in this open-label study. The number and percentage of study participants who experience at least 1 TEAE as well as the 95% exact CI for the incidence of TEAEs overall and within each specific Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) will be presented.

Treatment-related AEs will be identified as those that are at least possibly related to study drug based on the investigator's assessment. The number and percentage of study participants with treatment-related AEs, SAEs, TEAEs leading to study discontinuation, and TEAEs leading to death will also be summarized by SOC and PT. For each SOC and each PT, a study participant will be counted only once for study participant-incidence

tabulations. For summaries by severity or relationship, for a given study participant, the highest severity and relationship for a specific PT will be considered.

Descriptive statistics for laboratory values and vital sign measurements at each timepoint will be summarized. Clinically significant laboratory values may be tabulated.

Shift tables for laboratory parameters will be presented.

Shift tables for Clinical Assessments of Suicidality will also be presented to show the change in answers (yes/no) from baseline to post baseline visits.

Abnormal findings in physical examinations will be listed.

The 28-day seizure frequencies as captured in the seizure diary will be calculated for baseline and post baseline study periods for all seizure types and for subtypes of drop and nondrop. Percent change in 28-day seizure frequency from baseline to all post baseline study visits will also be summarized descriptively for all seizure types and for subtypes of drop and nondrop.

Concomitant medications will be coded using the World Health Organization Drug Dictionary. A table summarizing concomitant medications and a by-study participant listing of concomitant medications will include all medications taken during the study regardless of the timing for the start of medication.

Descriptive statistics and 95% CIs for efficacy variables at each timepoint will be displayed. Line graphs of time course of change (or percent change) from baseline will be presented for the secondary efficacy endpoints and for the average dose.

Version and Date of Protocol: Version 4.0; 17 September 2020

List of Abbreviations

Abbreviation	Definition
ABC	Aberrant Behavior Checklist
ABC-I	Aberrant Behavior Checklist-Irritability subscale
[redacted]	[redacted]
AE	adverse event
AS	Angelman syndrome
$AUC_{0-\infty}$	area under the concentration-time curve from 0 to infinite hours
ß-hCG	beta-human chorionic gonadotrophin
BID	twice daily
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impressions-Improvement
CGI-I-AS	Clinical Global Impressions-Improvement-Angelman syndrome
CGI-S-AS	Clinical Global Impressions-Severity-Angelman syndrome
C_{max}	maximum plasma concentration
CSHQ	Children's Sleep Habits Questionnaire
CSR	clinical study report
DRF	diagnostic review form
EAS	enrolled analysis set
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
EOT	end of treatment
FAS	full-analysis set
FDA	US Food and Drug Administration
GABA	gamma-aminobutyric acid
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IRB	institutional review board
LAR	legally acceptable representative
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
PedQoLI	Pediatric Quality of Life Inventory
PBPK	physiologically based pharmacokinetic

Abbreviation	Definition
PT	preferred term
QD	once daily
SAE	serious adverse event
SIF	seizure identification form
SOC	system organ class
SS	safety analysis set
TEAE	treatment-emergent adverse event
UBE3A	ubiquitin protein ligase E3A
UBE3A	ubiquitin protein ligase E3A gene
ULN	upper limit of normal
VABS-3	Vineland Adaptive Behavior Scale, 3rd Edition

1 Introduction

Ovid Therapeutics Inc. (Ovid) is developing OV101 (gaboxadol) for the treatment of rare genetic disorders that are associated with severe developmental and behavioral challenges that have no approved therapies, such as Angelman syndrome (AS) and Fragile X syndrome. Gaboxadol was initially developed for the treatment of insomnia by H. Lundbeck A/S and Merck, but its development was discontinued in 2007 for commercial reasons. Extensive nonclinical and clinical data were generated during the initial stages of development, including data from exposure to gaboxadol in more than 4000 adult study participants (950 study participant-years) with insomnia and approximately 500 adult study participants in non–insomnia-related studies.

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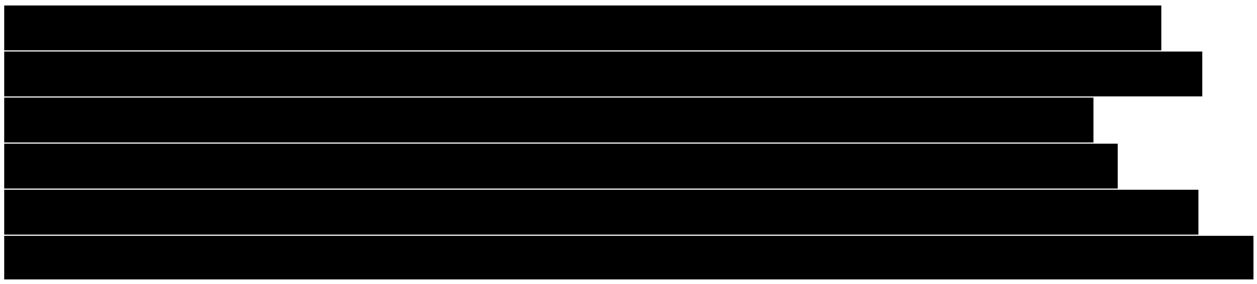
OV101 is the first highly selective, extrasynaptic gamma-aminobutyric acid (GABA) receptor agonist that binds orthosterically to the δ-subunit of extrasynaptic GABA receptors. The mechanism of action of OV101 is unique among GABAergic agents, including benzodiazepines, zolpidem and other zolpidem-like drugs, neurosteroids, and drugs that act on GABA metabolism or uptake. Research has shown that absence (or dysfunction) of UBE3A results in an aberrant increase in the uptake of GABA, which is the main inhibitory neurotransmitter in the brain. OV101 is the first highly selective GABA receptor agonist that acts on α4δ-containing GABA A-receptors. These receptors mediate tonic inhibition and sleep maintenance. In a mouse model of AS, OV101 was shown to restore tonic inhibition in UBE3A-deficient cerebellar neurons and

correct motor abnormalities in UBE3A-deficient mice (Egawa et al 2012). These results suggest that OV101 may alleviate the motor dysfunction observed in individuals with AS. Importantly, OV101's ability to potentiate tonic inhibition is unlike any other GABAergic agent, including benzodiazepines, zolpidem, zaleplon, zopiclone, barbiturates, neurosteroids, and drugs that act on GABA metabolism or uptake. In addition to the data on presynaptic dysfunction leading to reduced tonic inhibition, there are additional studies which speak to the potential of OV101 in AS, including modulation of sleep and cognition domains that are impaired in study participants with AS (Ramamoorthi and Lin 2011; Brickley and Mody 2012; Egawa and Fukuda 2013; Deidda et al 2014; Berry et al 2015; Dissel et al 2015).

Phase 2 and Phase 3 studies in adult study participants with primary insomnia demonstrated that OV101 is effective in restoring classical sleep parameters (sleep induction and sleep maintenance) and slow wave sleep, resulting in an improvement in the quality and restorative effects of sleep.

A randomized, double-blind, placebo-controlled Phase 2 study (OV101-15-001, STARS; NCT02996305) evaluated the safety, tolerability, and efficacy of OV101 in adolescents and adults with AS over 12 weeks of treatment (Bird et al 2019). Eighty-eight participants with AS (13 to 49 years old) were randomly assigned to 1 of 3 groups: once-daily (QD) dose of OV101 nightly (15 mg), twice-daily (BID) dose of OV101 (10 mg morning and 15 mg night), and placebo. The safety and tolerability of OV101 from Baseline to Week 12 was evaluated by comparing the frequency and severity of adverse events (AEs) and serious AEs (SAEs) in the OV101 treatment groups to those in the placebo group. OV101 was generally safe and well tolerated, with a similar incidence of AEs across all treatment groups: most AEs were mild. Treatment discontinuations due to AEs were low (placebo, 1; OV101 QD, 0; OV101 BID, 3). The most frequent AEs across all treatment groups were vomiting, somnolence, irritability, aggression, pyrexia, and upper respiratory infection. The AEs occurring in the OV101 treatment groups with greater frequency than placebo were pyrexia, rash, seizure, enuresis, myoclonic epilepsy, otitis media, and viral infection. Two study participants had an SAE of seizure: 1 study participant in the BID group deemed "Possibly Related" and 1 study participant in the QD group deemed "Not Related."



This open-label study (OV101-18-002) will evaluate the long-term (160-week) safety and efficacy of OV101 in study participants with AS who either have completed previous Ovid studies (OV101-15-001, OV101-16-001, or OV101-19-001) or are siblings (with AS) of study participants with AS who have completed previous Ovid studies of OV101.

2 Study Objectives and Assessments Related to Endpoints

2.1 Primary Objective

The primary objective of this study is to evaluate the long-term safety and tolerability of OV101 in individuals with AS assessed by the incidence and severity of AEs and SAEs in study participants who are at least 2 years old at the time of enrollment into this study.

2.2 Secondary Objectives

The secondary objectives of this study are the following:

- To evaluate the long-term efficacy of OV101 treatment assessed by changes in behavior and sleep in study participants with AS who are at least 4 years old at the time of enrollment into this study
- To evaluate long term efficacy as assessed by clinical global impressions of severity and improvement scales, VABS, CHSQ, PedsQL, and Sleep Diary in study participants with AS who are at least 4 years old at the time of enrollment into this study.
- To evaluate the long-term safety and tolerability of OV101 treatment assessed by changes in suicidality assessments, vital sign measurements, laboratory assessments, physical examinations, and seizure frequency in study participants with AS who are at least 2 years old at the time of enrollment into this study.

2.3 Exploratory Objectives

The exploratory objective of this study is the following:

- To explore the relationships among study endpoints (e.g., behavior and sleep), where appropriate

3 Investigational Plan

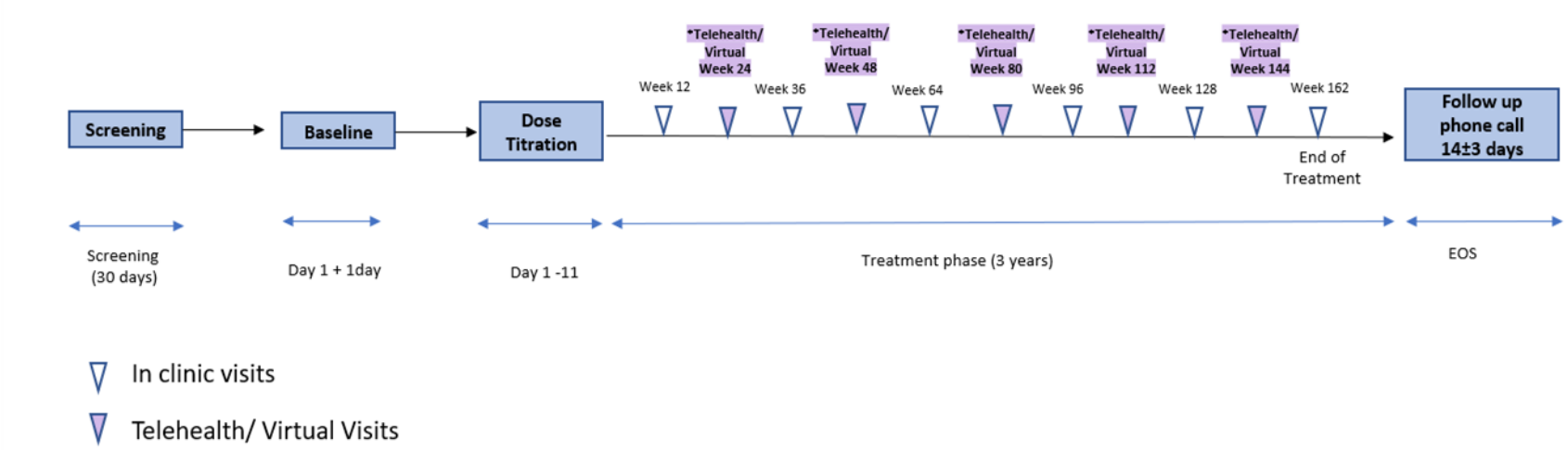
3.1 Study Design

This will be an open-label, long-term safety study for evaluation of treatment with OV101 in approximately 170 study participants with AS who either have completed previous Ovid studies (OV101-15-001, OV101-16-001, or OV101-19-001) or are siblings (with AS) of study participants with AS who have completed previous Ovid studies of OV101 There will be no placebo treatment. The study will be conducted at approximately 20 sites (total) in the United States, Australia, Europe, and Israel. As this study will enroll study participants who may have completed previous studies for different periods of time before entering this study (as well as study participants with AS who have not been themselves enrolled in an Ovid study), study participants may be required to complete screening and baseline visits before receiving OV101 under this protocol.

The study will comprise a screening period of up to 30 days; a baseline visit on Day 1 for baseline assessments; it is recommended that first dose of study drug be taken at the site unless a patient is unable to attend a clinic visit in person (e.g. due to COVID-19 restrictions) in which case the first dose of study drug to be taken in the evening of Day 1 (at bedtime), and clinic visits for safety and efficacy assessments over a 3-year treatment period (Figure 3-1). After the baseline visit, the clinic visits will occur at Weeks 12, 36, 64, 96, 128, and 160 (end of treatment [EOT]). If a patient cannot attend an in-person visit, a home visit may be conducted by a trained mobile healthcare professional to perform study assessments e.g. vital signs, body system assessment, clinical lab draws, review/collection of study materials.

Telehealth/virtual visits will occur at Weeks 24, 48, 80, 112, and 144. A follow-up phone safety visit at the end of study (EOS) will occur approximately 14 days after the last dose of study drug (EOT) to assess safety and tolerability associated with discontinuation of treatment. A home nurse visit will replace a virtual visit if the latter is not feasible. A study participant will be considered to have completed the study after completing the EOS phone visit. The schedule of activities for this study is fully presented in Table 6-1.

Figure 3-1 Study Design Schematic



*All study participants will be titrated in accordance with the titration schedule.

*Neptune study participants EOT visit may serve as a baseline visit for ELARA.

[redacted]

*Telehealth/Virtual visits for dose adjustments may be made throughout the treatment phase at the discretion of the investigator

The following study participants will be required to complete screening and baseline visits (and assessments) to determine eligibility before receiving OV101 under this protocol:

- Study participants who completed OV101-15-001 or OV101-16-001
- Study participants who are siblings of study participants who have completed OV101-15-001, OV101-16-001, or OV101-19-001
- Study participants who completed treatment in OV101-19-001 more than 2 weeks before completing the baseline visit under this protocol (OV101-18-002)

For study participants required to complete the screening and baseline visits, the planned duration of study participation is approximately 166 weeks from the start of screening to the EOS visit, including 160 weeks of treatment with OV101.

For study participants completing the EOT visit for OV101-19-001 two weeks or less before enrolling in this OV101-18-002 protocol, the OV101-19-001 EOT visit may serve as the baseline visit for OV101-18-002. Clinical laboratory results assessed at EOT in OV101-19-001 will serve as baseline clinical laboratory results in OV101-18-002. For such study participants, the maximum planned duration of study participation would be approximately 162 weeks or until commercially available.

Study participants who meet all eligibility criteria will be enrolled on Day 1 (baseline visit) and start the study drug that evening at bedtime (not in the clinic). Each study participant's legally acceptable representative (LAR)/caregiver will receive a package of study drug at the baseline visit, sufficient to last until the Week 12 visit.

As presented in Figure 3-1, each study participant's dose of OV101 will be titrated to a maintenance dose, as tolerated by the study participant [redacted]. The maximum tolerated dose (up to 15 mg at bedtime) will be maintained to the EOT. [redacted]

Phone calls to manage titration will occur on Days 6 and 11 for all study participants. [redacted] Phone calls to manage dose titration, [redacted] will occur 5 days later to assess tolerability.

At the Week 12, 36, 64, 96, and 128 visits, each study participant's LAR/caregiver will receive a package of study drug sufficient to last until the next scheduled visit at the maximum possible dose. Unused study drug will be returned to the site following each scheduled visit.

The sleep diary is to be completed over the 7-day periods immediately preceding the clinic visits when sleep diaries are scheduled to be reviewed; a calendar will be issued to ensure that the diary information collection starts on the appropriate days. Phone calls to remind LAR/caregivers to start recording diaries will be made 14 days before each study participant's expected next visit date. The LAR/caregivers will complete seizure diaries each day during the treatment period and should be returned to the site at each visit.

Safety information will be collected during phone calls and during clinic visits. If a study participant experiences any AEs or is unable to take the study drug as prescribed, the caregiver/LAR is instructed to contact the study center. Dose adjustments are permitted for study participants who are unable to tolerate the specified dosing regimen (Section 5.2.1).

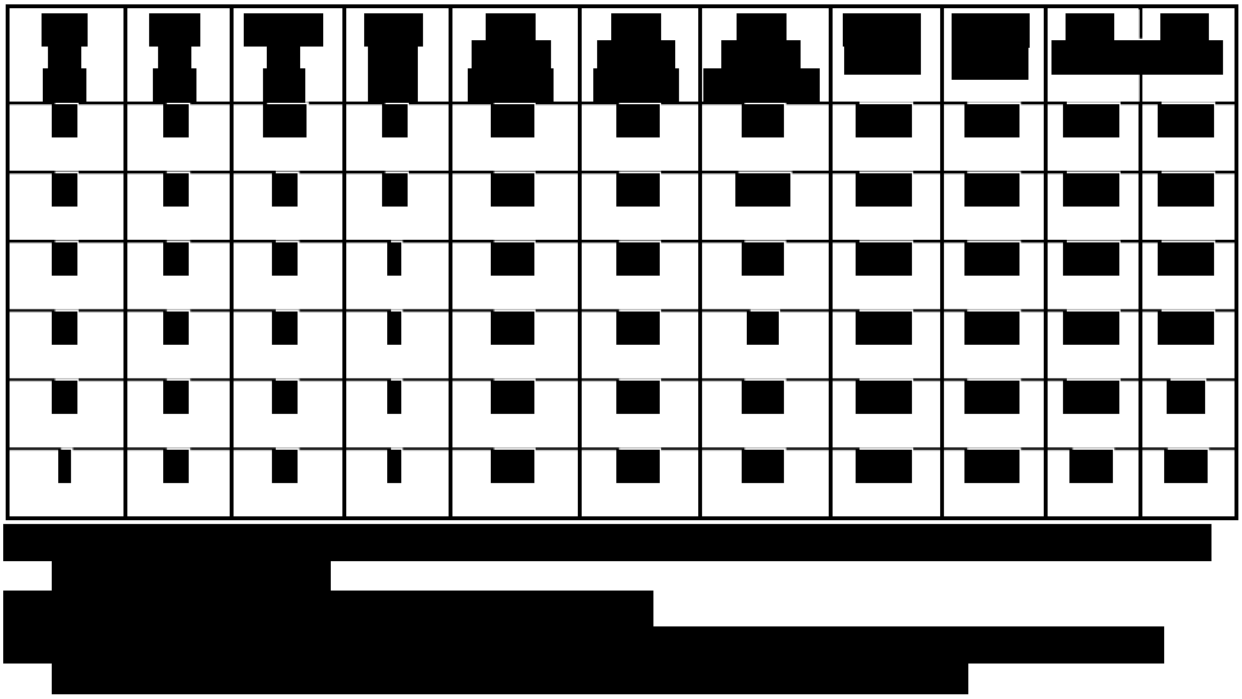
At the investigator's discretion throughout the study, study participants may be evaluated at unscheduled clinic visits for reasons related to study participant safety. At unscheduled visits, study participants will be queried about AEs, changes in concomitant medications, and suicidality, and safety laboratory assessments may be conducted. Periodic interim review of safety data will be performed as part of routine pharmacovigilance activities and to support regulatory submission.

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

4 Study participant Selection and Withdrawal Criteria

4.1 Selection of Study Population

Approximately 170 study participants will be enrolled at approximately 15 sites (total) in the United States, Australia, Germany, Netherlands, and Israel. Study participants will be assigned to study treatment only if they meet all the inclusion criteria and none of the exclusion criteria. Deviations from the inclusion and exclusion criteria are not allowed.

Study participants will be individuals with AS who either have completed previous Ovid studies (OV101-15-001, OV101-16-001, or OV101-19-001) or are siblings (with AS) of study participants with AS who have completed previous Ovid studies of OV101.

4.1.1 Inclusion Criteria

Each study participant must meet all the following criteria to be enrolled in this study:

1. Ovid study enrollment criteria:
    - Has completed the OV101-15-001 or OV101-16-001 study up to the EOS, or
    - Has completed the OV101-19-001 study up to the EOT, or
    - Is a sibling of a study participant with AS who has completed OV101-15-001, OV10116001, or OV101-19-001.
2. Has a previous diagnosis of AS with molecular confirmation.
3. Is at least 2 years old and has a body weight of at least 9 kg.
4. Has an LAR/caregiver capable of providing informed consent and able to attend all scheduled study visits, oversee the administration of study drug, and provide feedback regarding the study participant's symptoms and performance as described in the protocol.
5. Provides assent to the protocol (to the extent possible and in accordance with local institutional review board [IRB] and regulatory requirements) and has a LAR/caregiver who will provide written informed consent. Study participants providing assent must do so at the same visit as LAR/caregiver written informed consent is provided.
6. Can swallow study drug capsules with water or ingest the contents of study drug capsules after sprinkling the capsule contents onto up to 1 teaspoon of low-fat semiliquid food.

7. If a study participant is currently receiving a regimen of concomitant medications such as antiepileptic medication, gabapentin, clonidine, trazodone, melatonin, and/or a special dietary regimen, that study participant's regimen is stable for at least 4 weeks before Day 1 (first day of study drug administration) and will be maintained throughout the duration of the study (in the judgment of the investigator).
8. Has LAR/caregiver(s) who agree not to post any of the study participant's personal medical data or information related to the study on any website, message board, online support group, or social media site (e.g., Facebook, Instagram, Twitter) until notified that the study is completed.
9. Female study participants who are of childbearing potential (defined as having experienced their first menarche) must agree to use either a highly effective or acceptable form of birth control during the study and for 30 days following the last dose of the study drug. Highly effective contraceptive methods are as follows:

    - Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
        - Oral
        - Intravaginal
        - Transdermal
    - Progestogen-only hormonal contraception associated with inhibition of ovulation:
        - Oral
        - Injectable
        - Implantable
    - Intrauterine device
    - Intrauterine hormone-releasing system
    - Bilateral tubal occlusion
    - Vasectomized partner
    - Sexual abstinence

    Acceptable birth control methods that result in a failure rate of more than 1% per year include:

    - Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action

- Male or female condom with or without spermicide*
- Cap, diaphragm, or sponge with spermicide*

*A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

4.1.2 Exclusion Criteria

Study participants meeting any of the following criteria will be excluded from the study:

10. Discontinued from the OV101-15-001, OV101-16-001, or OV101-19-001 study due to safety reasons causally related to OV101.
11. Has a circumstance, condition, concomitant disease (e.g., gastrointestinal, renal, hepatic, endocrine, respiratory, or cardiovascular system disease), or any clinically significant finding that could interfere with the conduct of the study or that would pose an unacceptable risk to the study participant in this study.
12. Has poorly controlled seizures defined as any of the following:
    - Weekly seizures of any frequency with a duration of more than 3 minutes each
    - Weekly seizures occurring more than 3 times per week, each with a duration of less than 3 minutes
    - Investigator assessment
13. Has any of the following laboratory abnormalities: total bilirubin >1.5 × upper limit of normal (ULN), unless known Gilbert's syndrome; alanine aminotransferase or aspartate aminotransferase >2.5 × ULN; serum creatinine >1.2 × ULN; absolute neutrophil count $<1.5 \times 10^9$/L; platelets $<80 \times 10^9$/L; hemoglobin <80 g/L; or thyroid stimulating hormone >1.25 × ULN or <0.8 × lower limit of normal. Retesting of clinical laboratory parameters may be allowed after consultation with the medical monitor or designee.
14. Use of benzodiazepines, zolpidem, zaleplon, zopiclone, eszopiclone, barbiturates, or ramelteon for sleep, or minocycline or levodopa within the 4 weeks prior to Day 1 or during the study. Benzodiazepines administered as needed or regularly scheduled for indications other than insomnia and benzodiazepines for seizure control are permitted.
15. Is at risk of harming self and/or others (based on investigator assessment).
16. With the exception of an Ovid study of OV101, has enrolled in any clinical or used any investigational agent or device, or has participated in any investigational procedure, within the 30 days before screening or does so concurrently with this study.

17. Is allergic to OV101 or any excipients of study drug.
18. The study participant or LAR/caregiver is unable to comply with study requirements (based on investigator assessment).

4.2 Withdrawal of Study participants from Study Treatment and/or the Study

Study participants who discontinue treatment during the study will be encouraged by investigators to continue to participate in all scheduled clinic visits and assessments, and study data will be collected for these study participants per protocol.

Discontinuation of a study participant from treatment early (before Week 160) for any reason will initiate procedures for discontinuation of the study participant from the study, including EOT and EOS visits (Section 3.1). For study participants who stopped study treatment early (before Week 160), an EOT visit should be conducted within 2 weeks after the last day of study drug. After completing the EOT visit, an EOS visit should be completed within 2 weeks after completing the EOT visit. The duration of the study is defined for each study participant as the date signed written informed consent is provided through the EOS visit.

4.2.1 Reasons for Withdrawal/Discontinuation

Study participants may withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. Study drug administration may be stopped early at the discretion of the investigator (or designee) if a study participant does not tolerate the dosing regimen. Every effort should be made to keep study participants in the study. The reasons for study participants not continuing in the study will be recorded. A study participant may be withdrawn from the study for any of the following reasons:

1. The study participant does not continue to meet the protocol inclusion or exclusion criteria.
2. The study participant has a serious or intolerable AE that, in the investigator's opinion, requires withdrawal from the study.
3. The study participant has laboratory safety results that reveal clinically significant changes from baseline in hematological or biochemical assessments.
4. The study participant has symptoms (or an intercurrent illness) that are not consistent with the protocol requirements or that justify withdrawal.
5. The study participant is lost to follow-up.
6. Other reasons (e.g., development of contraindications to use of study drug).

7. The study participant (or his/her LAR/caregiver) withdraws assent (consent), or the investigator or sponsor decides to discontinue the study participant's participation in the study.

The investigator will also withdraw a study participant if Ovid terminates the study. Upon occurrence of a serious or intolerable AE, the investigator will confer with the medical monitor and/or sponsor. If a study participant is discontinued because of an AE, the event will be followed until it is resolved. Any study participant may withdraw his/her consent at any time.

4.2.2 Handling of Withdrawals

Study participants are free to withdraw from the study or study treatment at any time upon request. Study participant participation in the study may be stopped at any time at the discretion of the investigator or at the request of the sponsor.

Study participants who stop study treatment or active participation in the study will no longer receive study drug. When a study participant withdraws from the study treatment or active participation in the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the electronic case report form (eCRF) using the electronic data capture (EDC) system. Whenever possible, all study participants who stop study treatment or withdraw from the study prematurely will complete the EOT and EOS assessments. Study participants who fail to return for final assessments will be contacted by the site (2 documented phone calls followed by 1 registered letter, as applicable) in an attempt to have them comply with the protocol.

It is vital to obtain follow-up data on any study participant withdrawn or who withdraws because of an AE or SAE. In every case, efforts must be made to undertake protocol-specified safety follow-up procedures.

4.2.3 Replacements and Rescreening

Enrollment in this extension study is open to all study participants meeting the eligibility criteria. Study participants who fail to satisfy all inclusion and exclusion criteria at Screening may be rescreened 1 additional time at the discretion of the medical monitor or his/her designee (Section 6.1.1). Study participants identified for rescreening should be discussed with the medical monitor. There are no plans to replace study participants.

5 Study Treatments

All study participants will receive OV101. No study participant will receive placebo treatment in this open-label extension study. The planned doses of OV101 represent the intended therapeutic doses of OV101. See Section 5.2.1 for details of dosing.

5.1 Study participant Number Assignment

Study participant numbers for this study will be assigned at Screening.

5.2 Treatments Administered

OV101 will be supplied as capsules containing 5-mg, 2-mg, or 0.5-mg of study drug. At clinic visits at Baseline and at Weeks 12, 36, 64, 96, and 128, each study participant's primary LAR/caregiver will receive enough capsules to cover OV101 administration until the next visit.

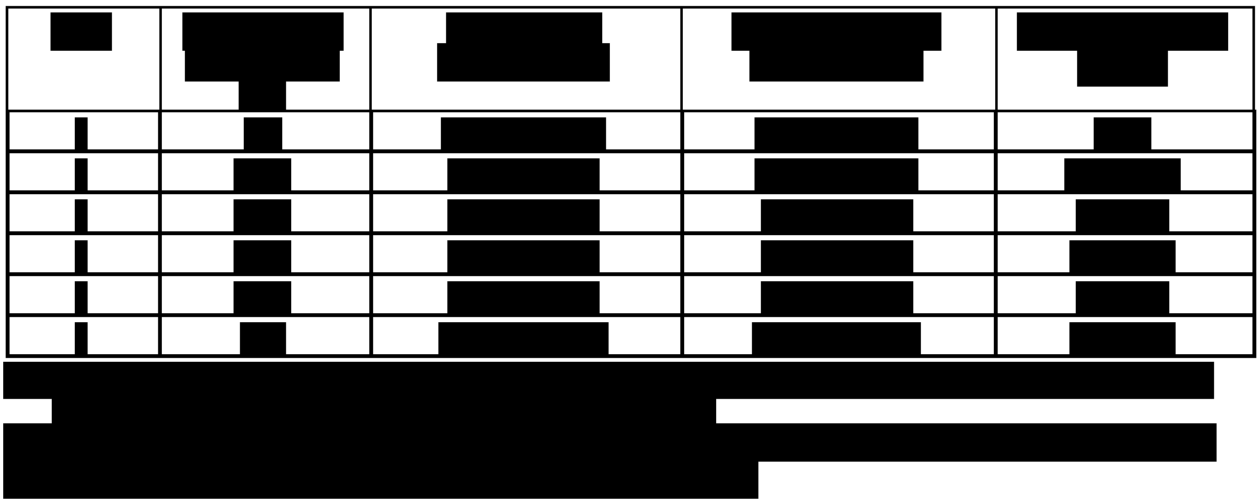
Study participants will take all doses orally (assisted by a LAR/caregiver, if necessary), in the evening at bedtime. Capsules may be opened, with the contents sprinkled onto up to 1 teaspoon of low-fat semiliquid food (e.g., applesauce, yogurt, pudding) for ingestion, but this approach must be followed consistently throughout the study. The capsule contents must not be placed directly in liquid. The LAR/caregiver must document in the medication diary (Section 5.6) specifically how the capsules were taken (e.g., swallowed whole or taken in up to 1 teaspoon of food).

On Day 1, study participants will take their first dose of study drug at the study site during the daytime, taking all subsequent doses at bedtime, starting with the evening of Day 2. The LAR/caregiver should make every effort to administer the drug at approximately the same time each night.

If a study participant misses a dose of study drug for any reason, unless within a 3-hour window of the usual administration time, the study participant should not make up the missed dose. The study participant should wait to take the next dose as scheduled and take a single dose at that time. It is important that the dosing regimen be documented in the medication diary by the LAR/caregiver and monitored by the study site to ensure that appropriate dosing is being followed. Study participants experiencing dose interruptions should be evaluated by the investigator in conjunction with the medical monitor.

5.2.1 Dose Titration

[redacted]



[redacted]

[redacted]

[redacted]

5.2.1.2 Down-Titration for All Study participants

The investigator may initiate down-titration by 1 capsule based on the investigator assessments of tolerability and AEs, or medical necessity. If down-titration is initiated, then the investigator should reassess tolerability with the modified dose regimen within 3 days of the dosing change.

If tolerability is not acceptable (e.g., excessive somnolence, dizziness, vomiting, or change in behavior) at any time during the study, the investigator should discuss the situation with the medical monitor. Unscheduled clinic visits are optional at any time to confirm tolerability. Any event of poor tolerability must be documented as an AE. The study site will document any dose adjustments or changes in dosing in the eCRF and the supporting rationale must be documented in the medical record or other appropriate source document. Adverse events triggering any down-titration must be reported.

For study participants enrolled in this study, the daily dose [redacted] may not be lower than the reduced maintenance dose indicated in Table 5-2. If at any point in the study a down titration is considered due to significant loss of weight, this should be discussed and agreed to in consultation with the medical monitor prior to any change.

[redacted]

5.3 Description of Study Drug

[redacted]

All capsules are imprinted with a dark blue band on the cap and body. Each capsule contains white to off-white powder. Excipients will be [redacted]

Note that the original white capsule currently in use will be used till completion.

5.4 Management of Clinical Supplies

Bulk capsules of OV101 will be shipped to the vendor, who will package, label, and deliver the kits to each study site.

5.4.1 Study Drug Packaging and Storage

Study drug will be packaged as capsules of OV101 in bottles or cards. A clinical label will be affixed to the outside of each bottle/card. The label will specify the sponsor name (Ovid Therapeutics Inc.); study participant number; protocol number; bottle/card number; number of

capsules (each bottle/card); "Evening," and "Take as directed." The recommended storage conditions and expiry date (where required) will be stated on the product label. At the study site, study drug must be stored in a secure area (e.g., a locked cabinet), protected from moisture, and kept at a controlled room temperature, 59°F to 77°F (15°C to 25°C). Study participants and LARs/caregivers must keep all study drug in the original bottles/cards and maintain it at room temperature.

5.4.2 Study Drug Accountability

The investigator will maintain accurate records of receipt of all study drug, including dates of receipt. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each study participant in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drug will be reconciled and retained or destroyed according to applicable regulations.

5.4.3 Other Supplies

No other clinical supplies will be provided to study sites.

5.5 Overdose Reporting

An overdose is any dose of study treatment given to a study participant or taken by a study participant that exceeds the dose described in the protocol. Any overdose, with or without associated AEs, must be recorded in the eCRF. Any AEs associated with an overdose should be reported in the relevant AE/SAE sections in the eCRF. Any associated SAEs must be promptly reported to Ovid using SAE reporting procedures (Section 6.2.1.5). Overdoses without signs or symptoms do not need to be recorded as AEs.

5.5.1 Treatment of Overdose

In the event of a suspected overdose, the appropriate supportive clinical care should be provided as dictated by the study participant's clinical status.

5.6 Medication Errors

A medication diary will be maintained by the LAR/caregiver on behalf of the study participant for the duration of the treatment period to confirm dosing dates and times and to permit monitoring for medication compliance and medication errors. The medication diary will be reviewed at each clinic/home health visit by either the site investigator, study coordinator or home health nurse if the study participant is unable to come to clinic due to Covid-19. If a dose is

missed (beyond the 3-hour dosing window), this should be noted, and the study participant should resume prescribed dosing the following evening (without doubling the dose).

5.6.1 Treatment of Medication Errors

An example of a medication error is overdose; treatment of overdose is described in Section 5.5.1.

5.7 Blinding

This is an open-label study: there will be no blinding.

5.8 Treatment Compliance

Study participant compliance will be determined by comparing the capsule counts of returned study drug to the capsule count of study drug dispensed at the previous visit (Table 6-1). An investigator may suspend a study participant's administration of study drug for up to 2 weeks; suspension for longer than 2 weeks should be discussed with the medical monitor. Re-titration may not be necessary. The number of capsules remaining will be tracked and recorded. The LAR/caregiver will be questioned as to the reason(s) why unexpected remaining capsules have not been administered (e.g., forgot, study participant refused, study participant experienced AE or LAR/caregiver decided to reduce dose); the reason(s) and the approximate date and time of any missed doses will be recorded in the eCRF. The study participant's medication diary will be reviewed for supporting information.

The medication diary (Section 5.6) will serve as a strategy that may improve compliance in addition to serving as a method for monitoring adherence.

5.9 Prior and Concomitant Therapy

Study participants should be on stable regular or as-needed doses of prescribed medications and on stable nonmedication interventions (e.g., speech therapy, physical therapy, occupational therapy) for 4 weeks before Baseline (Day 1). Study participants should remain on the stable regimens until after the EOS visit. Additionally, unless required to treat AEs, there should be no new medications or changes to concomitant medications (e.g., products containing cannabidiol), approved dietary and herbal supplements, and nonmedication interventions during the study until after the EOS visit.

Use of all concomitant medications will be recorded in the study participant's eCRF. The minimum requirement is that drug name and the dates of administration are recorded. Concomitant medications include all prescription drugs, herbal products, vitamins, minerals, and

over-the-counter medications. Any changes in concomitant medications or significant nondrug therapies will also be recorded in the study participant's eCRF.

Any concomitant medication deemed necessary for the welfare of the study participant during the study may be given at the discretion of the investigator. However, it is the responsibility of the investigator to ensure that details regarding the medication are recorded in full in the eCRF.

5.9.1 Prohibited Medications and Therapies

Use of any GABAergic agents (e.g., acamprosate, baclofen, vigabatrin, tiagabine and riluzole) on a regular schedule is prohibited from the time informed consent is obtained to the end of a study participant's participation in the study. Sodium oxybate is also prohibited. Study participants who entered the study on a stable dose of gabapentin (i.e., stable dose for at least 4 weeks prior to randomization), may continue on the treatment as long as no dose modifications are expected during the study. Any change in gabapentin dose during the study must be captured and documented as a protocol deviation.

Use of benzodiazepines, zolpidem, zaleplon, zopiclone, eszopiclone, barbiturates, or ramelteon for sleep is prohibited within the 4 weeks prior to Day 1 or during the study. Benzodiazepines administered as needed or as a regularly scheduled dose for indications other than insomnia (e.g., seizures, anxiety) are permitted. Minocycline and levodopa are prohibited from 4 weeks prior to Day 1 to the end of a study participant's participation in the study.

Use of other investigational agents (e.g., products without market authorization [approved label]) is prohibited during the study.

5.9.2 Restrictions

Any prior or concomitant medication, including antiepileptic and/or behavioral medications, supplements, or special diets, must be at a stable dose for at least 4 weeks before Day 1, and must be maintained throughout the study.

Benzodiazepines prescribed on an as-needed basis for situational anxiety (e.g., for occasional procedures or events) or scheduled for indications that are not related to sleep (e.g., seizures, anxiety) are permitted.

Study participants should not consume alcohol during the study.

6 Study Assessments and Procedures

Before submitting to any study procedures, all potential study participants and/or LAR/caregivers will sign an informed consent form (ICF). Study participants and LAR/caregivers will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the study participants and LAR/caregivers. The investigator or designee will also sign the ICF.

The schedule of activities by clinic visit for this study is presented in Table 6-1. Telehealth/virtual visits should be consistent with local and individual institutions' policies and standard practices. Detailed instructions for virtual/phone visits will be provided in the investigators' virtual/phone visit study manual. A home nurse visit will replace a virtual visit if the latter is not feasible.

Table 6-1 Schedule of Activities by Study Visit

Visit Name[c]	Screening[a]	Baseline[b]	Phone Titration	Week 12	Week 24 Telehealth/Virtual Visit[p]	Week 36	Week 48 Telehealth/Virtual Visit[p]	Week 64	Week 80 Telehealth/Virtual Visit[p]	Week 96	Week 112 Telehealth/Virtual Visit[p]	Week 128	Week 144 Telehealth/Virtual Visit[p]	EOT	EOS[d] (Phone)
Window (days)	–[e]	+1	+3	±7	±5	±7	±5	±7	±5	±7	±5	±7	±5	±7	±5
Day[f]	–30 to -1	1	6, 11, 15	84	168	252	336	448	560	672	784	896	1008	1120	1134
Week	–	0	1-3	12	24	36	48	64	80	96	112	128	144	160	162
Obtain informed consent and assent	X														
Verify inclusion/ exclusion criteria	X	X													
Obtain medical history and demographic information	X	X													
Conduct clinical assessment for AS[g]	X														
Confirm prior molecular AS diagnosis[h]	X														
Physical examination	X	X		X	X	X	X	X	X	X	X	X	X	X	
Vital sign measurements	X	X		X		X	X	X		X		X		X	
Clinical laboratory tests	X	X[i]		X		X		X		X		X		X	
Pregnancy test[j]	X[j]	X[j]		X[j]		X[j]		X[j]		X[j]		X[j]		X[j]	

Visit Name[c]	Screening[a]	Baseline[b]	Phone Titration	Week 12	Week 24 Telehealth/Virtual Visit[p]	Week 36	Week 48 Telehealth/Virtual Visit[p]	Week 64	Week 80 Telehealth/Virtual Visit[p]	Week 96	Week 112 Telehealth/Virtual Visit[p]	Week 128	Week 144 Telehealth/Virtual Visit[p]	EOT	EOS[d] (Phone)
Window (days)	–[e]	+1	+3	±7	±5	±7	±5	±7	±5	±7	±5	±7	±5	±7	±5
Day[f]	–30 to -1	1	6, 11, 15	84	168	252	336	448	560	672	784	896	1008	1120	1134
Week	–	0	1-3	12	24	36	48	64	80	96	112	128	144	160	162
Adverse event inquiry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication inquiry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of suicidality: ABC-I[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Seizure diary issued SIF/DRF forms completed/submitted[o]	X	X		X		X		X		X		X	X		
Seizure diary review/collection		X		X		X		X		X		X	X	X	
Dispense medication diary		X		X	X	X	X	X	X	X	X	X	X		
Review/collect medication diary, assess compliance				X	X	X	X	X	X	X	X	X	X	X	
Dispense study drug		X		X	X	X	X	X	X	X	X	X	X		
Collect unused study drug				X	X	X	X	X	X	X	X	X	X	X	

Visit Name[c]	Screening[a]	Baseline[b]	Phone Titration	Week 12	Week 24 Telehealth/Virtual Visit[p]	Week 36	Week 48 Telehealth/Virtual Visit[p]	Week 64	Week 80 Telehealth/Virtual Visit[p]	Week 96	Week 112 Telehealth/Virtual Visit[p]	Week 128	Week 144 Telehealth/Virtual Visit[p]	EOT	EOS[d] (Phone)
Window (days)	–[e]	+1	+3	±7	±5	±7	±5	±7	±5	±7	±5	±7	±5	±7	±5
Day[f]	–30 to -1	1	6, 11, 15	84	168	252	336	448	560	672	784	896	1008	1120	1134
Week	–	0	1-3	12	24	36	48	64	80	96	112	128	144	160	162
Clinician-Completed Measures															
VABS-3[k]		X						X						X	
CGI-S-AS	X	X		X		X		X		X		X		X	
CGI-I-AS[l]				X		X		X		X		X		X	
Caregiver-Completed Measures															
CSHQ		X		X		X		X		X		X		X	
PedQoLI		X		X		X		X		X		X		X	
Sleep diary issued[m]	X	X		X		X		X		X		X			
Sleep Diary collected/ reviewed		X		X		X		X		X		X		X	

Abbreviations: ABC-I, Aberrant Behavior Checklist-Irritability subscale; AS, Angelman syndrome; CGI-I-AS, Clinical Global Impressions-Improvement-Angelman syndrome; CGI-S-AS, Clinical Global Impressions-Severity-Angelman syndrome; CSHQ, Children's Sleep Habits Questionnaire; EOS, end of study; EOT, end of treatment; PedQoLI, Pediatric Quality of Life Inventory; VABS-3, Vineland Adaptive Behavior Scale, 3rd Edition.

Notes: At the investigator's discretion, study participants may be evaluated at unscheduled clinic visits for reasons related to study participant safety. At unscheduled visits, study participants will be queried about adverse events, changes in concomitant medications, and suicidality; and safety laboratory assessments may be conducted. Efficacy assessments will be only for study participants who are at least 4 years old. If study drug is dispensed at unscheduled visit, dosage should be maintained at the same level as at the previous scheduled visit. If a down-titration is required for a clinical indication, this must be discussed with the medical monitor prior to making the change or at the earliest opportunity. Up-titration should not be performed at an unscheduled visit.

[a] For study participants entering this study within 2 weeks of completing the EOT visit of OV101-19-001, the screening activities can be verified or conducted at the baseline (Day 1) visit.

[b] If the screening and baseline visits can be completed within 14 days, the following assessments do not need to be repeated at the baseline visit: medical history, clinical assessment, physical examination, clinical laboratory tests, and determination of concomitant medications. For study participants entering this study within 2 weeks of completing the EOT visit of OV101-19-001, the EOT visit activities need not be repeated.

[c] If a study participant could not attend an in person visit, a telehealth/virtual or home visits, may be conducted by a trained mobile healthcare professional to perform study assessments e.g. vital signs, body system assessment, clinical labs draws, review/collection of study materials Baseline visits must be conducted on site and not remotely for patients who did not complete an OV101 antecedent study (eg, siblings [with AS] of study participants with AS who have completed previous Ovid studies of OV101).

[d] An ET study participant should complete both EOS and EOT visit assessments.

[e] Screening is to be conducted for up to 30 days (inclusive) before Day 1; study participants who meet all entry criteria can start treatment at any time during the screening period.

[f] There is no Day 0.

[g] Signs and symptoms of AS.

[h] Review documentation of previous molecular AS testing from the OV101-15-001, OV101-16-001 study, or OV101-19-001.

[i] If the baseline visit occurs within 14 days of the clinical laboratory tests during screening or during the study participant's EOT visit in OV101-19-001, clinical laboratory testing does not need to be performed at the baseline visit.

[j] Serum pregnancy testing is to be completed at screening and baseline visits. At subsequent visits, urine pregnancy testing is performed.

[k] The VABS-3 will be assessed by a trained qualified rater based on an interview of the study participant's caregiver. For each study site, the same rater is to be used throughout the study. As an exception, another sponsor-trained qualified rater in VABS-3 may be used

[l] Within 24 hours prior to the study participant's visit at Week 12 (the first CGI-I-AS assessment), the investigator must review the study participant's baseline CGI-S-AS score and investigator notes. Within 24 hours prior to the study participant's visit at Week 36 (and all subsequent visits with assessments of CGI-I-AS), the investigator must review the study participant's baseline CGI-S-AS score and investigator notes and the prior clinic visit's CGIIAS score and investigator notes. The same clinician rater, trained in CGI-S-AS and CGI-I-AS rating by the sponsor, must be used throughout the study to assess a given study participant. It is recommended that the same rater be used at a given site. As an exception, a clinician sub-investigator, trained in CGISAS and CGI-I-AS rating by the sponsor, may be used.

[m] The sleep diary is to be completed over the 7-day periods immediately preceding the clinic visits when sleep diaries are scheduled to be reviewed; a calendar will be issued to ensure that the diary information collection starts on the appropriate days. Phone calls to remind legally acceptable representative/caregivers to start recording diaries will be made 14 days before each study participant's expected next visit date.

[n] The entire Aberrant Behavior Checklist – Community (ABC-C) will be administered. Only ABC-I will be used to evaluate the potential for self-harm

[o] Seizure Identification Form and Diagnostic Review Form (SIF/DRF) will be completed by site personnel for every eligible study participant. This information will be faxed or emailed to The Epilepsy Study Consortium (TESC) for review and approval. The SIF/DRF will be used to ensure that the seizures are classified accurately. SIF and DRF forms will be collected for patients who have enrolled/completed the study if feasible.

[p] A home nurse visit will replace a virtual visit if the latter is not feasible.

6.1 Study Visits

6.1.1 Screening Period

Study participants entering this study within 2 weeks of completing the EOT visit of OV101-19-001 do not need to have a screening period; the screening activities can be verified or conducted at the baseline (Day 1) visit. All other study participants will be screened for participation in the study up to 30 days before Baseline (Day 1), when the first dose will be administered. Study participants who meet all entry criteria can have their baseline clinic visit at any time during the screening period.

Written informed consent (from the study participant's LAR/caregiver) and assent (from the study participant) will be obtained before the study participant participates in any study procedure and begins the study screening procedures for eligibility. Assent will be obtained if the investigator believes that the study participant has the intellectual capacity to provide it, but assent may not be relevant based on the study participant's intellectual disability and/or age (Section 9.3).

Molecular confirmation of the diagnosis of AS was an inclusion criterion for OV101-15-001, OV101-16-001, and OV101-19-001. Blood tests for molecular confirmation of AS will not be performed unless the study participant is a sibling of a previous participant and does not have prior documented molecular confirmation.

During the screening period, the investigator will determine whether the LAR/caregiver and study participant are able to complete all questionnaires and assessments that require their contributions and will also assess their ability to comply with study procedures.

In preparation for participation in this trial, LAR/caregivers will be educated on the clinical safety data for OV101 obtained thus far and will be trained to report assessments and to identify, manage, and report any potential AEs.

The LAR/caregiver will be provided with a sleep diary for documenting the study participant's sleep and a seizure diary for documenting the study participant's seizures. The LAR/caregiver will record data in the sleep diary for at least 7 days before each clinic visit. A calendar reminder will also be provided for recording data in the sleep diary.

A study participant who does not meet the inclusion criteria or who meets an exclusion criterion will be considered a screen failure. Whether rescreening is acceptable will be discussed with the medical monitor. Rescreening will only be allowed once and only in cases where no safety risk is posed to the study participant (Section 4.2.3).

If a screening test result (laboratory or any other test) is considered uncertain or abnormal, the test may be repeated to confirm the result after approval from the medical monitor or designee.

6.1.2 Baseline Visit

For study participants entering this study within 2 weeks of completing the EOT visit of OV101-19-001, the EOT visit activities need not be repeated at the baseline visit. The EOT visit of OV101-19-001 can serve as the baseline visit for the present study. Screened study participants will return to the study site for the baseline (Day 1) visit, and the LAR/caregiver will bring the study participant's completed sleep and seizure diaries for review by study staff. Study staff will collect the sleep diary (for recording in the eCRF) and will review it for completeness. If quality issues are detected, study staff will again instruct the LAR/caregiver in the proper use of the sleep diary. A new sleep diary will be issued to the LAR/caregiver for use in the 7-day period preceding the Week 2 clinic visit. A calendar reminder will also be provided for the start of sleep diary assessments.

Before dispensing study drug, study site staff must confirm appropriate completion of the sleep and seizure diaries and fulfilment of all eligibility criteria (Section 4.1). Study participants who meet all eligibility criteria will receive study drug at Baseline as described in Section 5.2.

Screening and baseline assessments must be performed within a 30-day period. If the screening and baseline visits are separated by no more than 14 days, the following assessments do not need to be repeated at the baseline visit: medical history, clinical assessment, physical examination, clinical laboratory tests, and determination of concomitant medications.

6.1.3 Phone Visits for Dose Titration

Phone visits are scheduled to assess each study participant's tolerance for OV101 and to determine how to continue the dose titration. The investigator may initiate additional phone visits for managing dose titration or adjustment at his/her discretion. Phone visits for dose titration of all study participants will be scheduled for Days 6 and 11.

The LAR/caregivers will be queried about AEs, concomitant medications, and study participant suicidality (Table 6-1). Detailed instructions for the phone visits are presented in the investigators' phone visit study manual. Results of inquiries about AEs and changes in concomitant medications and assessment of suicidality must be documented and recorded in the eCRF.

6.1.4 Telehealth/Virtual Visits at Weeks 24, 48, 80, 112, and 144

Phone visits by a nurse, nurse practitioner, or similarly qualified person are scheduled during Weeks 24, 48, 80, 112, and 144 to conduct assessments as detailed in Table 6-1. Detailed instructions for the phone visits are presented in the investigators' virtual/ phone visit study manual. A home nurse visit will replace a virtual visit if the latter is not feasible.

6.1.5 Clinic Visits at Weeks 12, 36, 64, 96, and 128

Study participants will return to the study site for the Week 12, 36, 64, 96, and 128 visits. The LAR/caregiver will bring the study participant's completed sleep diary, seizure diary, medication diary, and study drug in original containers for review by study staff. Study staff will collect the sleep diary (for recording in the eCRF) and will review it for completeness. If quality issues are detected, study staff will again instruct the LAR/caregiver in the proper use of the sleep diary. New sleep and seizure diaries will be issued to the LAR/caregiver for use in the 7-day period preceding the next clinic visit. A calendar reminder will also be provided for the start of sleep diary assessments.

Review of the seizure diary will occur as described in Section 6.2.2.4.

Before dispensing study drug, study site staff must confirm appropriate completion of the sleep and seizure diaries and continued fulfilment of all eligibility criteria (Section 4.1). Study participants who continue to meet all eligibility criteria will receive study drug at Weeks 12, 36, 64, 96, and 128.

6.1.6 Week 160 or End-of-Treatment Clinic Visit

Study participants will return to the study site for the Week 160 visit. An EOT visit, with the same assessments as the Week 160 visit, should be scheduled for a study participant who discontinues study treatment before Week 160.

The LAR/caregiver will bring the study participant's completed sleep diary, seizure diary, medication diary, and study drug bottles/cards for review by study staff. Study staff will collect the sleep diary (for recording in the eCRF) and will review it for completeness.

6.1.7 End-of-Study Phone Visit

The EOS phone visit is scheduled to occur 2 weeks after the EOT visit to assess each study participant's response to discontinuation of treatment with OV101.

The LAR/caregivers will be queried about AEs, concomitant medications, and study participant suicidality (Table 6-1), and the investigator (or designee) will conduct the Clinical Global Impressions-Severity-Angelman syndrome (CGI-S-AS) and Clinical Global Impressions-Improvement-Angelman syndrome (CGI-I-AS) assessments. Detailed instructions for the phone visits are presented in the investigators' phone visit study manual. Results of inquiries about AEs and changes in concomitant medications and assessment of suicidality must be documented and recorded in the eCRF.

6.2 Safety and Tolerability Assessments

Safety and tolerability will be assessed by the frequency, severity, and causality of AEs and SAEs, vital sign measurements, laboratory assessments, physical examinations, suicidality assessments, and seizure diary. Safety and tolerability assessments will be conducted according to the schedule presented in Table 6-1.

6.2.1 Adverse Events

6.2.1.1 Definitions of Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or severity. Each study participant's LAR/caregiver will be instructed to contact the study center if the study participant experiences any AEs, including whether there was any change in the study drug administration (e.g., dose withheld, dose reduced, or dose missed).

An AE is defined as any untoward medical occurrence in a study participant enrolled into this study regardless of its causal relationship to study drug. Each study participant's LAR/caregiver will be instructed to contact the investigator at any time after enrollment if any new or worsening symptoms develop.

Treatment-emergent AEs (TEAEs) are defined as AEs that start or increase in severity after the first dose of study drug in this open-label study. All AEs occurring after the study participant receives the first dose of study drug must be reported to Ovid or its designee via the eCRF.

Anticipated day-to-day fluctuations of preexisting disease(s), condition(s), or behavior(s) present or detected at the start of the study that do not worsen are not AEs. Lack of drug effect is not an AE. Social and/or convenience situations and/or admissions to the hospital, where an untoward medical occurrence did not occur, are not AEs.

Cases of pregnancy that occur during maternal or paternal exposures to study drug are to be reported. Data on fetal outcome and breastfeeding are collected for regulatory reporting and drug safety evaluation.

Study staff will record the occurrence and nature of each study participant's preexisting conditions (e.g., prior to enrollment in ELARA), including clinically significant signs and symptoms of the disease under treatment in the study (e.g., seizures, motor dysfunction, sleep disruption, anxiety), as part of the medical history.

As seizures are often a baseline condition in study participants with AS, seizures should be reported as an AE in any of the following circumstances:

- There is a clear increase in the frequency of seizures compared to the study participant's baseline.
- There is an emergence of a new seizure type.
- The study participant experiences status epilepticus.
- The investigator believes the seizure should be captured as an AE (in which case the investigator should document their reasoning).

Seizures in this study participant population will be detected and assessed using the seizure diary (Section 6.2.2.4). Diaries will be collected at the study site during the study and will be analyzed by the sponsor along with the reportable SAEs in evaluating risks and benefits.

After the ICF is signed, study staff will record any change in the condition(s) and the occurrence and nature of any AEs. If a study participant experiences an AE after the ICF has been signed but before receiving study drug, the event will be reported and will be included in the study participant's medical history unless the event is serious, or the investigator feels the event may have been caused by a protocol procedure.

6.2.1.2 Serious Adverse Events

An SAE is defined as any event that:

- Results in death
- Is immediately life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the study participant or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

6.2.1.3 Eliciting and Documenting Adverse Events

Adverse events will be assessed beginning at enrollment (date of signed informed consent) and up to 30 days after the last dose of study drug. Adverse events must be followed until resolution or for 30 days after the study participant's last study drug dose, whichever comes first.

After informed consent is obtained, at every clinic, phone and/or home health visit, study participants and their LAR/caregivers will be asked a standard nonleading question to elicit any medically related changes in their wellbeing. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over the counter medications).

In addition to study participant observations, AEs identified from any study data (e.g., laboratory values, physical examination findings) or identified from the review of other documents (e.g., study participant diaries) that are relevant to study participant safety or considered to be clinically significant, in the medical and scientific judgment of the investigator, will be documented on the AE page in the eCRF.

6.2.1.4 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page in the eCRF. Information to be collected includes the following:

- Drug treatment
- Dose
- Event term
- Time of onset

- Investigator-specified assessment of severity and relationship to study drug
- Time of resolution of the event
- Seriousness
- Any required treatment or evaluations
- Outcome

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the study participant is screened and remains stable should not be reported as an AE. However, if the condition worsens at any time during the study, it should be recorded as an AE. In general, an elective procedure is not considered an AE unless it is required to address worsening of an underlying condition. In this case, the underlying AE should be reported and not the procedure.

Any abnormal laboratory test results (hematology or clinical chemistry) or other safety assessments (e.g., vital sign measurements), including those that worsen from baseline, that are felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as AEs.

6.2.1.5 Reporting Serious Adverse Events

All AEs must be recorded in the eCRF upon awareness.

Any AE that meets SAE criteria (Section 6.2.1.2) must immediately (i.e., within 1 business day) inform Ovid Drug Safety upon learning of any SAE that occurs (whether or not attributable to the study drug). It is the investigator's responsibility to ensure that SAE reporting procedures are followed appropriately. All SAE reports and any revisions to an SAE report must be sent to the email address provided below. All supporting source information concerning the SAE (e.g., hospital records) should also be provided by email.

[redacted]

If there is a question concerning an SAE, the site needs guidance regarding the reporting of an SAE, the site is returning a call from an Ovid Drug Safety specialist, the site urgently needs to report an SAE or make Ovid Drug Safety aware of an SAE, the safety hotline should be used (country-specific hotline numbers provided in a separate document).

If an SAE is reported via the hotline, the site should first submit the SAE paper form and then enter the SAE in the eCRF. Any AE that meets SAE criteria (Section 6.2.1.2) must be entered into the EDC system immediately (i.e., within 1 business day) after study staff first learn about the event, in addition to emailing the SAE Report form. Once the qualifying SAE data are entered into the EDC system, Ovid will be notified by an email alert that will contain high-level safety information.

All SAEs must be reported starting from the time that informed consent for study participation is provided. If the investigator becomes aware of an SAE within 30 days after the study participant's last dose of study drug or within 30 days after the last study visit, the SAE must be reported. Serious AEs must be followed until the event resolves, the event or sequelae stabilize, or it is unlikely that additional information can be obtained after demonstration of due diligence with follow-up efforts (i.e., the study participant or health care practitioner is unable to provide additional information, or the study participant is lost to follow-up). Serious AEs that occur more than 30 days after the last dose of study drug should be submitted to the sponsor if the investigator becomes aware, however, these do not need to be reported to the IRB/IEC or regulators unless the investigator or sponsor considers them related to study drug.

6.2.1.6 Suspected Unexpected Serious Adverse Reactions and Nonserious Adverse Events of Special Interest

The sponsor will promptly evaluate all suspected unexpected serious adverse reactions and nonserious AEs of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs and independent ethics committees (IECs), and applicable health authorities based on applicable legislation.

To determine reporting requirements for single AE cases, the sponsor will assess the expectedness of these events using the current OV101 investigator's brochure. (Ovid Therapeutics Inc. 2018).

The sponsor or its legal representative is responsible for notifying the relevant regulatory authorities of SAEs meeting the reporting criteria. This protocol will use the appropriate section of the current investigator's brochure as the Reference Safety Document. The expectedness and reporting criteria of an SAE will be determined by the sponsor from the Reference Safety Document.

6.2.1.7 Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the study participant's daily activities. The intensity of the AE will be rated as mild, moderate, or severe using the following criteria:

Mild:	An AE that is transient in nature and generally does not interfere with the study participant's normal activities.
Moderate:	An AE that is sufficiently discomforting to interfere with the study participant's normal activities.
Severe:	An AE that is incapacitating and prevents normal activities.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of the onset and duration of each episode.

6.2.1.8 Assessment of Causality

The investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the test article in causing or contributing to the AE will be characterized using the following classification and criteria:

Unrelated:	This relationship suggests that there is no association between the study drug and the reported event.
Possible:	This relationship suggests that treatment with the study drug caused or contributed to the AE, i.e., the event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the study drug but could also have been produced by other factors.

Probable: This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the study drug seems likely. The event disappears or decreases on cessation or reduction of the dose of study drug.

Definite: This relationship suggests that a definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the study drug is re-administered.

6.2.1.9 Follow-Up of Study participants Reporting Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF and followed to satisfactory resolution, until the investigator deems the event to be chronic or not clinically significant or until the study participant is considered to be stable.

6.2.2 Other Safety Assessments

Safety assessments other than AEs (Section 6.2.1) include assessment of suicidality, vital sign measurements, laboratory assessments (Section 6.7), physical examinations, and seizure diary.

6.2.2.1 Clinical Assessment of Suicidality

The full ABC-Irritability subscale (ABC-I) will be administered. The ABC-I will be used to assess suicidality instead of the Columbia-Suicide Severity Rating Scale, since cognitive impairment in patients with AS interferes with the understanding of the concept of suicide. Most individuals with AS are not able to communicate thoughts of suicidality, so the study participant's irritability reported by the LAR/caregiver is being used as a surrogate measure of suicidality. The investigator will review the scale items with the LAR/caregiver at each scheduled timepoint. If grading worsens, the investigator must decide whether that indicates a potential for self-harm by the study participant, and if so, must document it as an AE and closely monitor it until resolution. The entire Aberrant Behavior Checklist – Community (ABC-C) will be administered, although only the ABC-I will be used to assess the potential for self-harm.

6.2.2.2 Vital Sign Measurements

Vital sign measurements will include height, weight, blood pressure, heart rate, and temperature. Measurements of blood pressure, heart rate, and temperature should be attempted after the study participant has been resting in a supine or sitting position for at least 10 minutes.

6.2.2.3 Physical Examinations

A physical examination will include a relevant general assessment of: head, eyes, ears, nose and throat; neck; heart; chest (including lungs); abdomen; extremities; skin; lymph nodes; as well as neurological and cardiovascular systems.

6.2.2.4 Seizure Diary

The seizure diary is a caregiver-reported clinical outcome assessment measure that captures the total number and duration of seizures. Caregivers will record the number, duration, and type of seizures each day using the paper seizure diary. Please also see Section 6.2.1.1 for AE reporting criteria for these seizure events.

The caregiver will be trained by the site with specific instructions beginning with the screening visit to ensure compliance in recording seizures. The seizure diary will be completed each day during the study, beginning at Screening (Baseline for study participants entering this study within 2 weeks of completing the EOT visit of OV101-19-001) and continuing through the EOT. Seizure diaries will be collected and reviewed by the investigator with the study participant's caregiver for proper recording at specified timepoints (Table 6-1). Seizure Identification Form and Diagnostic Review Forms (SIF/DRF) will be completed by site personnel for every eligible study participant. This information will be faxed or emailed to The Epilepsy Study Consortium (TESC) for review and approval. The SIF/DRF will be used to ensure that the seizures are classified accurately. SIF and DRF forms will be collected for patients who have enrolled/completed the study if feasible.

For the prospective baseline period, the seizure frequency (expressed as a 28-day frequency) will be calculated as

(number of seizures) / (number of days seizures were assessed) × 28

Seizure frequency calculated through this method will be used to confirm the eligibility.

6.3 Exposure During Pregnancy and/or Lactation

OV101 should not be administered to pregnant or lactating females because the potential for adverse reactions to OV101 in pregnant females, fetuses, and nursing infants is unknown.

Pregnancy data will be collected during this study for all study participants. Exposure during pregnancy (also referred to as exposure in-utero) can be the result of either maternal exposure or transmission of drug product via semen following paternal exposure.

Exposure during pregnancy must be recorded and the study participant followed until the outcome of the pregnancy is known (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality), even if the study participant discontinues study drug or discontinues from the study.

If a study participant within this study or a study participant's partner becomes pregnant while treated or exposed to study drug, the investigator must submit a pregnancy form to Ovid via the same method as SAE reporting (Section 6.2.1.5). Pharmacovigilance will supply the investigator with a copy of a "Pregnancy Reporting and Outcome Form/Breastfeeding." When the outcome of the pregnancy becomes known, the form should be completed and returned to Ovid or Ovid Pharmacovigilance delegate. If additional follow-up is required, the investigator will be requested to provide the information.

Exposure of an infant to an Ovid product during breastfeeding must also be reported and any AEs experienced by the infant must be reported to Ovid Pharmacovigilance or designee via email (Section 6.2.1.5).

Pregnancy is an outcome of an event and should not be reported as an AE unless there is a suspicion that study drug may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and may meet criteria for an SAE (such as ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly). Elective abortions without complications should not be reported as AEs

6.4 Pregnancy

Female study participants who are of childbearing potential (defined as having experienced their first menarche) must agree to use either a highly effective or acceptable form of birth control during the study and for 30 days following the last dose of the study drug. Highly effective contraceptive methods are as follows:

a. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

- Oral
- Intravaginal
- Transdermal

b. Progestogen-only hormonal contraception associated with inhibition of ovulation:

- Oral
- Injectable
- Implantable

c. Intrauterine device

d. Intrauterine hormone-releasing system

e. Bilateral tubal occlusion

f. Vasectomized partner

g. Sexual abstinence

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

a. Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action.

b. Male or female condom with or without spermicide.

c. Cap, diaphragm, or sponge with spermicide.

d. A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

For male study participants with women of childbearing potential partners, there are no restrictions. Female study participants who have experienced menarche and are not surgically sterile will undergo serum (or urine) beta-human chorionic gonadotrophin (ß-hCG) pregnancy testing at clinic visits shown in Table 6-1. After the screening and baseline visits, if serum is not obtainable, urine pregnancy testing is allowed. Any study participant with a positive pregnancy test result at Screening or Baseline must be excluded from the study. A serum ß-hCG pregnancy test must be performed if any female study participant is suspected of becoming pregnant during the study.

If pregnancy occurs at any time during the study, study drug must be discontinued immediately (or not started). Pregnancy is not regarded as an AE unless there is a suspicion that a study drug may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs during study participation must be reported using the same procedures as an SAE (Section 6.2.1.5) but using a clinical study pregnancy form. The pregnancy must be followed-up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the study participant is discontinued from the study. Pregnancy complications and elective terminations for medical reasons should not be reported as an AE or SAE. Spontaneous miscarriages must be reported as an SAE.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the study participant has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to Ovid Drug Safety.

6.5 Contraception and Pregnancy Avoidance Procedures

Please refer to Section 6.4 for detailed contraception requirements.

Study participants will be provided with information on acceptable methods of contraception as part of the study participant informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy during the study and for 30 days after the last dose of study drug and avoidance of donation of ova or sperm during the course of the study and for 90 days after the last dose of study drug. This may be signed by the LAR/caregiver of the study participant.

Female study participants who have experienced menarche must have a negative serum ß-hCG pregnancy test at Screening (Visit 1) and a negative serum ß-hCG pregnancy test on Day 1 (Visit 2), before receiving any dose of study drug. If pregnancy results cannot be collected at Visit 2, the reason should be documented in the source document, the results of the serum pregnancy test obtained at Visit 1 must be confirmed to be negative by the investigator prior to randomization, and results of a serum pregnancy test at Visit 2 must be confirmed to be negative before the study participant can receive the first dose of study drug. During the study, study participants will receive continued guidance with respect to the avoidance of pregnancy and ova or sperm donation as part of the study procedures. An additional serum ß-hCG pregnancy test will be performed at the EOT visit.

6.6 Safety Monitoring Committee

The Safety Monitoring Committee is described in Section 11.1.1.

6.7 Laboratory Analyses

The following clinical analytes will be assessed:

Hematology (safety assessment): hematocrit; hemoglobin; red blood cell count with indices (mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration); reticulocytes; white blood cell count and differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) reported as percentages and absolute values; and platelets (platelet count, prothrombin time and partial thromboplastin time, international normalization ratio).

Clinical chemistry (safety assessment): albumin; alkaline phosphatase; blood urea nitrogen; gamma-glutamyl transferase; calcium; creatinine; glucose; cholesterol (high-density lipoprotein and low-density lipoprotein [calculated] and homogenous low-density lipoprotein); triglycerides; phosphate; potassium; alanine aminotransferase; aspartate aminotransferase; lactate dehydrogenase; sodium; chloride; bilirubin (total, direct); total protein; uric acid; and creatine phosphokinase.

6.7.1 Sample Collections

Blood samples collected from study participants will be forwarded to a central laboratory for analysis. Further details regarding sample collections and processing and specific testing can be found in the central laboratory manual (provided to study sites as a separate document).

All samples for clinical laboratory analysis will be collected as described in the central laboratory manual, according to the schedule of activities (Table 6-1). Samples for hematology, clinical chemistry, or urinalysis (pregnancy testing only) will be used only for the evaluation of safety and tolerability.

Blood samples will be collected only for clinical laboratory safety assessments. The maximum volume of blood to be collected per study participant over the course of the study is estimated to be less than 175 mL.

6.8 Efficacy Assessments

Efficacy assessments will be conducted according to the schedule presented in Table 6-1. The efficacy assessments, grouped by efficacy domain and participant source, are presented in Table 6-2. Every effort should be made to have the same LAR/caregiver complete the LAR/caregiver-reported assessments. Additionally, every effort should be made to have the same investigator and raters complete the clinician assessments.

Efficacy assessments are only to be conducted in study participants who are at least 4 years old at study entry. If a study participant is 2 to 3 years old at study entry and turns 4 years old during the course of the study, only safety assessments are to be continued.

Table 6-2 Efficacy Assessments by Domain and Participant Source

Domain	LAR/Caregiver Assessment	Clinician Assessment
Sleep	• Children's Sleep Habits Questionnaire • Sleep diary	–
Motor	–	• Vineland Adaptive Behavior Scale (Motor domain)
Global functioning and quality of life	• Pediatric Quality of Life Inventory	• Vineland Adaptive Behavior Scale (Socialization, Communication, Daily Living Skills, and Maladaptive Behavior domains) • CGI-AS scales

Abbreviations: CGI-AS, Clinical Global Impressions-Angelman syndrome; LAR, legally acceptable representative.

6.8.1 Caregiver Assessments

6.8.1.1 Children's Sleep Habits Questionnaire

The Children's Sleep Habits Questionnaire (CSHQ) is a retrospective, 33-item caregiver questionnaire that has been used in studies to examine sleep behavior in young children (Owens et al 2000). The CSHQ includes items relating to sleep domains that encompass the major presenting sleep complaints in this age group, evaluating the child's sleep based on sleep behaviors within 8 different subscales: bedtime resistance, sleep-onset delay, sleep duration, anxiety around sleep, behavior occurring around night waking, parasomnias, sleep-disordered breathing, and morning waking/daytime sleepiness. Caregivers will be asked to recall sleep behaviors occurring over the 7 days immediately preceding specified timepoints outlined in Table 6-1. Items are rated on a 3-point scale: "usually" if the sleep behavior occurred 5 to 7 times/week; "sometimes" for 2 to 4 times/week; and "rarely" for 0 to 1 time/week. The scoring of some items can be reversed to consistently make a higher score indicative of more disturbed sleep.

6.8.1.2 Sleep Diary

A sleep diary will be completed by each study participant's LAR/caregiver, on behalf of the study participant. Endpoints assessed by the sleep diary are presented in Section 7.2.1. The sleep diary will be completed each day during the 7 days immediately preceding each clinic visit after screening.

At each clinic visit when a sleep diary is issued (Table 6-1), a calendar will be issued to remind the LAR/caregiver when next to start recording data in the sleep diary. In addition, 14 days before the study participant's expected next visit date, study staff will phone the LAR/caregiver as a reminder to start recording data in the sleep diary.

Sleep diaries will be collected at each clinic visit, starting with the baseline visit (Table 6-1) and continuing through the EOT visit.

6.8.1.3 Pediatric Quality of Life Inventory

The Peds QL® Cerebral Palsy, Multidimensional Fatigue, and Family Impact modules will be administered in this study (Varni et al 2004; Varni et al 2005). The 22-item Cerebral Palsy module assesses daily activities, school activities, movement and balance, pain and hurt, fatigue, eating activities, and speech and communication. The 18-item Multidimensional Fatigue module assesses general fatigue, sleep/rest fatigue, and cognitive fatigue. The 36-item Family Impact module assesses the impact of pediatric chronic health conditions on caregivers and family, including caregiver-reported assessments of physical, emotional, social, and cognitive functioning, communication, and worry. It also assesses caregiver-reported family daily activities and family relationships.

For this study, the Peds QL® Cerebral Palsy, Multidimensional Fatigue, and Family Impact should be performed for all study participants, including those over the age of 25.

6.8.2 Clinician Assessments

6.8.2.1 Vineland Adaptive Behavior Scale

The Vineland Adaptive Behavior Scale, 3rd Edition (VABS-3) is a standardized psychometric instrument designed to measure personal and social skills needed for everyday living (Sparrow et al 2005; Sparrow et al 2016). The VABS-3 is administered via a caregiver using a semi-structured interview format and assesses 4 main adaptive domains: communication (receptive, expressive, and written), socialization (interpersonal relationships, play and leisure, coping skills), daily living skills (personal, domestic, community), and motor skills (fine and gross). It also includes a maladaptive behavior scale for identifying behavior problems in children through 18 years of age. The scale has been found to have good internal consistency, test-retest reliability, and validity (Sparrow et al 2016). The VABS-3 interview form will be used to evaluate study participants on the communication, socialization, daily living skills, motor skills, and maladaptive behavior domains to assess their overall functioning. This assessment is an interview of the caregiver by a trained qualified rater, and for each study site, the same rater is to

be used throughout the study. As an exception, another sponsor-trained qualified rater may be used.

6.8.2.2 Clinical Global Impressions - Angelman Syndrome Scales

The CGI-S-AS scale with AS-specific anchors will be used by the investigator to assess the severity of symptoms, and the CGI-I-AS scale will be used by investigators to assess improvement from Baseline. The CGI-S-AS captures specific characteristics commonly present in the AS population; the CGI-I-AS captures clinical impression that reflects the rater's estimate of change from the initiation (Baseline) of treatment. Both the CGI-S-AS and the CGI-I-AS assessments will be conducted by a rater with experience in AS and trained in CGI-S-AS and CGI-I-AS rating by the sponsor. It is highly preferable that each site uses the same rater. Whenever possible, the same rater (the principal investigator) at each site must evaluate a given study participant throughout the study. As an exception, a clinician sub-investigator, trained in CGI-S-AS and CGI-I-AS rating by the sponsor, may be used.

The baseline CGI-S-AS will be accompanied by detailed investigator notes. Each CGI-I-AS rating will also be accompanied by detailed investigator notes [redacted] To reduce recall bias, within 24 hours prior to the study participant's clinic visit at Week 12 (the first CGI-I-AS assessment), the investigator must review the study participant's baseline CGI-S-AS score and investigator notes. Within 24 hours prior to the study participant's visit at Week 36 (and all subsequent visits with assessments of CGI-I-AS), the investigator must review the study participant's baseline CGI-S-AS score and investigator notes and the prior clinic visit's CGI-I-AS score and investigator notes. If the CGI-I-AS assessment is missing at a study visit, the reason for the absence will be noted in the eCRF.

7 Statistical and Analytical Plan

7.1 Safety Endpoints

The following safety endpoints will be evaluated for study participants who are at least 2 years old at study entry:

- Incidence of SAEs, TEAEs, treatment-related TEAEs, and TEAEs leading to study discontinuation
- Vital sign measurements
- Clinical safety laboratory values
- Physical examination
- Assessment of suicidality (ABC-I; Section 6.2.2.1)
- The 28-day seizure frequency (Section 6.2.2.4)

7.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints below are not listed in order of importance. Efficacy assessments are only to be conducted in study participants who are at least 4 years old at study entry. If a study participant is 2 to 3 years old at study entry and turns 4 years old during the course of the study, only safety assessments are to be continued.

7.2.1 LAR/Caregiver-Completed Endpoints (for Study participants at Least 4 Years Old)

- Change from baseline in the CSHQ total and subscale scores
- Change from baseline in sleep diary parameters:
    - Latency of sleep onset (LSO), defined as time from beginning of rest period to start of sleep onset
    - Sleep efficiency, defined as the percentage of total sleep time out of duration of the rest period
    - Total daytime sleep, defined as duration of sleep time in the active interval

7.2.2 Clinician-Completed Endpoints (for Study participants at Least 4 Years Old)

- CGI-I-AS scores

- Change from baseline in CGI-S-AS scores:
    - The CGI-S-AS symptoms overall score
    - The CGI-S-AS domain scores
- Change from baseline in the VABS-3 overall composite and subscale scores:
    - Communication domain and its subdomains
    - Socialization domain and its subdomains
    - Daily Living Skills domain and its subdomains
    - Maladaptive Behavior domain and its subdomains

7.3 Exploratory Endpoints

The exploratory efficacy endpoints below are not listed in order of importance.

7.3.1 LAR/Caregiver-Completed Endpoints (for Study participants at Least 4 Years Old)

- Change from baseline in PedQoLI total and subscale scores

7.3.2 Clinician-Completed Endpoints (for Study participants at Least 4 Years Old)

- Change from baseline in the VABS-3 Motor Skills domain and its subdomains

7.3.3 Endpoints for Relationship Exploration

- Endpoints of interest may be identified to explore the relationships among them.

7.4 Sample Size Calculations

This is an open-label extension study from 3 prior protocols, and siblings of study participants completing those studies are eligible to enroll; thus, sample size calculation is not based on power calculations. The number of study participants enrolled in the study will be dependent on the number of study participants who are eligible and consent to participate in the extension study. Approximately 170 study participants will be enrolled in the study.

7.5 Analysis Sets

The following analysis sets will be used in the statistical analyses.

Enrolled Analysis Set (EAS): The EAS will consist of all study participants enrolled in the extension study.

Safety Analysis Set (SS): The SS will consist of all study participants who receive at least 1 dose of study drug.

Full-Analysis Set (FAS): The FAS will consist of all study participants who receive at least 1 dose of study drug and have at least 1 post baseline efficacy assessment.

The EAS will be used for summaries of study participant disposition, demographics and other baseline characteristics. All safety evaluations will be carried out on the SS. All efficacy evaluations will be carried out on the FAS.

7.6 Subgroup Analysis

Subgroup statistical analyses may be performed and will be detailed in a statistical analysis plan.

7.7 Statistical Analysis Methodology

The detailed methodology for the summary and statistical analyses of the data collected in this study will be documented in a separate statistical analysis plan.

All statistical analysis will be performed using SAS® software (SAS Institute Inc., Cary, NC) Version 9.4 or higher.

Unless otherwise specified, baseline will be defined as the last non-missing evaluation prior to or on the date that the first dose of treatment is taken in this study.

Descriptive statistics (number of study participants, mean, SD, median, minimum, and maximum) will be presented for continuous variables and frequency and percentage will be presented for categorical and ordinal variables. If there are missing values, the number missing will be presented, but without a percentage. All data collected will be included in by -study participant data listings. Two--sided 95% CIs will be provided where appropriate. Graphical displays will be utilized to investigate trends over time overall and by relevant subgroups as needed.

Separate analyses of selected endpoints, including but not limited to CGI-I-AS, CGI-S-AS, and seizure diary data, will be performed for the study participants who have participated in STARS and the study participants who have participated in the NEPTUNE study (Study OV101-19-001).

7.7.1 Analysis of Primary Endpoints - Safety

All safety analyses will be performed on the SS.

All AEs will be coded using latest version of MedDRA and will be classified by MedDRA system organ class (SOC) and preferred term (PT).

The number and percentage of study participants who experience at least 1 TEAE as well as the 95% exact CI for the incidence of TEAEs overall and within each specific SOC and PT will be presented.

Treatment emergent adverse event is defined as newly or worsening AEs start from the first dose of study medication till 30 days after the last dose of study medication.

Treatment-related AEs will be identified as those that are at least possibly related to study drug based on the investigator's assessment. The number and percentage of study participants with treatment-related AEs, SAEs, TEAEs leading to study discontinuation, and TEAEs leading to death will also be summarized by SOC and PT.

For each SOC and each PT, a study participant will be counted only once for study participant-incidence tabulations. For summaries by severity or relationship, for a given study participant, the highest severity and relationship for a specific PT will be considered.

Descriptive statistics for the observed values and changes from baseline to each post baseline visit with respect to clinical laboratory and vital sign measurements will be summarized. Clinically significant laboratory values may be tabulated.

Shift tables for laboratory parameters will be presented. For each continuous laboratory parameter, results will be categorized as low, normal, and high based on the laboratory normal ranges. Frequencies and percentages will be presented for the shifts in these categories from baseline to each posttreatment assessment timepoint.

Suicidality assessed by ABC-I will be summarized descriptively at baseline and all post baseline study visits. Change from baseline to all post baseline study visits also will be summarized descriptively.

Abnormal findings in physical examinations will be listed.

The 28-day seizure frequencies as captured in the seizure diary will be calculated for baseline and post baseline study periods for all seizure types and for subtypes of drop and nondrop. Percent change in 28-day seizure frequency from baseline to all post baseline study visits will also be summarized descriptively for all seizure types and for subtypes of drop and nondrop.

Concomitant medications will be coded using the World Health Organization Drug Dictionary. A table summarizing concomitant medications and a by-study participant listing of concomitant medications will include all medications taken during the study regardless of the timing for the start of medication.

7.7.2 Analysis of Secondary Efficacy Endpoints

Descriptive statistics and 95% CIs for efficacy variables at each timepoint will be displayed. Line graphs of time course of change (or percent change) from baseline will be presented for the secondary efficacy endpoints and for the average dose.

For CGI-I-AS and CGI-S-AS endpoints, analyses will be conducted for the subset of study participants that had valid CGI-S-AS measurements at baseline. The long-term durability will be assessed on the improvement from the baseline at previous study.

7.7.3 Analyses of Exploratory Efficacy Endpoints

Exploratory endpoints will be analyzed using the same methods as used for the secondary efficacy endpoints. For the endpoints of interest for their relationships, suitable analysis methods will be specified in the statistical analysis plan.

7.7.4 Other Analyses

7.7.4.1 Demographics and Other Baseline Characteristics

Demographic and background information variables and study participant disposition will be listed by study participant and summarized using frequency distributions for categorical variables and descriptive statistics for continuous variables. Relevant medical history/current medical conditions will be summarized by MedDRA SOC and PT.

Background information will consist of data collected in the molecular AS testing, and clinical assessment of AS.

The above analyses will be performed using the EAS.

7.7.4.2 Drug Treatments

7.7.4.2.1 Study Drug

Using the SS, duration (days) of exposure to study drug and treatment compliance will be listed by study participant and summarized descriptively by dose. Frequency and percentages for study participant disposition and reasons for discontinuation of study drug will be presented.

7.7.4.2.2 Prior and Concomitant Medications

Using the EAS, prior and concomitant medications will be listed by study participant and summarized descriptively.

7.7.5 Interim Analyses

Periodic data review will be performed to support regulatory submissions as needed.

8 Data Quality Assurance

This study will be conducted according to the International Council for Harmonisation (ICH) E6 (R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH guidance on quality and risk management.

Standard operating procedures are available for all activities relevant to the quality of this study. Designated staff will be responsible for implementing and maintaining quality assurance and quality control systems to ensure that the study is conducted and that data are generated, documented, and reported in compliance with the study protocol, Good Clinical Practice (GCP), and Good Laboratory Practice requirements as well as applicable regulatory requirements and local laws, rules, and regulations relating to the conduct of the clinical trial.

An authorized quality assurance auditor will audit the study data and procedures at periodic intervals as indicated. Domestic or foreign regulatory authorities, the IRB or IEC, and a sponsor-authorized auditor may request access to all study documentation for an on-site inspection or audit. The investigator must notify the sponsor of any regulatory authority inspections and forward copies of the inspection report to the sponsor.

Electronic data systems will be in accordance with applicable aspects of US Title 21 Code of Federal Regulations (CFR) Part 11, ICH guidelines, GCP, local laws and legislation, and the Health Insurance Portability and Accountability Act.

8.1 On-Site Audits

At any time, quality assurance representatives of the sponsor and/or regulatory bodies may visit the unit to carry out an audit of the study in compliance with regulatory guidelines and company policy. Such audits will require access to study records, documentation, and regulatory files. At all times, study participant privacy will be of utmost importance and respected. Typically, sufficient notice will be given to the investigator to prepare for the visit.

8.2 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the study participants treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include such documents as questionnaire results, sleep diaries, and computerized or otherwise automated assessments.

Investigative site staff will enter study participant data into [redacted] (the eCRF program). The analysis data sets will be a combination of these data and data from other sources (e.g., laboratory data).

Clinical data management will be performed in accordance with applicable sponsor standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data. Adverse event terms will be coded using MedDRA, an internal validated medical dictionary, and concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant medications will be coded using the World Health Organization Drug Dictionary.

After database lock, each study site will receive a CDROM containing all its site specific eCRF data as entered into the EDC system for the study, including full discrepancy and audit history. Additionally, a CDROM copy of all the site's data from the study will be created and sent to the sponsor for storage. [redacted] maintain a duplicate CDROM copy for their records. In all cases, study participant initials will not be collected or transmitted to the sponsor.

9 Ethics

9.1 Independent Ethics Committee or Institutional Review Board

Federal regulations and the ICH guidelines require that approval be obtained from an IRB/IEC before participation of human study participants in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study participants, and any other written information regarding this study to be provided to the study participant or the study participant's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6 (R2): GCP will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply the sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to study participants.

9.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, the protocol, and all applicable regulations.

9.3 Study participant Information and Consent

A written informed consent in compliance with applicable regulatory authority regulations shall be obtained from each adult competent study participant (or from the LAR/caregiver of a minor or adult of diminished mental capacity, as applicable) before the study participant enters the study or any unusual or non-routine procedure that involves risk to the study participant is performed. For minors or adults of diminished mental capacity, an assent document will be presented and assent obtained before the study participant participates in any study procedure. Informed consent and assent template documents may be provided by the sponsor to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent and assent should be reviewed by the sponsor or its designee or both before IRB submission. Once reviewed, the consent and assent will be

submitted by the investigator to his/her IRB for review and approval before the start of the study. If the ICF is revised during the study, all active participating study participants and LAR/caregivers (as applicable) must sign the revised forms.

Before recruitment and enrollment, each prospective study participant's LAR/caregiver and study participant (as applicable) will be given a full explanation of the study and will be allowed to read the approved ICF/assent. Once the investigator is assured that the LAR/caregiver and study participant understand the implications of participating in the study, the LAR/caregiver and study participant will be asked to give consent/assent to participate in the study by signing/approving the ICF/assent.

The investigator shall retain the signed original ICFs/assents and give copies of the signed original forms to the LAR/caregivers and study participants, as applicable.

10 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be study participant to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

10.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain study participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the study participant (or the study participant's legal guardian or LAR/caregiver), except as necessary for monitoring and auditing by the sponsor, its designee, the US Food and Drug Administration (FDA) or other applicable regulatory agency, or the IRB/IEC.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

10.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the study and for 1 year following the completion of the study.

Neither [redacted] is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither [redacted] is financially responsible for further treatment of the study participant's disease.

10.3 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6 (R2) 8.2 and Title 21 of the CFR by providing essential documents, including but not limited to the following:

- IRB/IEC approval.

- Original investigator-signed investigator agreement page of the protocol.
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572 for sites in the United States, Clinical Investigator Form for sites outside of the United States.
- Curriculum vitae for the investigator and each sub-investigator listed on Form FDA 1572 or Clinical Investigator Form.
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- IRB/IEC-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the study participant or legal guardian.
- Laboratory certifications and normal ranges for any local laboratories used by the site, in accordance with 42 CFR 493.

10.4 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6 (R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before the enrollment of study participants begins.

10.5 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6 (R2) and all applicable guidelines and regulations.

10.6 Adverse Events and Study Report Requirements

By participating in this study, the investigator agrees to submit reports of SAEs to the sponsor and/or IRB/IEC according to the timeline and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

10.7 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any reports required.

10.8 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10.9 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

The data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data and publication thereof will not be unduly withheld.

11 Study Management

The administrative structure will include a scientific steering committee, an external safety monitoring committee, an event adjudication committee, and an independent statistician.

11.1 Monitoring

11.1.1 External Safety Monitoring Committee

The Safety Monitoring Committee will consist of at least 3 external, independent, non-Ovid experts responsible for monitoring the safety data to ensure that the study does not pose unacceptable risks to the study participants.

11.1.2 Monitoring the Study

The medical monitor, as a representative of the sponsor, has the obligation to follow the study closely.

The study medical monitor may visit the investigator and study site at periodic intervals, in addition to maintaining necessary telephone and letter contact. The study medical monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff.

All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

11.1.3 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency access to all study records.

The investigator should promptly notify the sponsor [redacted] of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

11.2 Management of Protocol Amendments and Deviations

11.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the study participant, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator's IRB/IEC for approval before study participants can be enrolled into an amended protocol.

11.2.2 Protocol Deviations

The investigator or designee must document and explain in the study participant's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study participants without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the study participant or investigator that results in a significant, additional risk to the study participant. Significant deviations can include nonadherence to inclusion or exclusion criteria, or nonadherence to FDA regulations or ICH GCP guidelines, and will lead to the study participant being withdrawn from the study (Section 4.2).

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal investigators will be notified in writing by the monitor of deviations. The IRB/IEC should be notified of all protocol deviations in a timely manner.

11.3 Study Termination

Although Ovid has every intention of completing the study, Ovid reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last study participant completes the last visit (includes the phone EOS visit).

11.4 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the clinical study reports (CSRs) are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that the CSRs in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of CSRs.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the CSR. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the CSR, the sponsor will provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate. The study results will be posted on publicly available clinical trial registers.

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13 Pandemic Addendum

The purpose of this addendum is to safeguard the safety of study participants, ensure continuation of study conduct, and preserve the integrity of the study, in case of a general public health crisis such as the COVID-19 pandemic. This addendum addresses situations in which scheduled in-person clinic visits are not feasible due to local, regional or national restrictions. If a patient cannot attend an in-person visit, a home visit may be conducted by a mobile healthcare professional trained to perform study assessments e.g. vital signs, body system assessment, clinical labs draws, review/collection of study materials.

Specifically, the addendum aims to ensure:

- Continued safe study conduct and participation of existing patients
- Uninterrupted supply of study drug
- Integrity of data capture and minimization of missing data

Written communication from sponsor Medical Advisor or Clinical Operations Lead is required before any portion of this addendum is put into effect. The communication shall be documented and captured in the Trial Master File.

The Principal Investigator holds the ultimate responsibility for the safety and well-being of study participants and as always, shall maintain compliance with the current local and health authority guidelines and recommendations pertaining to the pandemic.

This guidance is categorized below by the different stages of study participant participation in the ELARA study:

Guidance for study participants scheduled to undergo study screening

Guidance for Screening visits occurring within 2 Weeks of Completing NEPTUNE study

- Study Participants who are scheduled to roll over to ELARA within 2 weeks of completing NEPTUNE are NOT required to complete a separate screening visit for ELARA. Per protocol their data for the last visit in NEPTUNE will be used for the ELARA baseline visit. Therefore, please skip the Guidance for Screening below and go to Guidance for Baseline.

Guidance for Screening Visits beyond 2 Weeks of Completing NEPTUNE

- 2-3-year-old study Participants MUST be scheduled for ONSITE screening
- Consider remote screening via telehealth/virtual and/or telephone for Participants ≥4 years old
    - Telehealth/virtual platform selection is at investigator discretion and should be consistent with local and individual institution's policies and standard practice. A home nurse visit will replace a virtual visit if the latter is not feasible.
- Informed consent/assent should be sent to the study participant and LAR/caregiver either electronically (PDF format) or by mail prior to the scheduled screening visit
    - Informed consent/assent can be performed via Telehealth/virtual and/or Telephone during the Screening Visit and documented in the source document

with the date and time of the verbal consent/assent. A home nurse visit will replace a virtual visit if the latter is not feasible

- Documentation of the consent/assent must be captured in the Study Participant's source documents. Please ensure the following is documented:
  - The date and time of the consent/assent.
  - Method of consent/assent (Telehealth/virtual or Telephone). A home nurse visit will replace a virtual visit if the latter is not feasible.
  - Individuals who signed consent/assent (site personnel and participant's LAR/caregiver).
  - Method by which the signed consent/assent will be provided to the site.

Study participant/LAR/caregiver can provide proof of wet ink signature via fax, scan or picture. Site should advise LAR/caregiver to bring in the original ICF/assent along with the addendum with wet ink signature at next possible on-site visit or via courier envelope provided by the site at their earliest convenience.

- [redacted]
- Screening visit clinical labs, vital sign testing, and weight measurement may be performed at a local lab or by the home health nurse.
- Copies of seizure and sleep diary forms should be sent to LAR/caregivers.
  - Electronic copies may be provided if LAR/caregivers can print physical copies.
  - Instructions for completion of diary forms should be provided verbally/in writing.
  - Pre-paid envelopes should be provided to support the return shipping of the diaries. *The study title and/or protocol number should NOT be noted on the envelope*.
- Update EDC as soon as possible to allow planning of Investigational Product (IP) shipment.
- Notify [redacted] plan support for IP shipment arrangement

Guidance for Baseline Visits for Participants scheduled within 2 Weeks of completing NEPTUNE

- Whenever possible, the Baseline Visit should be completed onsite.
- If an onsite visit is not possible, a remote visit including assessment of the CGI-S-AS, VABS3, and other Reported Outcomes required per protocol may be performed via each site's institution-approved Telehealth/virtual system and/or Telephone. A home nurse visit will replace a virtual visit if the latter is not feasible.
- Notify [redacted] advance of the visit to define IP shipment arrangements.

- Informed consent/addendum/assent should be sent to the study participant and LAR/caregiver either electronically (pdf format) or by mail prior to the scheduled Baseline visit.
    - Informed consent/addendum/assent can be performed via Telehealth/virtual and/or Telephone during the Baseline Visit and documented in the source document with the date and time of the verbal consent/assent. A home nurse visit will replace a virtual visit if the latter is not feasible.
    - Documentation of the consent/assent must be captured in the study participant's source documents. Please ensure the following is documented:
        - The date and time of the consent/assent.
        - Method of consent/assent (Telehealth/virtual or Telephone).
        - Individuals who signed consent/assent (Site personnel and Participant's LAR/caregiver).
        - Method by which the signed consent/assent will be provided to the Site.

Study Participant can provide proof of wet ink signature via fax, scan or picture. Site should advise Caregiver to bring in the original ICF/assent with wet ink signature at next possible on-site visit or via courier envelope provided by the Site at their earliest convenience.

- For remote screening, ensure that the Study Participant has access to [redacted] Baseline Visit clinical labs, vital sign testing, and weight measurement may be performed at a local lab or by the home health nurse.
- Copies of seizure and sleep diary forms should be sent to LAR/caregivers.
    - Electronic copies may be provided if LAR/caregivers can make physical copies.
    - Instructions for completion of diary forms should be provided verbally/in writing to the LAR/caregivers.
    - Pre-paid envelopes should be provided by the site to the LAR/caregivers by the site to support the shipping of the diaries.
- ALL scale administrations should capture the CGI-S-AS/CGI-I-AS, PedsQL, and CSHQ data on the paper source even when administered by phone. Please still use [redacted] to score the Vineland-3.
- Update EDC accordingly.

Guidance for Baseline Visits for study participants scheduled beyond 2 Weeks of completing NEPTUNE

- For these study participants a Screening Visit must have been performed prior to Baseline.
- Baseline visits can ONLY occur when study participants can appear ON-SITE.
- If the baseline visit cannot be conducted within 28 days of the Screening Visit, this should be captured as a Protocol Deviation due to COVID-19 restrictions, but not a

screen fail of the Study Participant. IWRS and EDC will not automatically screen fail study participants

- Every attempt should be made to follow Baseline Visit procedures per the Schedule of Activities (SOA).
    - Any deviation should be appropriately documented.
- IP will be provided to the study participant at the site.
- Please collect and review seizure and sleep diaries per protocol and epilepsy consortium instructions.
    - Provide physical/electronic PDF copies of diaries (seizure, sleep, medication).
    - Pre-paid envelopes should be provided to the LAR/caregivers by the site to support the shipping of the diaries.
- Update EDC when diaries are received.

Guidance for Weeks 12, 36, 64, 96, and 124 Clinic Visits

- Schedule the visit as close as possible to planned visit date to allow adequate time to ship IP.
- If an onsite visit is not possible, a remote visit including AE/SAE collection, assessment of the CGI-AS, CGI-S,-AS, VABS3, and other PROs required per protocol may be performed via your institution-approved (HIPAA compliant) home visit, Telehealth/virtual system and/or Telephone software, which also should be compliant and consistent with local and individual institution's policies and standard practice.
- ALL scale administrations should capture the CGI-S-AS/CGI-I-AS, PedsQL, and CSHQ data on the paper source even when administered by phone. [redacted] should be used to score the VABS-3.
- Clinical labs and vital signs required per SOA may be performed at a local lab or by the home health nurse.
- IP with kit number to be assigned to the study participant.
    - Please organize the courier to pick up and deliver the IP to the study participant.
    - Alternatively, your site can inform vendor (via email) to pick up the IP and ship to the study participant directly by providing the shipment orders by email. Delivery addresses, including contact information and consignee details will be provided to the vendor. Unused study drug should be returned to the site at each visit.
- Copies of seizure and sleep diary forms should be sent to LAR/caregivers.
    - Electronic copies may be provided if LAR/caregivers can print physical copies.
    - Pre-paid envelopes should be provided to support the shipping of the diaries. *The study title and/or protocol number should NOT be noted on the envelope*.
- Update EDC when diaries are received.

****The guidance below is only for sites still operating under Protocol Version 1.0. Sites utilizing Protocol Version 3.0 (which allows rollover from Neptune) may disregard this section*

Protocol Version 1.0 - Guidance for Week 24, 48, 80, 112 and 144

- Schedule the visit as close as possible to planned visit date to allow adequate time to ship IP.

- A remote visit should be completed to monitor the study participant and collect AE/SAE assessments via telehealth/virtual and/or telephone.
    - Telehealth/virtual platform selection is at investigator discretion and should be consistent with local and individual institution's policies and standard practice.
- Clinical labs and vital signs required per SOA may be performed at a local lab.

Guidance pertaining to the EOT Visit

- Whenever possible, the EOT Visit should be completed onsite.
- If an onsite visit is not possible, a remote visit to monitor the study participant and collect AEs and assessment of the CGI-I-AS, CGI-S,-AS, VABS3, and other PROs required per protocol may be performed via a home visit, institution-approved Telehealth/virtual system and/or Telephone
- ALL scale administrations should capture the CGI-S-AS/CGI-I-AS, PedsQL, and CSHQ data on the paper source even when administered by phone. [redacted] should be used to score the VABS-3.
- Clinical labs and vital signs required per SOA may be performed at a local lab.
- Unused IP to be shipped back to site for reconciliation.
- Ensure study participant diaries are collected and reviewed appropriately.

Please ensure that all protocol deviations resulting from the COVID-19 pandemic are communicated [redacted] appropriately documented. If at any time during the conduct of the ELARA study /a study participant contracts COVID-19 infection or any reportable infectious disease, the local health authority requirements regarding treatment/reporting/quarantine should be followed. The event should be reported as an AE/SAE and the investigator should determine if study treatment should be continued, temporarily interrupted, or discontinued.