CLINICAL STUDY PROTOCOL

[redacted]

A MulticeNter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 3 Study to Evaluate the Efficacy and Safety of OV101 in PediaTric IndividUals With AngelmaN SyndromE (NEPTUNE)

PROTOCOL NUMBER OV101-19-001

Sponsor: Ovid Therapeutics Inc.
1460 Broadway
New York, NY 10036

Sponsor Contact: [redacted]

Medical Monitor: [redacted]

Date of Amendment 5: 26 January 2021 (Version 6.0)
Date of Amendment 4: 27 June 2020 (Version 5.0)
Date of Amendment 3: 19 June 2020 (Version 4.0)
Date of Amendment 2: 18 April 2020 (Version 3.0)
Date of Amendment 1: 31 January 2020 (Version 2.0)
Date of Original Protocol: 30 May 2019 (Version 1.0)

CONFIDENTIAL

Protocol Approval – Sponsor Signatory

Study Title	A MulticeNter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 3 Study to Evaluate the Efficacy and Safety of OV101 in PediaTric IndividUals With AngelmaN SyndromE (NEPTUNE)
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Amendment 5	Version 6.0
Date:	26 January 2021

Protocol accepted and approved by:

[redacted]

03 February 2021
Date

Protocol Approval –Coordinating Investigator

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[redacted]

[redacted]

Signature Date

Protocol Approval – Lead Statistician

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[redacted]

[redacted]

[redacted]

Protocol Amendment 5 (Version 6.0) Summary of Changes

Rationale for Amendment 5

Protocol Amendment 5 (Version 6.0) includes administrative changes only to clarify the serious adverse event reporting process for subjects that do not elect to enter the open-label extension study (Section 6.4.1.5).

Changes Implemented With Amendment 5:

Section 6.4.1.5 (new text in **bold/underlined** type; no deletions were made in this amendment):

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 subject's last dose of study drug or within 30 days after the last study visit, the SAE must be reported **unless the patient has signed the consent to enroll into the ELARA open label extension study**. 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 subject or health care practitioner is unable to provide additional information, or the subject is lost to follow-up). **For subjects who do not sign the informed consent to enroll into the ELARA open label extension study,** 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/EC or regulators unless the investigator or Sponsor considers them related to study drug.

Declaration of Investigator

I have read and understood all sections of the protocol entitled "A MulticeNter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 3 Study to Evaluate the Efficacy and Safety of OV101 in PediaTric IndividUals With AngelmaN SyndromE (NEPTUNE)" 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 current protocol (Version 1.0, dated 30 May 2019), the International Council for Harmonisation harmonised 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 subjects. I agree to administer study treatment only to subjects 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. Subject 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:
OV101-19-001

Title:
A MulticeNter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 3 Study to Evaluate the Efficacy and Safety of OV101 in PediaTric IndividUals With AngelmaN SyndromE (NEPTUNE)

Sponsor:
Ovid Therapeutics Inc.
1460 Broadway
New York, NY 10036

Study Phase:
Phase 3

Study Sites:
Approximately 15 study sites in the United States, Israel, Australia and/or Europe

Indication:
Angelman syndrome (AS)

Rationale:
Angelman syndrome is a severe, complex, and rare neurogenetic disorder with a prevalence estimated at 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 from both gene copies 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 as an orthosteric agonist to the α4- and δ-containing subunit of extrasynaptic GABA receptors. 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. The extrasynaptic GABA 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. Unlike many of these drugs that are allosteric modulators and therefore require endogenous GABA to function, OV101 is a GABA agonist and can function when GABA is deficient or absent. 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 subjects with AS.

Phase 2 and Phase 3 studies in adult subjects 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 exploratory efficacy measures of OV101 in adolescents and adults with AS over 12 weeks of treatment. The STARS study was the first industry-sponsored clinical study in AS. Overall, OV101 had a favorable safety profile and was well tolerated. OV101 had a statistically significant effect on the CGI-I, a measure of global function, included as an exploratory measure. Exploratory and post-hoc analyses suggested that improvements seen on the CGI-I were likely driven by sleep, gross and fine motor function, behavior, and communication.

NEPTUNE (OV101-19-001) will be a multicenter, randomized, placebo-controlled, parallel -group study to evaluate the efficacy and safety of OV101 in pediatric subjects with AS. Subjects who complete the study will be eligible to enroll in the ongoing OV101-18-002 (ELARA) open-label extension study, provided they meet the eligibility criteria for ELARA.

Objectives:

All efficacy study objectives will be assessed in the pediatric AS study population of subjects who are 4 to 12 years old. All safety study objectives will be assessed in the pediatric AS study population of subjects who are 2 to 12 years old.

Primary Objective:

- To evaluate the efficacy of OV101 versus placebo as assessed by the Clinical Global Impressions-Improvement-Angelman syndrome (CGI-I-AS) score at Week 12.

Key Secondary Objectives:

The purpose of the key secondary objectives is to fulfil a recommendation of the EMA for a responder analysis.

- To evaluate the efficacy of OV101 vs placebo as assessed by the proportion of subjects who experience any meaningful improvement on study treatment (defined as CGI-I-AS score of 1, 2, or 3 at Week 12)
- To evaluate the efficacy of OV101 vs placebo as assessed by the proportion of subjects who experience a response of much improved or very much improved (defined as CGI-I-AS score of 1 or 2 at Week 12)

Other Secondary Objectives:

Other secondary efficacy objectives of this study are:

[redacted]

- To evaluate the efficacy of OV101 versus placebo on Communications, Socialization, Daily Living Skills, Motor Skills, and Maladaptive Behavior domains assessed by the Vineland Adaptive Behavior Scale, 3rd Edition (VABS-3).
- To evaluate the efficacy of OV101 versus placebo based on the Clinical Global Impressions-Severity-Angelman syndrome (CGI-S-AS) Symptoms Overall score.
- To evaluate the relationships of CGI-S-AS Symptoms Overall and CGI-S-AS domains at baseline with CGI-I-AS at Week 12.

[redacted]

Safety Objectives:

The safety objectives of this study are to evaluate the safety and tolerability of OV101 in subjects 2 to 12 years old, including seizure diary data and assessment of suicidality.

Study Population:

Inclusion Criteria:

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

1. Is male or female and 2 to 12 years old (inclusive) at the time of informed consent.
2. Has a diagnosis of AS with molecular confirmation.
3. Has a CGI-S-AS score of 3 or more.
4. Meets the following age-appropriate body weight criterion:

   a) Subjects 2 to 3 years old must have a minimum body weight of 9 kg.

   b) Subjects 4 years and older must be between 17 kg and 64 kg (inclusive).

5. Has a legally acceptable representative (LAR)/caregiver capable of providing written informed consent and able to attend all scheduled study visits, oversee the administration of study drug, and provide feedback regarding the subject's symptoms and performance as described in the protocol.
6. Provides assent to the protocol (to the extent possible and in accordance with local institutional review board [IRB] and regulatory requirements). Subjects providing assent must do so at the same visit as LAR/caregiver written informed consent is provided.
7. Can swallow study drug capsules with water or ingest the contents of study drug capsules after sprinkling the contents of each capsule onto up to 1 teaspoon of low-fat semiliquid food.
8. If a subject is currently receiving a regimen of concomitant medications such as antiepileptic medication, gabapentin, clonidine, trazodone, melatonin, or a special diet regimen, that subject'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).
9. If a subject is a sibling in a family with multiple children diagnosed with AS, then only one of the siblings may enroll in study. The eldest eligible subject should be enrolled (investigator discretion may be used to enroll a younger sibling instead).
10. Has LAR(s)/caregiver(s) who agree not to post any of the subject's personal medical data or information related to the study on any website, message board(s), online support group(s), or social media site (e.g., Facebook, Instagram, Twitter, etc.) until notified that the study is completed.
11. Female subjects who are of child-bearing 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. 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.

Exclusion Criteria:

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

1. Has a circumstance or concomitant disease (e.g., gastrointestinal, renal, hepatic, endocrine, respiratory, or cardiovascular system disease), condition, or any clinically significant finding at screening that could interfere with the conduct of the study or that would pose an unacceptable risk to the subject in the opinion of the investigator.
2. Has poorly controlled seizures defined as any of the following:
   a. Weekly seizures of any frequency with a duration more than 3 minutes.
   b. Weekly seizures occurring more than 3 times per week, each with a duration of less than 3 minutes.
   c. Investigator assessment.
3. 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.
4. 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 for situational anxiety related to occasional procedures or events are permitted, and benzodiazepines are also permitted for seizure control.

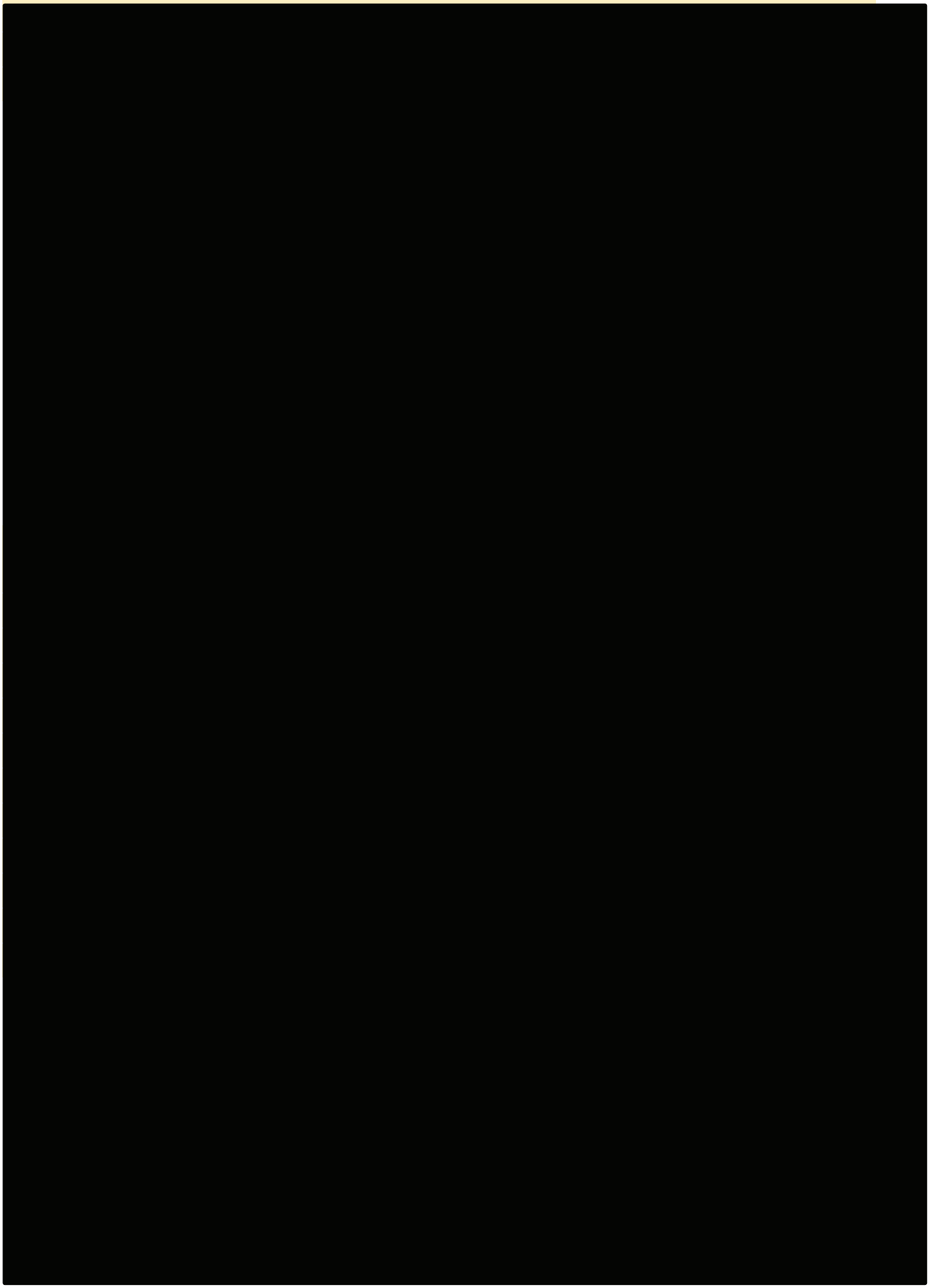
5. [redacted]
6. Is at risk of harming self and/or others (based on investigator assessment).
7. Has enrolled in any other interventional clinical study or used any investigational agent or device, or has participated in any investigational procedure, within the 30 days before screening or does so concurrently with this study.
8. Is allergic to OV101 or any excipients of study drug.
9. The subject or LAR/caregiver is unable to comply with study requirements (based on investigator assessment).
10. Is a family member of the investigator and/or study site staff.

Study Design:
The study will comprise a screening period within the 28 days preceding Day 1; a visit on Day 1 for baseline assessments, the first dose of study drug, and sparse sampling of blood; subsequent doses of study drug taken each evening approximately 30 minutes before bedtime for 12 weeks starting on Day 2; and study site visits for efficacy and safety assessments over a 12-week treatment period. After the baseline visit, the study site visits will occur at Week 6 and Week 12 (end of treatment [EOT]). Phone safety visits will occur during up-titration of the study drug (Day 6 and Day 11). Unless a subject decides to participate in the ELARA open-label extension study, an end of study (EOS) phone safety visit will occur approximately 2 weeks after the last dose of study drug to assess safety and tolerability associated with discontinuation of treatment. Subjects eligible for and willing to enroll in the ELARA study will have the NEPTUNE EOT visit be their NEPTUNE EOS visit, and their NEPTUNE EOT visit will serve as their ELARA baseline visit. A subject will be considered to have completed the NEPTUNE study after completing the EOS visit. The total duration of the study for a subject will be approximately 18 weeks.

Random assignment of subjects for efficacy assessment (to either OV101 or placebo treatment in a 1:1 ratio) will be stratified by subject age at screening and by region, with a maximum of 12 subjects per study site (unless authorized by Sponsor). The randomization strata for age at screening will be 9 to 12 years old (inclusive) and 4 to 8 years old (inclusive), with at least 24 subjects per age category. The randomization strata for region will be US and outside US. Approximately 5 subjects 2 to 3 years old (inclusive) will be enrolled for safety [redacted] assessments only and will be assigned to treatment with OV101. Within each age group, dosing will be assigned based on body weight at screening.

For each subject, after informed consent is obtained, screening assessments will be completed within the 28 days preceding Day 1 (baseline). On Day 1, each subject who meets all eligibility criteria will receive the first assigned blister cards of study drug capsules according to the treatment code (except for subjects 2 to 3 years old, who will receive study drug capsules in bottles), sufficient to last until the Week 6 visit, when blister cards (or bottles for ages 2 to 3 years) will be collected and unused study drug will be counted. Study drug will be similarly dispensed at the Week 6 visit, and blister cards (or bottles for ages 2 to 3 years) will be collected and unused study drug will be counted at the Week 12 visit. Caregivers/LARs will be provided an additional blister card in case of unexpected delays for study visits (e.g., inclement weather/flight delays).

[redacted]



[redacted]

The LAR/caregivers will complete paper seizure diaries on behalf of subjects throughout the study, from issuance during screening (and at study visits) through Week 12 (EOT).

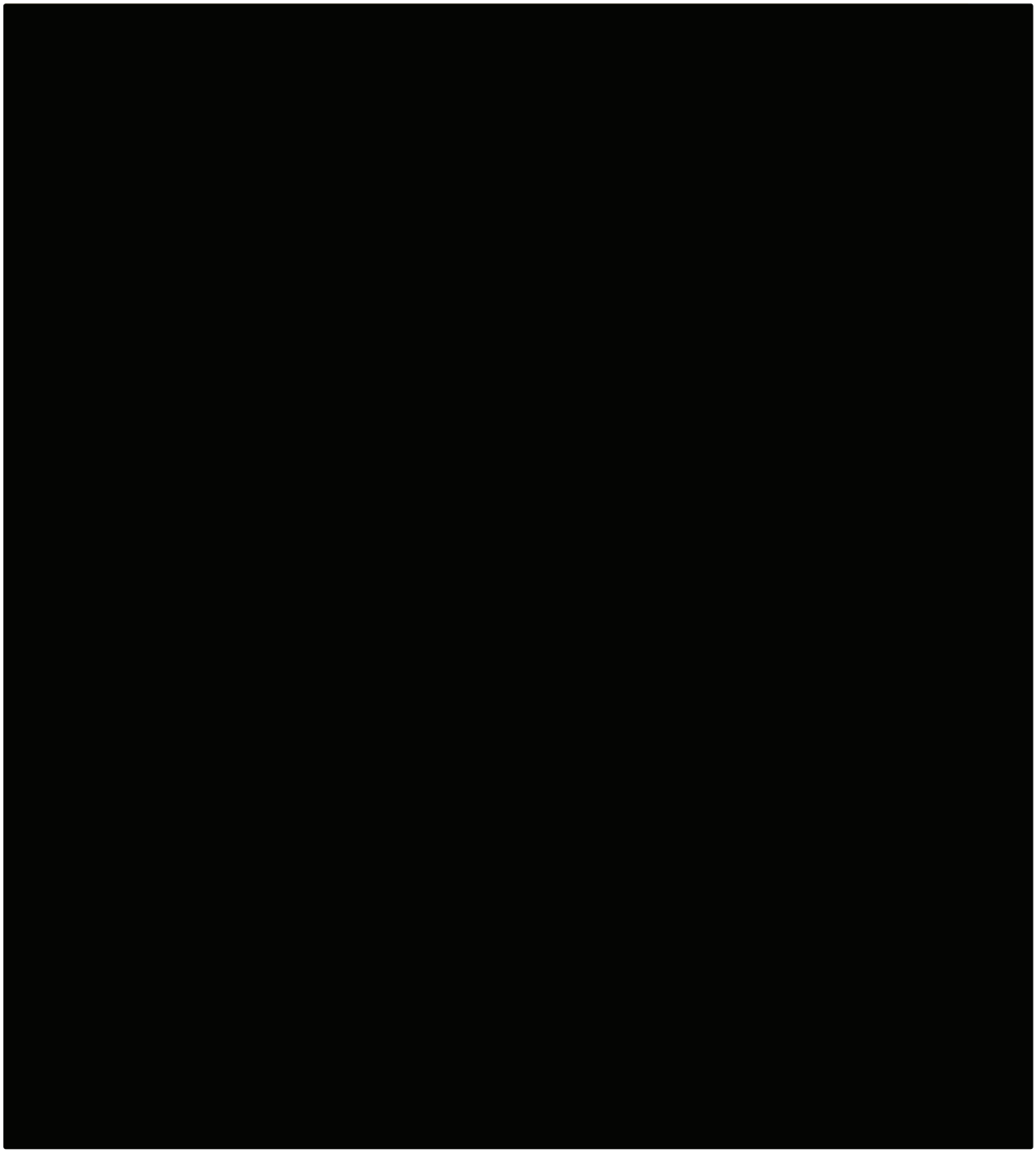
Safety information will be collected during phone calls on Day 6 and Day 11 and during the EOS visit, as well as during every study site visit. Each subject's LAR/caregiver will be instructed to contact the study center if the subject experiences any adverse events (AEs), is unable to take the study drug as prescribed, [redacted]
At the investigator's discretion throughout the study, subjects may be evaluated at unscheduled clinic visits for reasons related to subject safety. At unscheduled visits, subjects will be queried about AEs and changes in concomitant medications and evaluated for suicidality. Safety laboratory assessments may be conducted. Periodic interim review of safety data will be performed by the IDMC and as part of routine pharmacovigilance activities.

Estimated Study Duration:
After informed consent is obtained, screening assessments will be conducted within the 4 weeks preceding baseline, followed immediately by treatment for 12 weeks and a 2-week follow-up period (for subjects not enrolling into the ELARA study), for a maximum duration of individual subject participation of 18 weeks. Four study site visits are scheduled for each subject.

For subjects choosing to participate in the ELARA open-label extension study, the NEPTUNE EOT visit will coincide with the baseline visit for ELARA, and there will be only 3 scheduled study site visits. For NEPTUNE subjects participating in ELARA, the EOS visit that occurs approximately 2 weeks after the EOT will take place in the ELARA study only.

Efficacy Assessments:
Efficacy assessments will include the CGI-I-AS; the CGI-S-AS; the VABS-3; the [redacted]

[redacted]



Safety Assessments:
Safety assessments will include frequency, severity, and causality of AEs (including serious AEs [SAEs] and AEs leading to study discontinuation), and other safety assessments including assessment of suicidality (ABC-I), collection of seizure diaries, clinical laboratory assessments, vital sign measurements, and physical examinations. A total of up to 7 mL of blood is expected to be taken for laboratory measurements at each of screening, baseline, Week 6, and Week 12 visits. Total blood collected will not exceed 20 mL in a 30-day period. This is in accordance with the US Department of Health and Human Services, Office for Human Research Protections recommendations of 3 ml/kg, up to 50 ml total within 8 weeks (Table 2 in Howie 2011).

Study Drug, Dosage, and Route of Administration:
All doses of study drug will be administered orally. OV101 [redacted]

[redacted]

Placebo capsules will be identical in appearance to the capsules containing OV101 and have the same excipient ingredients but will not contain the active compound.
Study drug dosage will be assigned based on body weight at the screening visit. Study drug will be titrated from the starting dose to the maintenance dose according to Table 1.

If at randomization on Day 1 a subject is assigned to placebo, the number of capsules per dose will correspond to the number of OV101 capsules for a subject of the same weight.

Dosing will be initiated at the starting dose for the first 5 days. On Day 6, tolerability will be assessed by the investigator. If there are no tolerability concerns (e.g., excessive somnolence, dizziness, vomiting, negative behavior changes) and no AE related to the study drug has been observed since Day 1 by the LAR/caregiver or the investigator, then the dose of OV101 will be increased to the maintenance dose for the duration of the study. The maintenance dose identified at screening will remain consistent throughout the study. If tolerability concerns are observed on Day 6, the subject will discontinue study drug.

[redacted]

[redacted]

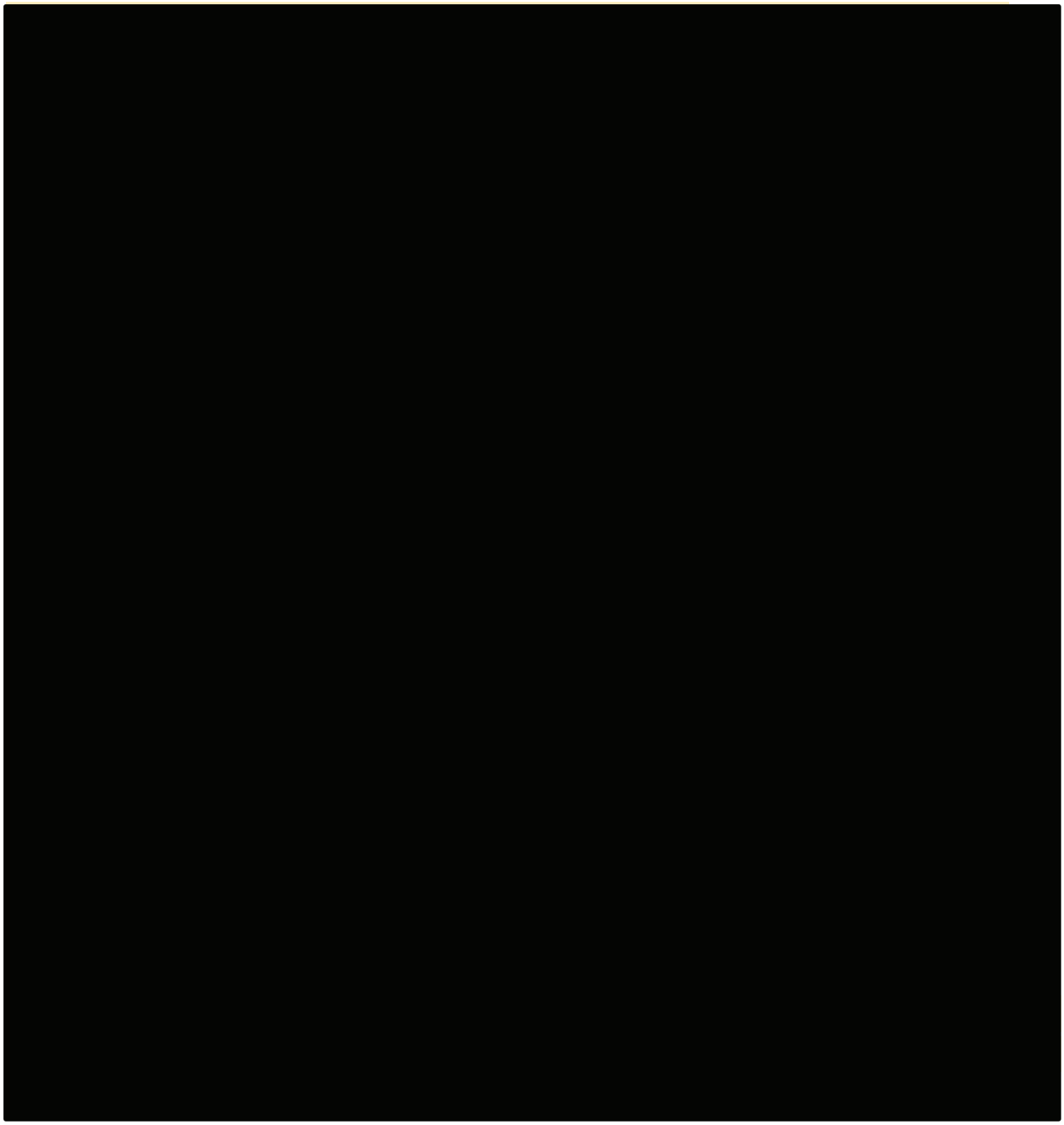
The subject's maintenance dose for the duration of the study will be set based on the subject's weight at the screening visit, and the subject should continue taking the maintenance dose after the Day 6 assessment until the EOS. Tolerability will again be assessed during the Day 11 phone call while the subject is taking the maintenance dose. The investigator may initiate down-titration on Day 11 by 1 capsule (Table 2) based on 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. No further changes in dose regimen should be made after Day 15.

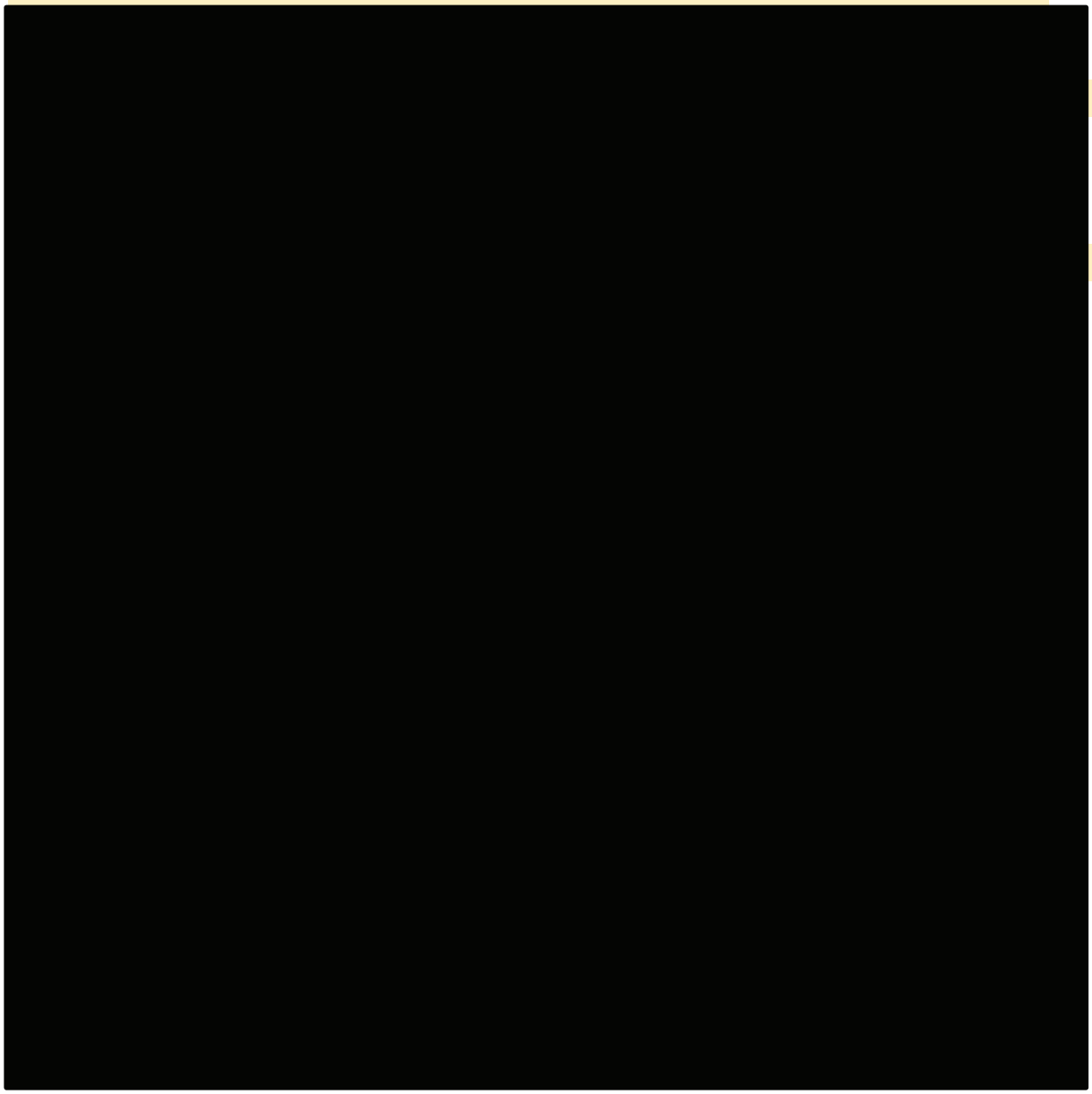
If tolerability is not acceptable at any other time during the 12 weeks of treatment, the investigator should discuss the situation with the medical monitor or his/her delegate. Any intolerability must be documented as an AE. The daily dose may not be lower for any subject than the reduced maintenance dose indicated in Table 2. If a subject cannot tolerate the reduced maintenance dose, that subject must discontinue treatment. Any dose adjustments or changes in dosing must be documented in the electronic case report form and supporting rationale must be documented in the medical record or other appropriate source document.

[redacted]

Sample Size:

Approximately 90 subjects 4 to 12 years old (inclusive) will be randomly assigned in a 1:1 ratio into OV101 or placebo treatment groups for both efficacy and safety assessments. Randomization will be stratified by age categories: 9 to 12 years old (inclusive) and 4 to 8 years old (inclusive), with at least 24 subjects per age category, and by region: US and outside US. Approximately 5 subjects 2 to 3 years old (inclusive) will be included and treated with OV101 for safety assessments only. Approximately 95 subjects will be enrolled in the study at approximately 15 study sites with no more than 12 subjects per study site (unless authorized by the Sponsor).





Statistical Methods:

All statistical analyses will be performed using SAS® Version 9.4 or higher. All clinical study data will be presented in subject data listings. Data summaries will be presented for all endpoints and will include descriptive statistics (number of subjects, mean, SD, first quartile, median, third quartile, minimum, and maximum) for continuous variables, and frequency and percentage for categorical and ordinal variables. If there are missing values, the number of missing will be presented, but without a percentage. For all analyses, 'baseline' will refer to the most recent non-missing value obtained immediately prior to administration of first dose.

For the primary efficacy analysis, the CGI-I-AS will be analyzed as a continuous outcome variable. A Mixed Model Repeated Measures (MMRM) Analysis of Variance (ANOVA) model will be fitted using restricted maximum likelihood (REML) for CGI-I-AS with fixed effects for visit, randomized treatment, the visit-by-treatment interaction, age group, and region. An unstructured within subject-covariance structure will be specified as the first choice, and if the model fails to converge, alternative covariance structures will be tested as detailed in the SAP. If a structured covariance is used, then a robust sandwich estimator will be utilized for estimating the variance of the treatment effect estimate. From the model, the Week 12 difference between least squared means of OV101 and placebo groups will be presented along with the corresponding 95% confidence interval and 2-sided P value.

Generalized Estimating Equations (GEE) method will be used for the analysis of key secondary endpoints: CGI-I-AS response (at least minimally improved) and CGI-I-AS response (at least much improved). GEE models will include the response variable at each visit as the dependent variable, and fixed effects for visit (Week 6 and Week 12), randomized treatment, the visit-by-treatment interaction, age group (randomization stratification variable: age 4 to 8 years versus age 9 to 12 years), and region (randomization stratification variable: US versus outside US). An unstructured working correlation for the binary outcome variable will be assumed for the model parameter estimation, and if the model fails to converge, alternative covariance structures will be tested as detailed in the SAP. If there is no response in either treatment arm at the Week 6 visit, the GEE model will be substituted with a logistic regression for the Week 12 CGI-I-AS response variable with effects for the randomized treatment and the two randomization stratification variables. From the model (GEE or logistic regression, as appropriate), the Week 12 odds ratio will be presented along with the corresponding 95% confidence interval and 2-sided P value.

All other continuous efficacy endpoints with post baseline assessments at Week 6 and Week 12 will be analyzed by an MMRM Analysis of Covariance (ANCOVA) model for the change from baseline for the endpoint fitted with fixed effects for visit, randomized treatment, the

visit-by-treatment interaction, age group, region, and the corresponding baseline as a covariate. An unstructured within subject -covariance structure will be specified as the first choice, and if this analysis fails to converge, alternative covariance structures will be tested as detailed in the SAP. From the model, the Week 12 difference between least squared means of OV101 and placebo groups will be presented along with the corresponding 95% confidence interval and 2-sided *P* value.

Endpoints based on composite and subdomain scores from VABS-3 assessments will be analyzed as continuous outcome variables using an ANCOVA model with effects for randomized treatment, age group, region, and the corresponding baseline as a covariate. A test for a significant treatment-by-baseline interaction will be performed in a separate model (including the above terms plus the interaction term), using a 0.100 alpha level. If the treatment-by-baseline interaction is significant, then the ANCOVA assumptions are violated and an ANOVA model will be used instead. From the final model(s), the difference between least squared means of OV101 and placebo groups will be presented along with the corresponding 95% confidence intervals and 2-sided *P* values.

Descriptive statistics will be used to summarize all safety endpoints by treatment group. Two-sided 95% CIs will be presented where meaningful. Data summaries will be displayed for incidence of AEs, clinical laboratory variables, vital signs, body weight and body mass index, physical examinations, suicidality assessed by ABC-I, and seizure diary data.

For AEs, all treatment-emergent AEs (TEAEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by MedDRA system organ class and preferred term and treatment group. Detailed listings of TEAEs, SAEs, related AEs, and discontinuations due to AEs will be provided. The incidence of TEAEs, discontinuations due to TEAEs, drug-related, and serious TEAEs will be summarized. Incidence of TEAEs by severity and relationship to study drug will also be presented. Incidence of TEAEs will be summarized separately for subjects 2 to 3 years old (inclusive). Other safety data for subjects 2 to 3 years old (inclusive) will only be presented in listings and will be displayed in by -subject graphs, as appropriate.

For clinical laboratory tests, changes from baseline to each post baseline visit with respect to clinical chemistry and hematology results will be summarized descriptively. Each laboratory parameter will be classified as low, normal, or high relative to the parameter's reference range and will be summarized with shift tables. Listings of subjects with abnormal results will be provided.

Vital signs, weight, and body mass index will be summarized descriptively at baseline and all post baseline study visits by treatment group. Change from baseline to all post baseline study visits will be summarized descriptively by treatment group.

Physical examinations (general appearance; skin; head, ear, eye, nose, and throat; neck; lymph node; chest; heart; abdominal cavity; limb; central nervous system; and musculoskeletal) at baseline will be summarized. Shifts from baseline to post baseline study visits in each body system/site will be summarized by treatment group.

Suicidality and seizure diary data will be summarized descriptively at baseline and all post baseline study visits by treatment group. Change from baseline to all post baseline study visits also will be summarized descriptively by treatment group.

List of Abbreviations

Abbreviation	Definition
ABC-I	Aberrant Behavior Checklist-Irritability subscale
AE	adverse event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AS	Angelman syndrome
[redacted]	
ß-hCG	beta-human chorionic gonadotrophin
BID	twice daily
CFR	Code of Federal Regulations
[redacted]	
CGI-I	Clinical Global Impressions-Improvement
CGI-I-AS	Clinical Global Impressions-Improvement-Angelman syndrome
CGI-S-AS	Clinical Global Impressions-Severity-Angelman syndrome
[redacted]	
CSR	clinical study report
CTSC	Clinical Trial Steering Committee
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EOS	end of study
EOT	end of treatment
FAS	full analysis set
FDA	Food and Drug Administration
GABA	gamma-aminobutyric acid
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	independent ethics committee
IRB	institutional review board
LAR	legally acceptable representative
[redacted]	
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
MMRM	Mixed Model Repeated Measures
[redacted]	
PPS	per protocol set
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SIF/DRF	Seizure Identification Form and Diagnostic Review Form
SS	safety set
TEAE	treatment-emergent adverse event
[redacted]	
Ube3a	ubiquitin protein ligase E3A
UBE3A	ubiquitin protein ligase E3A gene
ULN	upper limit of normal
VABS-3	Vineland Adaptive Behavior Scale, 3rd Edition

Definition of Terms

Term	Definition
Day 1	The first day of study drug administration
ELARA	Study OV101-18-002, an open-label extension study
NEPTUNE	Study OV101-19-001
OV101	gaboxadol
Ovid	Ovid Therapeutics Inc.
[redacted]	
STARS	Study OV101-15-001

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. Extensive nonclinical and clinical data were generated during the initial stages of development, including data from exposure to gaboxadol in more than 4,300 adult subjects with insomnia and approximately 500 adult subjects in non-insomnia -related studies.

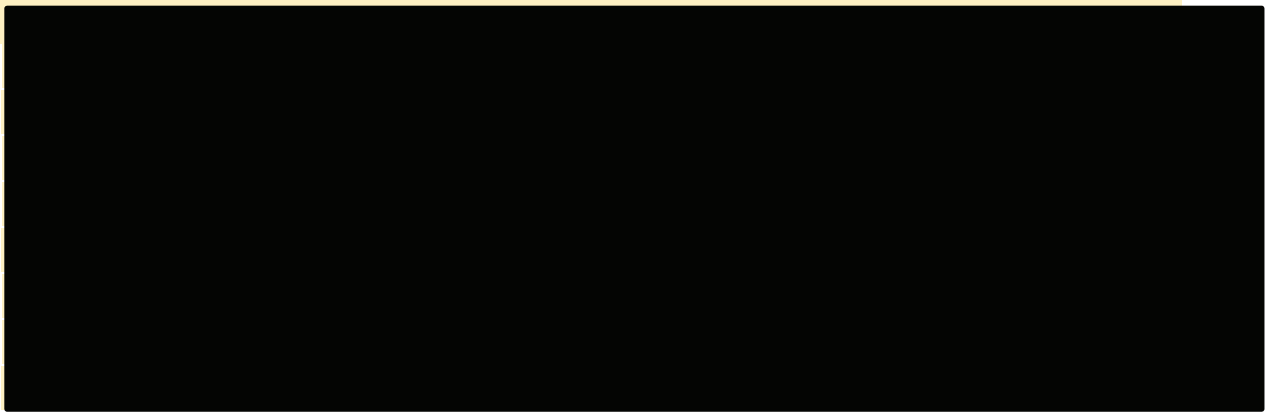
Angelman syndrome is a severe, complex, and rare neurogenetic disorder with a prevalence estimated at 1 in every 10,000 to 24,000 live births (Petersen et al 1995; Steffenburg et al 1996; Mertz et al 2013). The condition is associated with impaired expression of the ubiquitin protein ligase E3A gene (*UBE3A*). While *UBE3A* is expressed from both gene copies 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 (Williams et al 2006).

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 as an orthosteric agonist to the α4- and δ-containing subunit of extrasynaptic GABA receptors. 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. The extrasynaptic GABA 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. Unlike many of these drugs that are allosteric modulators and therefore require endogenous GABA to function, OV101 is a GABA agonist and can function when GABA is deficient or absent. 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 subjects 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 subjects 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 exploratory measures of efficacy of OV101 in adolescents and adults with AS over 12 weeks of treatment. The STARS study was the first industry Sponsored clinical study in AS. Overall, OV101 had a favorable safety profile and was well tolerated. OV101 had a statistically significant effect on the Clinical Global Impressions-Improvement (CGI-I), a measure of global function included as an exploratory measure. Exploratory and post-hoc analyses suggested that improvements seen on the CGI-I were likely driven by sleep, gross and fine motor function, behavior, and communication.

Eighty-eight subjects 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 and severity 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. Serious adverse events of seizure were reported in 2 subjects, both of whom had a previous history of seizures: 1 subject in the QD dose experienced a seizure and that was deemed unrelated to study drug and treatment was continued; 1 subject experienced 2 events of seizure in the BID dose group that was assessed as possibly related to study drug by the investigator, and treatment was discontinued. Overall, the data are consistent with a favorable risk profile.

Clinical efficacy measures used to compare OV101 versus placebo during the 12 weeks of treatment included the CGI-I, Aberrant Behavior Checklist, Anxiety, Depression and Mood Scale, [redacted] and modified Performance-Oriented Mobility Assessment-Gait tool.

For the CGI-I Symptoms Overall domain at Week 12, the Mixed Model Repeated Measures (MMRM) analysis showed a significant improvement for OV101 compared to placebo for the OV101 groups combined (P=0.0103) and for the OV101 QD group (P=0.0006). At Week 12, subjects in the OV101 QD group showed significant improvement in CGI-I Symptoms Overall regardless of age.

For the CGI-I Sleep domain at Week 12, the MMRM analysis showed a significant improvement for OV101 compared to placebo for the OV101 groups combined (P=0.0236) and for the OV101 QD group (P=0.0141).

In post hoc analyses at Week 12, most subjects in the OV101 groups combined (54.5%) had responses of minimally improved (34.5%) or much improved (20.0%) for CGI-I Symptoms

Overall, compared to 22.2% of subjects in the placebo group (14.8% minimally and 7.4% much improved). The percentages of subjects with improvement were larger in the OV101 QD group (66.6%; 29.6% minimally, 37.0% much improved) than in the OV101 BID group (42.8%; 32.1% minimally, 10.7% much improved).

NEPTUNE (OV101-19-001) will be a multicenter, randomized, placebo-controlled, parallel-group study to evaluate the efficacy and safety of OV101 in pediatric subjects with AS. Subjects who complete the study will be eligible to enroll in the ongoing OV101-18-002 (ELARA) open-label extension study, provided they meet the eligibility criteria for ELARA.

2 Study Objectives

All efficacy study objectives will be assessed in the pediatric AS study population of subjects who are 4 to 12 years old. All safety study objectives will be assessed in the pediatric AS study population of subjects who are 2 to 12 years old.

2.1 Primary Objective

- To evaluate the efficacy of OV101 versus placebo as assessed by the Clinical Global Impressions-Improvement-Angelman syndrome (CGI-I-AS) score at Week 12.

2.2 Secondary Objectives

Key Secondary Objectives:

The purpose of the key secondary objectives is to fulfil a recommendation of the EMA for a responder analysis.

- To evaluate the efficacy of OV101 vs placebo as assessed by the proportion of subjects who experience any meaningful improvement on study treatment (defined as CGI-I-AS score of 1, 2, or 3 at Week 12)
- To evaluate the efficacy of OV101 vs placebo as assessed by the proportion of subjects who experience a response of much improved or very much improved (defined as CGI-I-AS score of 1 or 2 at Week 12

Other Secondary Efficacy Objectives:

[redacted]

- To evaluate the efficacy of OV101 versus placebo on Communications, Socialization, Daily Living Skills, Motor Skills, and Maladaptive Behavior domains assessed by the Vineland Adaptive Behavior Scale, 3rd Edition (VABS-3).
- To evaluate the efficacy of OV101 versus placebo based on the Clinical Global Impressions-Severity-Angelman syndrome (CGI-S-AS) Symptoms Overall score.
- To evaluate the relationships of CGI-S-AS Symptoms Overall and CGI-S-AS domains at baseline with CGI-I-AS at Week 12.

2.5 Safety Objectives

The safety objectives of this study are to evaluate the safety and tolerability of OV101 in subjects 2 to 12 years old, including seizure diary data and assessment of suicidality.

3 Investigational Plan

3.1 Study Design

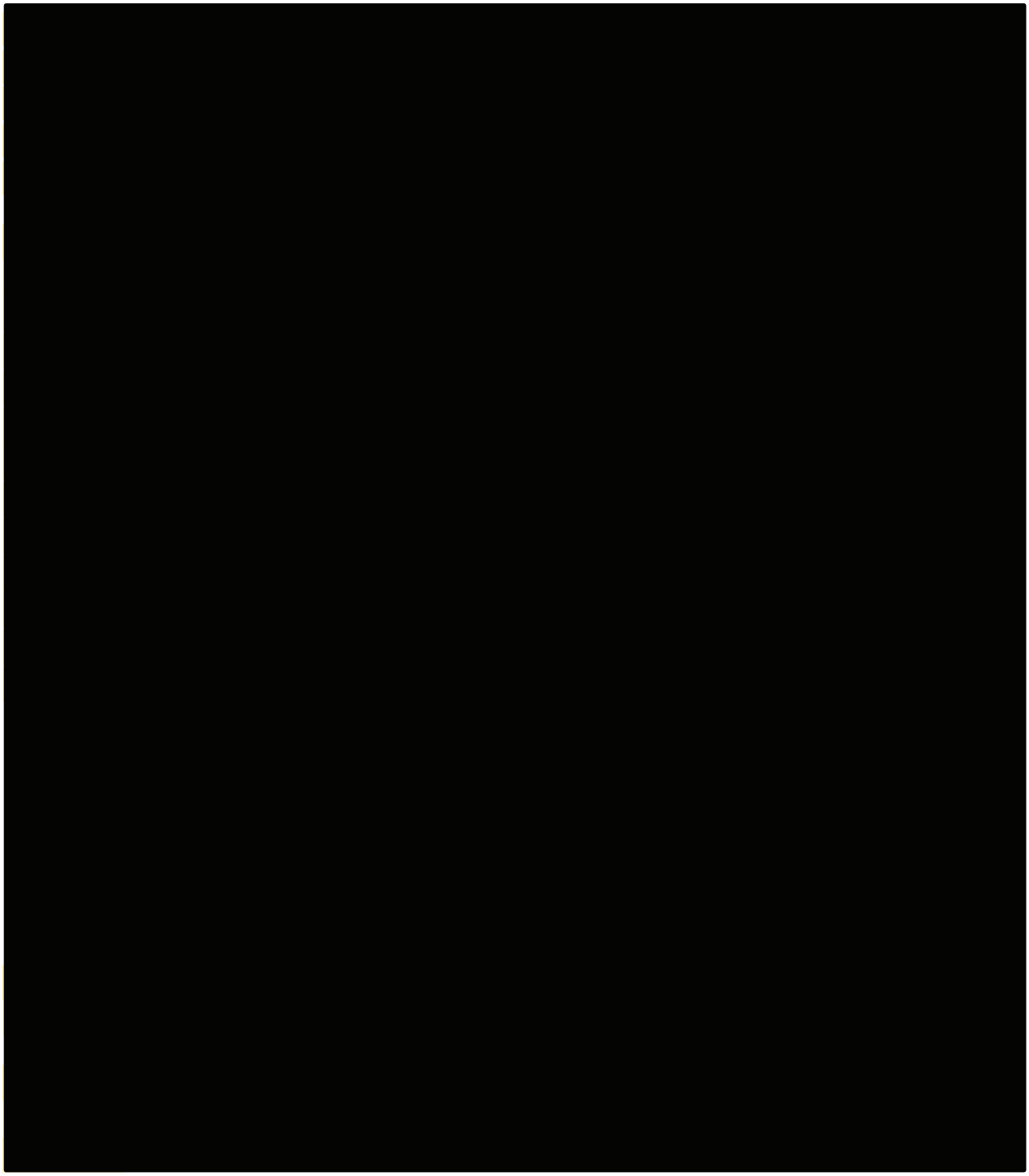
This will be a Phase 3, randomized, double-blind, placebo-controlled, parallel-group study, conducted in clinic settings, to evaluate the efficacy and safety of OV101 in pediatric subjects with AS. Male and female subjects with a previous diagnosis of AS (with molecular confirmation) will be eligible for inclusion (Section 4.1). The study will comprise a screening period within the 28 days preceding Day 1; a visit on Day 1 for baseline assessments, the first dose of study drug, and sparse sampling of blood; subsequent doses of study drug taken each evening approximately 30 minutes before bedtime for 12 weeks starting on Day 2; and study site visits for efficacy and safety assessments over a 12-week treatment period. After the baseline visit, the study site visits will occur at Week 6 and Week 12 (end of treatment [EOT]). Phone safety visits will occur during up-titration of the study drug (Day 6 and Day 11). Unless a subject decides to participate in the ELARA open-label extension study, an end of study (EOS) phone safety visit will occur approximately 2 weeks after the last dose of study drug to assess safety and tolerability associated with discontinuation of treatment. Subjects eligible for and willing to enroll in the ELARA study will have the NEPTUNE EOT visit be their NEPTUNE EOS visit, and their NEPTUNE EOT visit will serve as their ELARA baseline visit. A subject will be considered to have completed the NEPTUNE study after completing the EOS visit. For NEPTUNE subjects participating in ELARA, the EOS visit that occurs approximately 2 weeks after the EOT will take place in the ELARA study only. The total duration of the study for a subject will be approximately 18 weeks. The schedule of activities for this study is fully presented in Table 6–1.

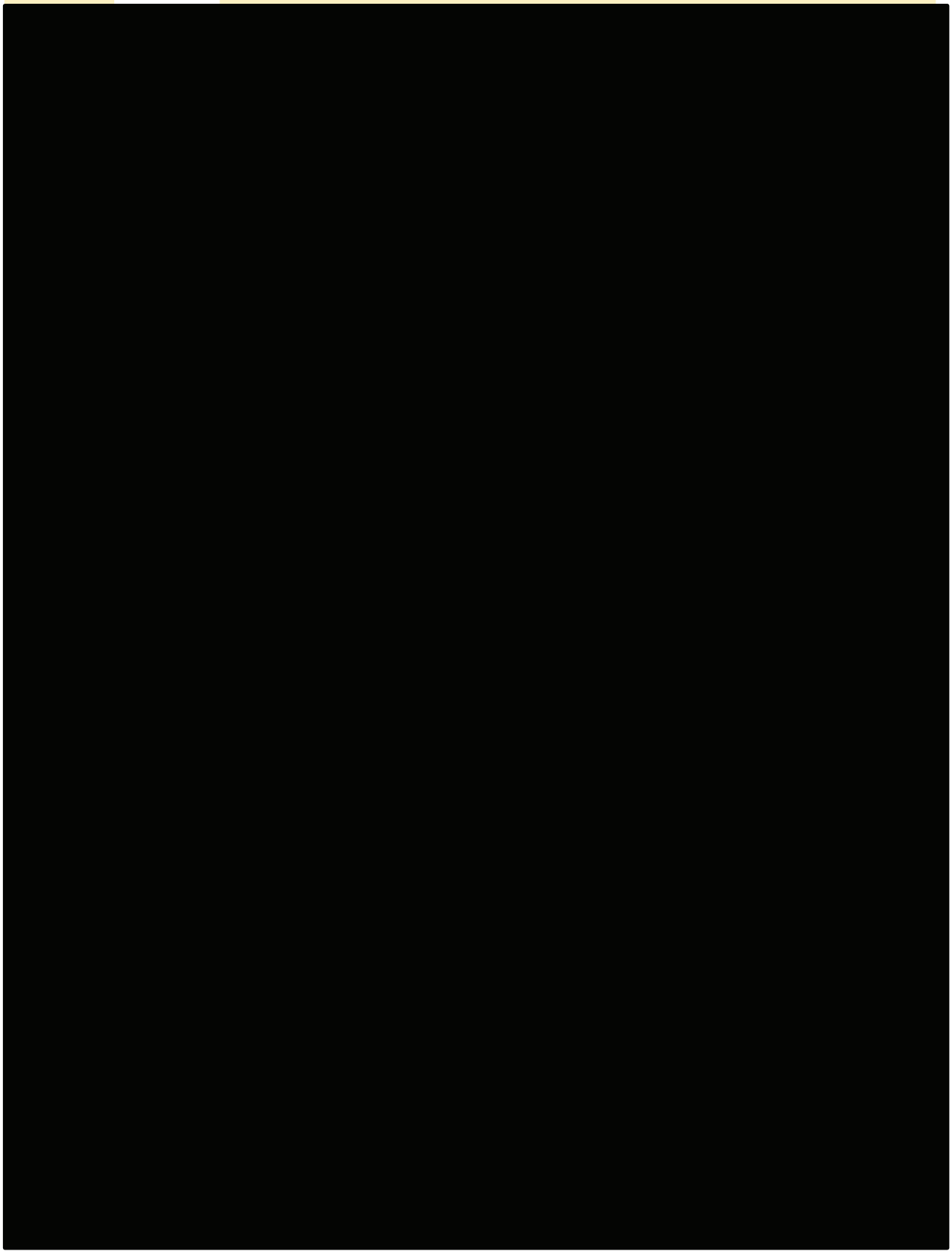
Approximately 95 subjects will be enrolled in the study at approximately 15 study sites in the United States, Israel, Australia and/or Europe. Approximately 90 subjects 4 to 12 years old (inclusive) will be enrolled for both efficacy and safety assessments, and not more than 12 of these subjects will be enrolled at a study site (unless authorized by Sponsor). Random assignment of subjects for efficacy assessment (to either OV101 or placebo treatment in a 1:1 ratio) will be stratified by age at screening [9 to 12 years old (inclusive) and 4 to 8 years old (inclusive)] and by region (US and outside US). There will be at least 24 subjects per age group. Approximately 5 subjects 2 to 3 years old (inclusive) will be enrolled for safety [redacted] assessments only and will be assigned to treatment with OV101. Within each age group, dosing will be assigned based on body weight (Table 5–1).

For each subject, after informed consent is obtained (Section 9.3), screening assessments will be completed within the 28 days preceding Day 1 (baseline). On Day 1, eligible subjects will receive study drug capsules according to treatment code (sufficient to last until the Week 6 visit).

Caregivers/LARs will be provided an additional blister card in case of unexpected delays for study visits (e.g., inclement weather/flight delays). Study drug will be similarly dispensed at the Week 6 visit. Unused study drug will be collected and counted at Week 6 and 12.

3.1.1 Rationale of Dosing





4 Subject Selection and Withdrawal Criteria

4.1 Selection of Study Population

Approximately 95 subjects will be enrolled at approximately 15 study sites, with a goal of having 80 subjects evaluable for efficacy by completing 12 weeks of treatment (Section 3.1). Subjects will be assigned to study treatment only if they meet all inclusion criteria and none of the exclusion criteria.

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.1.1 Inclusion Criteria

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

1. Is male or female and 2 to 12 years old (inclusive) at the time of informed consent.
2. Has a diagnosis of AS with molecular confirmation.
3. Has a CGI-S-AS score (Section 6.2.1.1) of 3 or more.
4. Meets the following age-appropriate body weight criterion:

   a) Subjects 2 to 3 years old must have a minimum body weight of 9 kg.

   b) Subjects 4 years and older must be between 17 kg and 64 kg (inclusive).
5. Has an LAR/caregiver capable of providing written informed consent and able to attend all scheduled study visits, oversee the administration of study drug, and provide feedback regarding the subject's symptoms and performance as described in the protocol.
6. Provides assent to the protocol (to the extent possible and in accordance with local institutional review board [IRB] and regulatory requirements). Subjects providing assent must do so at the same visit as LAR/caregiver written informed consent is provided.
7. Can swallow study drug capsules with water or ingest the contents of study drug capsules after sprinkling the contents of each capsule onto up to 1 teaspoon of low-fat semiliquid food.

8. If a subject is currently receiving a regimen of concomitant medications such as antiepileptic medication, gabapentin, clonidine, trazodone, melatonin, or a special diet regimen, that subject'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).
9. If a subject is a sibling in a family with multiple children diagnosed with AS, then only one of the siblings may enroll in study. The eldest eligible subject should be enrolled (investigator discretion may be used to enroll a younger sibling instead).
10. Has LAR(s)/caregiver(s) who agree not to post any of the subject's personal medical data or information related to the study on any website, message board(s), online support group(s), or social media site (e.g., Facebook, Instagram, Twitter, etc.) until notified that the study is completed.
11. Female subjects who are of child-bearing 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. Highly effective contraceptive methods are as follows:
12. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
13. Oral
14. Intravaginal
15. Transdermal
16. Progestogen-only hormonal contraception associated with inhibition of ovulation:
17. Oral
18. Injectable
19. Implantable
20. Intrauterine device
21. Intrauterine hormone-releasing system
22. Bilateral tubal occlusion
23. Vasectomized partner
24. 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

4.1.2 Exclusion Criteria

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

1. Has a circumstance or concomitant disease (e.g., gastrointestinal, renal, hepatic, endocrine, respiratory, or cardiovascular system disease), condition, or any clinically significant finding at screening that could interfere with the conduct of the study or that would pose an unacceptable risk to the subject in the opinion of the investigator.

2. Has poorly controlled seizures defined as any of the following:

    a. Weekly seizures of any frequency with a duration more than 3 minutes.

    b. Weekly seizures occurring more than 3 times per week, each with a duration of less than 3 minutes.

    c. Investigator assessment.

3. 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.

4. 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 for situational anxiety related to occasional procedures or events are permitted, and benzodiazepines are also permitted for seizure control.

5. [redacted]

6. Is at risk of harming self and/or others (based on investigator assessment).

7. Has enrolled in any interventional clinical study 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.

8. Is allergic to OV101 or any excipients of study drug.

9. The subject or LAR/caregiver is unable to comply with study requirements (based on investigator assessment).

10. Is a family member of the investigator and/or study site staff.

4.2 Discontinuation and Withdrawal of Subjects

Subjects who discontinue treatment during the study will be encouraged by investigators to continue to participate in all scheduled study site visits and assessments, and study data will be collected for these subjects per protocol. Study drug administration may be stopped early at the discretion of the investigator (or designee) if a subject does not tolerate the dosing regimen. Every effort should be made to keep subjects in the study.

Early withdrawal of a subject from the study (before Week 12) will initiate procedures for ending all subject participation in the study, including EOT and EOS assessments (Section 4.2.2). For subjects who are withdrawn early, an EOT visit should be conducted within 2 weeks after the last day of study drug. After completing the EOT visit, an EOS phone visit should be completed within 2 weeks after completing the EOT visit. The duration of the study is defined for each subject as the date signed written informed consent is provided through the EOS phone visit. The Sponsor may continue to enroll subjects to account for discontinuations, withdrawals, early terminations, etc.

4.2.1 Reasons for Withdrawal

Subjects 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. The reasons for subjects not continuing in the study will be recorded. A subject may be withdrawn from the study for any of the following reasons:

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

The investigator will also withdraw a subject if the Sponsor terminates the study. Upon occurrence of a serious or intolerable AE, the investigator will confer with the medical monitor and/or Sponsor. If a subject is discontinued because of an AE, the event will be followed until it is resolved.

4.2.2 Handling of Withdrawals

Subjects are free to withdraw from the study or study treatment at any time upon request. Subject participation in the study may be stopped at any time at the discretion of the investigator or at the request of the Sponsor.

Subjects who stop study treatment or active participation in the study will no longer receive study drug. When a subject 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 subjects who stop study treatment or withdraw from the study

prematurely will complete the EOT and EOS assessments. Subjects 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 subject 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

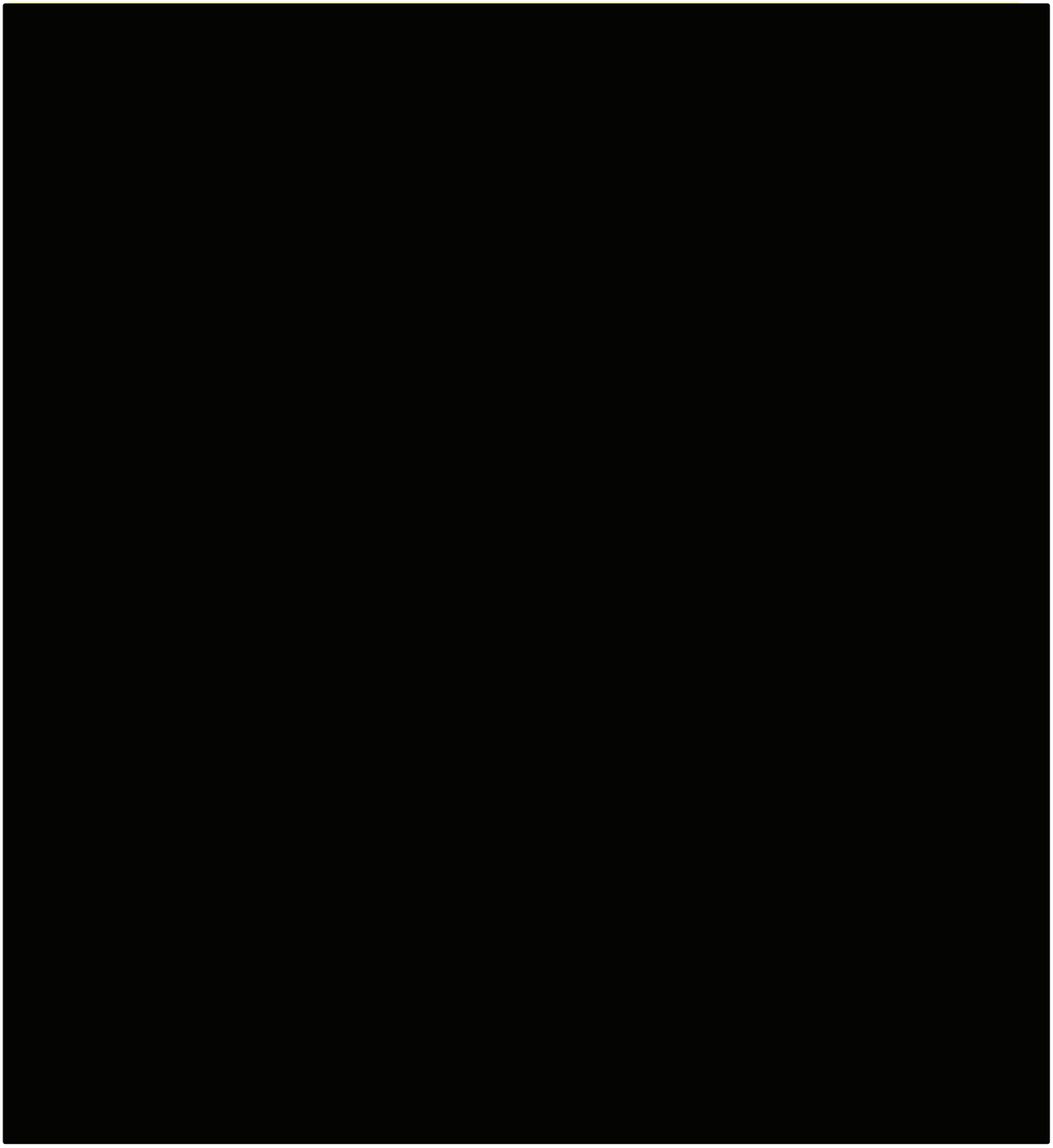
A sufficient number of subjects will be enrolled to ensure that at least 80 evaluable subjects (4 to 12 years old) complete 12 weeks of treatment.

A subject who does not meet the inclusion criterion or who meets an exclusion criterion will be considered a screen failure. Whether rescreening is acceptable will be discussed with the medical monitor or his designee. Rescreening may be allowed if the subject passed screening but could not be randomly assigned within the 28-day screening window due to logistical, personal, or other unforeseeable reasons. Rescreening will only be allowed once and only in cases where no safety risk is posed to the subject.

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.

5 Study Treatments

5.1 Method of Assigning Subjects to Treatment Groups



An interactive web response system will be used to administer the randomization schedule. The [redacted] biostatistics group will generate the randomization schedule using SAS® software (SAS Institute Inc, Cary, NC) Version 9.3 or later, which will link sequential subject randomization numbers to treatment codes.

5.2 Treatment Administration

Subjects will take all doses orally each evening (assisted by an LAR/caregiver, if necessary), at approximately the same time, approximately 30 minutes before anticipated bedtime, for the duration of the 12-week treatment period. Capsules may be opened, with the contents of each capsule 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 how capsules were taken (i.e., swallowed whole with water or opened with the contents of each capsule taken in up to 1 teaspoon of semiliquid food).

On Day 1, subjects will take their first dose of study drug at the study site during the daytime, taking all subsequent doses at night, 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 subject misses a dose of study drug for any reason, unless within a 3-hour window of the usual administration time, the subject should not make up the missed dose. The subject 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. Subjects experiencing dose interruptions should be evaluated by the investigator in conjunction with the medical monitor.

5.2.1 Dose Titration

Dosing will be initiated at the starting dose (Table 5–1) for the first 5 days. On Day 6, tolerability will be assessed by the investigator. If there are no tolerability concerns (e.g., excessive somnolence, dizziness, vomiting, negative behavior changes) and no AE related to the study drug has been observed since Day 1 by the LAR/caregiver or the investigator, then the dose of OV101 will be increased to the maintenance dose for the duration of the study. If tolerability concerns are observed on Day 6, the subject will discontinue study drug. Time windows for titrations and

The study site will document each titration step in the eCRF and in source documents. AEs triggering any down titration must be reported.

5.3 Identity of Investigational Product

Placebo capsules will be identical in appearance to the capsules containing OV101 and have the same excipient ingredients but will not contain the active compound.

will manufacture the OV101 and placebo capsules.

5.4 Management of Clinical Supplies

Bulk capsules of OV101 will be shipped to will package and label kits. will ship the kits directly to each study site.

5.4.1 Study Drug Packaging and Storage

[redacted]

5.4.2 Test Article 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 subject 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.

[redacted]

5.5 Overdose Management

An overdose is any dose of study treatment given to a subject or taken by a subject 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 on relevant AE/SAE sections in the eCRF. Any associated SAEs must be promptly reported to Ovid using the SAE reporting procedures (Section 6.4.1.5). 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 subject's clinical status.

5.5.2 Medication Errors

A medication diary will be maintained by the LAR/caregiver on behalf of the subject 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 the Week 6 and Week 12 clinic visits by either the site investigator or the study coordinator. If a dose is missed, this should be noted, and the dose should not be doubled at the next scheduled dose.

5.5.3 Treatment of Medication Errors

An example of a medication error includes overdose (treatment of overdose is described in Section 5.5.1).

5.6 Blinding

The study will be performed in a double-blind manner for subjects 4 to 12 years old (inclusive), with the subjects, LAR/caregivers, investigators, study personnel, monitors, and study Sponsor blinded to the identity of all study drug. All study drug will be supplied in identical packaging and will be similar in color, smell, taste, and appearance to enable double-blind conditions. Titrations will be conducted identically for all subjects in a weight band (Table 5–1), regardless of assignment to OV101 or placebo.

The study will not be blinded for subjects 2 to 3 years old, inclusive.

5.6.1 Breaking the Blind

A subject's treatment assignment will not be broken until after the last subject has completed the study and the database has been locked, unless medical treatment of the subject depends on knowing the study treatment the subject received. If the blind needs to be broken because of a medical emergency where medical management depends on knowing treatment allocation, the investigator may unblind an individual subject's treatment allocation. Before unblinding a subject's treatment assignment and as soon as possible, the investigator should make every effort to contact the medical monitor to discuss the medical emergency and the reason for revealing the treatment received by that subject. The treatment assignment will be unblinded through an interactive web response system. Reasons for treatment unblinding must be clearly explained and justified in the eCRF. The date on which the code was broken and the identity of the person responsible must also be documented. If a subject's treatment is unblinded, the Sponsor must be notified immediately. Unblinding should only be considered for the safety of the subject. The investigator should inform the Sponsor that the subject was unblinded; however, they are not required to reveal to the Sponsor the subject's treatment allocation.

When an AE is an unexpected related SAE, the blind will be broken by the Sponsor only for that specific subject. The blind will be maintained for persons responsible for the ongoing conduct of the study (e.g., monitors, investigators) and those responsible for data analysis and interpretation

of results at the conclusion of the study, such as biometrics personnel. Unblinded information will only be accessible to those who need to be involved in the safety reporting to health authorities, independent ethics committees (IECs), or IRBs. Investigators will receive only blinded information unless unblinded information is judged necessary for safety reasons.

The IDMC (Section 11.1.1) will have the ability to review unblinded data as needed to evaluate risk during the study.

5.7 Treatment Compliance

Subject compliance will be determined by comparing the capsule counts of returned study drug cards at the Week 6 and Week 12/EOT visits to the capsule count of study drug dispensed at the previous visit. 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, subject refused, subject experienced AE or LAR/caregiver decided to reduce dose), the reason(s) will be recorded, and the approximate date and time of any missed doses will be also be recorded in the eCRF.

5.8 Prior and Concomitant Therapy

Subjects should be on stable doses of prescribed medications and on stable nonmedication interventions (e.g., speech therapy, physical therapy, occupational therapy) for 4 weeks before Day 1 and should remain on the stable regimens until after the EOS visit. If subjects are to enroll in the ELARA open-label extension study, study drug will be provided so that the baseline visit can be conducted in conjunction with the NEPTUNE EOT visit. Additionally, unless required to treat AEs, there should be no new medications or changes to concomitant medications, 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 subject's eCRF. The minimum requirement is that the 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 will also be recorded in the subject's eCRF.

Any concomitant medication deemed necessary for the welfare of the subject 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.

5.8.1 Prohibited Medications and Therapies

Use of any GABAergic agents (e.g., acamprosate, baclofen, vigabatrin, tiagabine, riluzole, and gabapentin) on a regular schedule is prohibited from the time informed consent is obtained to the end of a subject's participation in the study. Subjects 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 for situational anxiety related to occasional procedures or events are permitted, and benzodiazepines are also permitted for seizure control.

Minocycline and levodopa are prohibited from 4 weeks prior to Day 1 to the end of a subject's participation in the study

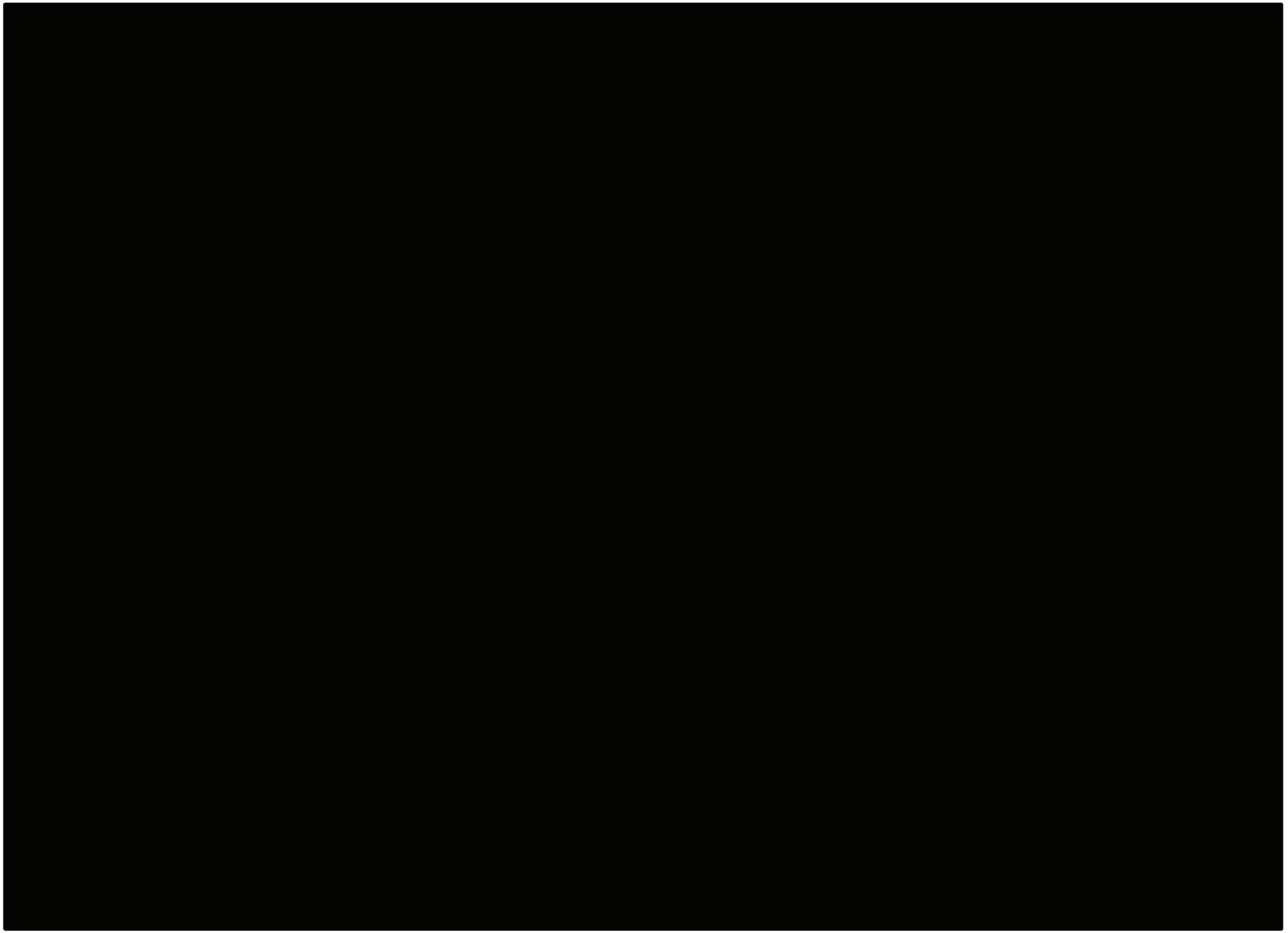
Use of other investigational agents is prohibited during the study.

5.8.2 Restrictions

Any 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 duration of the study.

Benzodiazepines administered as needed for situational anxiety (e.g., for occasional procedures or events) are permitted, as are benzodiazepines for seizure control.

6 Study Assessments and Procedures



6.1 Screening Assessments

Screening assessments, used only for determining eligibility for the study or establishing a baseline medical history, include confirmation of the molecular diagnosis of AS.

6.2 Efficacy Assessments

Efficacy assessments will be conducted only for patients in the 4 to 12 year age groups according to the schedule presented in Table 6–1.

6.2.1 Efficacy Assessments

Detailed instructions for the conduct of study assessments and procedures will be provided in the study manual.

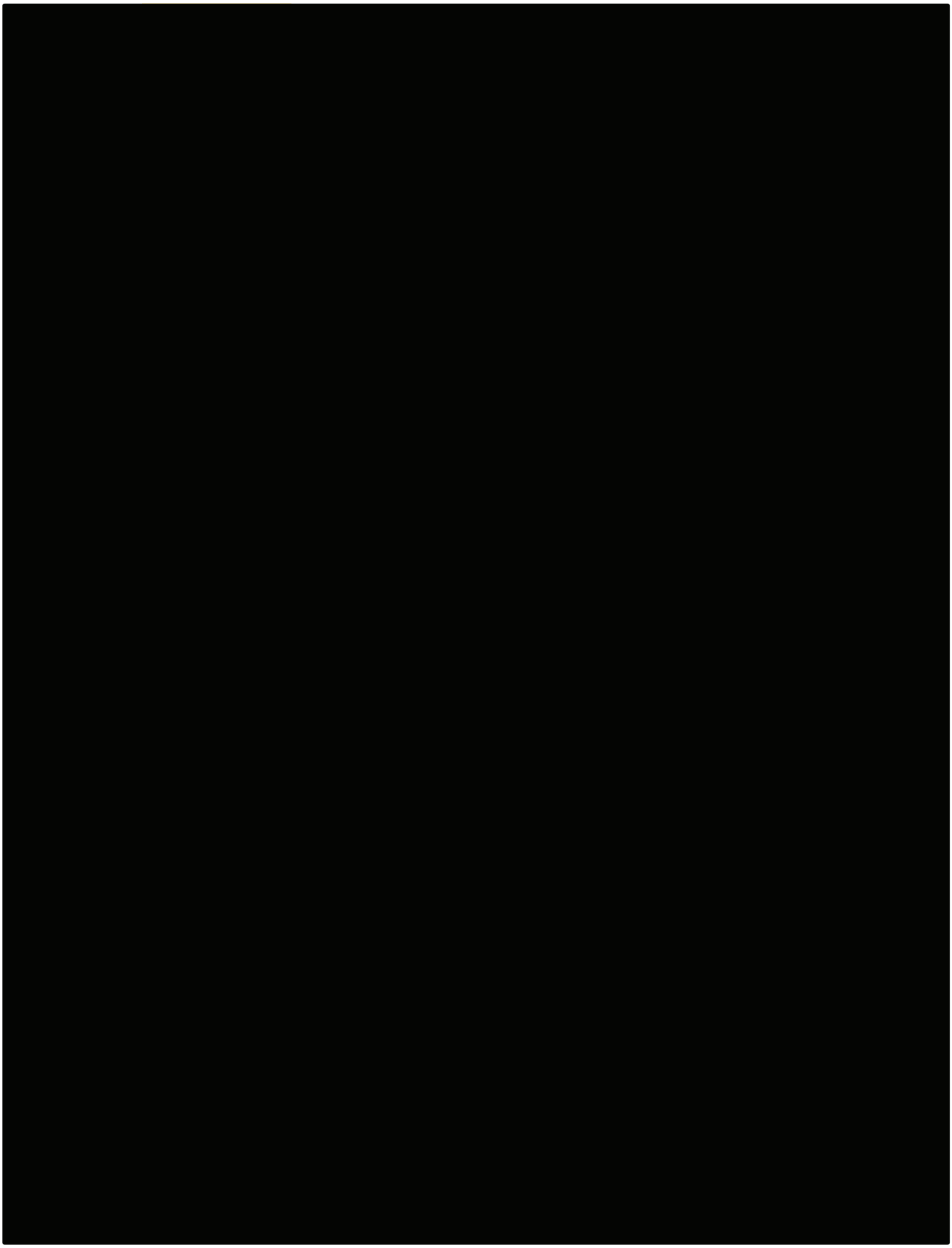
6.2.1.1 Clinical Global Impressions Scales

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 recommended that each site uses the same rater. The same rater (the principal investigator) at each site must evaluate a given subject 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 subsequent CGI-I-AS rating (at Week 6 and Week 12 visits) will also be accompanied by detailed investigator notes. To reduce recall bias, within 24 hours before the Week 6 CGI-I-AS rating, the rater will review the CGI-S-AS rating and investigator notes from the baseline visit. Similarly, within 24 hours before the Week 12 CGI-I-AS rating, the rater will review the CGI-S-AS ratings and investigator notes from the baseline visit and from Week 6. If the CGI-I-AS assessment is missing at Week 6 or Week 12, the reason for the absence will be noted on the eCRF.

6.2.1.2 Vineland Adaptive Behavior Scale, 3rd Edition

The 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 subjects 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 in VABS-3 may be used.



6.4 Safety Assessments

Safety assessments will include frequency, severity, and causality of AEs (including SAEs and AEs leading to study discontinuation), and other safety assessments including assessment of suicidality, collection of seizure diaries, clinical laboratory assessments, vital sign measurements, and physical examinations. Safety assessments will be conducted according to the schedule presented in Table 6–1 for all age groups (2 to 12 years of age).

6.4.1 Adverse Events

6.4.1.1 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 subject's LAR/caregiver will be instructed to contact the study center if the subject experiences any adverse events (AEs), is unable to take the study drug as prescribed, [redacted]

An AE is defined as any untoward medical occurrence in a subject enrolled into this study regardless of its causal relationship to study drug. Subjects will be instructed to contact the investigator at any time after enrollment if any symptoms develop.

Treatment-emergent AEs (TEAEs) are defined as AEs that start or increase in severity after the first dose of study drug in the study.

Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital) and anticipated day-to-day fluctuations of preexisting disease(s) or condition(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 in clinical studies, because the purpose of the clinical study is to establish drug effect.

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 site personnel will record the occurrence and nature of each subject's preexisting conditions, 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 subjects 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 subject's baseline.
- There is an emergence of a new seizure type.
- The subject experiences status epilepticus.

- The investigator believes the seizure should be captured as an AE (in which case the investigator should document his/her reasoning).

Seizures in this subject population will be detected and assessed using the seizure diary (Section 6.4.2.2). 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. The Sponsor will report the SAE events of seizure that meet these criteria in an aggregated, unblinded report at the end of the study.

After the informed consent form (ICF) is signed, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs. If a subject 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 subject's medical history unless the event is serious or the investigator feels the event may have been caused by a protocol procedure.

In addition, all AEs occurring after the subject receives the first dose of study drug must be reported to Ovid or its designee via the eCRF.

6.4.1.2 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 subject 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.

6.4.1.3 Eliciting and Documenting Adverse Events

Adverse events will be assessed beginning on the date of signed informed consent and up to 14 days after the last dose of study drug (unless a subject decides to participate in the ELARA open-label extension study) and must be followed until resolution or for 14 days after the subject's last study drug dose, whichever comes first.

Serious AEs that occur more than 30 days after the last dose of study drug need not be reported unless the investigator considers them related to study drug.

After informed consent is obtained, at every clinic visit and phone visit, subjects and their LAR/caregiver will be asked a standard nonleading question to elicit any medically-related changes in their well-being. 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 subject observations, AEs identified from any study data (e.g., laboratory values, physical examination findings) or identified from the review of other documents (e.g., subject diaries) that are relevant to subject 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.

6.4.1.4 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 the subject 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.

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.

6.4.1.5 Reporting Serious Adverse Events

All nonserious AEs must be recorded in the eCRF upon awareness.

Any AE that meets SAE criteria (Section 6.4.1.2) 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 provided. All supporting source information concerning the SAE (e.g., hospital records) should also be provided by fax or email.

Country-specific fax numbers will be provided in a separate document.
Email: ovidCTsafety@ovidrx.com

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 6.4.1.2) must be entered into the EDC system immediately (i.e., within 1 business day) after site personnel first learn about the event, in addition to faxing/emailing the SAE Report form. Once the qualifying SAE

data are entered into the EDC system, Ovid will be notified by an email alert, which 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 subject's last dose of study drug or within 30 days after the last study visit, the SAE must be reported unless the patient has signed the consent to enroll into the ELARA open label extension study. 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 subject or health care practitioner is unable to provide additional information, or the subject is lost to follow-up). For subjects who do not sign the informed consent to enroll into the ELARA open label extension study, 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/EC or regulators unless the investigator or Sponsor considers them related to study drug.

6.4.1.6 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 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 Appendix 1 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.

6.4.1.7 Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the subject'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 subject's normal activities.
Moderate:	An AE that is sufficiently discomforting to interfere with the subject'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 onset and duration of each episode.

6.4.1.8 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 study drug 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.

6.4.1.9 Follow-Up of Subjects 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 subject is considered stable.

6.4.2 Other Safety Assessments

Safety assessments other than AEs (Section 6.4.1) include assessment of suicidality, collection of seizure diaries, clinical laboratory analyses (Section 6.7), vital sign measurements, and physical examinations.

6.4.2.1 Assessment of Suicidality

The ABC-I will be used to assess suicidality instead of the Columbia-Suicide Severity Rating Scale, since cognitive impairment in Angelman syndrome patients interferes with the understanding of the concept of suicide. Most individuals with AS are not able to communicate thoughts of suicidality, so the subject'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 time point. If grading worsens, the investigator must decide whether that indicates a potential for self-harm by the subject, 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.

6.4.2.2 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. Also, refer to Section 6.4.1.1 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 12 weeks of treatment beginning at screening and continuing through the EOT. Seizure diaries will be collected and reviewed by the investigator with the subject's caregiver for proper recording at the baseline, Week 6, and Week 12 (or EOT) study site visits. Seizure Identification Form and Diagnostic Review Forms (SIF/DRF) will be completed by site personnel for every eligible subject. 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

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

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

6.4.2.3 Vital Sign Measurements

Vital sign measurements will include blood pressure, temperature, heart rate, and respiratory rate. Measurement of vital signs should be attempted after the subject has been resting in a supine or sitting position for at least 10 minutes.

6.4.2.4 Physical Examinations

Height, weight, and head circumference will be measured as part of the physical examination, but height will be measured only at the screening visit. A physical examination will include a relevant general assessment of: general appearance; skin; head, eyes, ears, nose and throat; neck; lymph nodes; chest (including lungs); heart; abdomen; extremities; nervous system; and musculoskeletal system.

6.4.2.5 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 subjects. 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.

For all Ovid products, both in development or post-approval, exposure during pregnancy must be recorded and the subject followed until the outcome of the pregnancy is known (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality), even if the subject discontinues study drug or discontinues from the study.

If a subject within this study or a subject'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. 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 or fax (Section 6.4.1.5).

Pregnancy is not regarded 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

6.5 Safety Monitoring Committee

An IDMC (Section 11.1.1) will provide safety monitoring. Oversight of the study conduct and IDMC will be provided by the Clinical Trial Steering Committee (CTSC; Section 11.1.2).

Routine pharmacovigilance oversight will be provided by Ovid Drug Safety.

6.6 Pregnancy

Female subjects 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. 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 subjects with women of child-bearing potential partners, there are no restrictions. Female subjects who have experienced menarche will undergo serum beta-human chorionic gonadotrophin (ß-hCG) pregnancy testing at study site visits shown in Table 6–1 (as part of the sampling for clinical laboratory tests). Any female subject with a positive pregnancy test result at Screening must be excluded from the study. A serum ß-hCG pregnancy test must be performed if any female subject 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 6.4.1.5) 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 subject 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 subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to Ovid Drug Safety.

6.7 Laboratory Analyses

The following clinical analytes will be assayed as safety assessments:

Hematology: 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: 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; magnesium, phosphate; potassium; alanine aminotransferase; aspartate aminotransferase; lactate dehydrogenase; sodium; chloride; bilirubin (total, direct); total protein; uric acid; and creatine phosphokinase.

Pregnancy testing: Serum ß-hCG for female subjects who have experienced menarche. Serum pregnancy testing will be conducted at screening and baseline. Serum pregnancy testing is recommended at subsequent visits; however, urine pregnancy testing is allowed if serum is not obtainable. If serum cannot be collected, the reason should be documented in the source document and, for sexually active female subjects, the results of the serum pregnancy test obtained at Visit 1 must be confirmed to be negative by the investigator before randomization.

6.8 Sample Collections

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

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

Blood samples will be collected for clinical laboratory, safety assessments, [redacted] A total of up to 7 mL of blood is expected to be taken for laboratory measurements at

each of the screening, baseline, Week 6, and Week 12 visits. Total blood collected will not exceed 20 mL in a 30-day period. This is in accordance with the US Department of Health and Human Services, office for Human Research Protections recommendations of 3 ml/kg, up to 50 ml total within 8 weeks (Table 2 in Howie 2011).

[redacted]

6.9 Contraception and Pregnancy Avoidance Procedure

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation 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 subject. For additional details, refer to Section 6.6 for detailed contraception requirements.

Female subjects who have experienced menarche must have a negative serum/urine hCG pregnancy test at screening (Visit 1) and a negative serum 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 subject can receive the first dose of study drug. During the study, subjects 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/urine hCG pregnancy test will be performed at the final visit.

7 Statistical and Analytical Plan

7.1 General Considerations

All statistical analyses will be performed using SAS® Version 9.4 or higher. All clinical study data will be presented in subject data listings. Data summaries will be presented for all endpoints and will include descriptive statistics (number of subjects, mean, SD, first quartile, median, third quartile, minimum, and maximum) for continuous variables, and frequency and percentage for categorical and ordinal variables. If there are missing values, the number of missing values will be presented, but without a percentage.

For all analyses, "baseline" refers to the most recent non-missing value obtained immediately prior to administration of first dose, unless it is otherwise clearly defined.

Any substantial change to the data analysis methods described in the protocol will require an amendment. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP. Additional post hoc analyses of the data may be conducted as deemed appropriate.

7.2 Endpoints

7.2.1 Efficacy Endpoints

7.2.1.1 Primary Endpoint

- The CGI-I-AS score at Week 12

7.2.1.2 Key Secondary Endpoints

The key secondary endpoints will be utilized to fulfil a recommendation of the EMA for a responder analysis.

- CGI-I-AS response (at least minimally improved) defined as CGI-I-AS score of 1, 2, or 3 at Week 12
- CGI-I-AS response (at least much improved) defined as CGI-I-AS score of 1 or 2 at Week 12

7.2.1.3 Other Secondary Endpoints

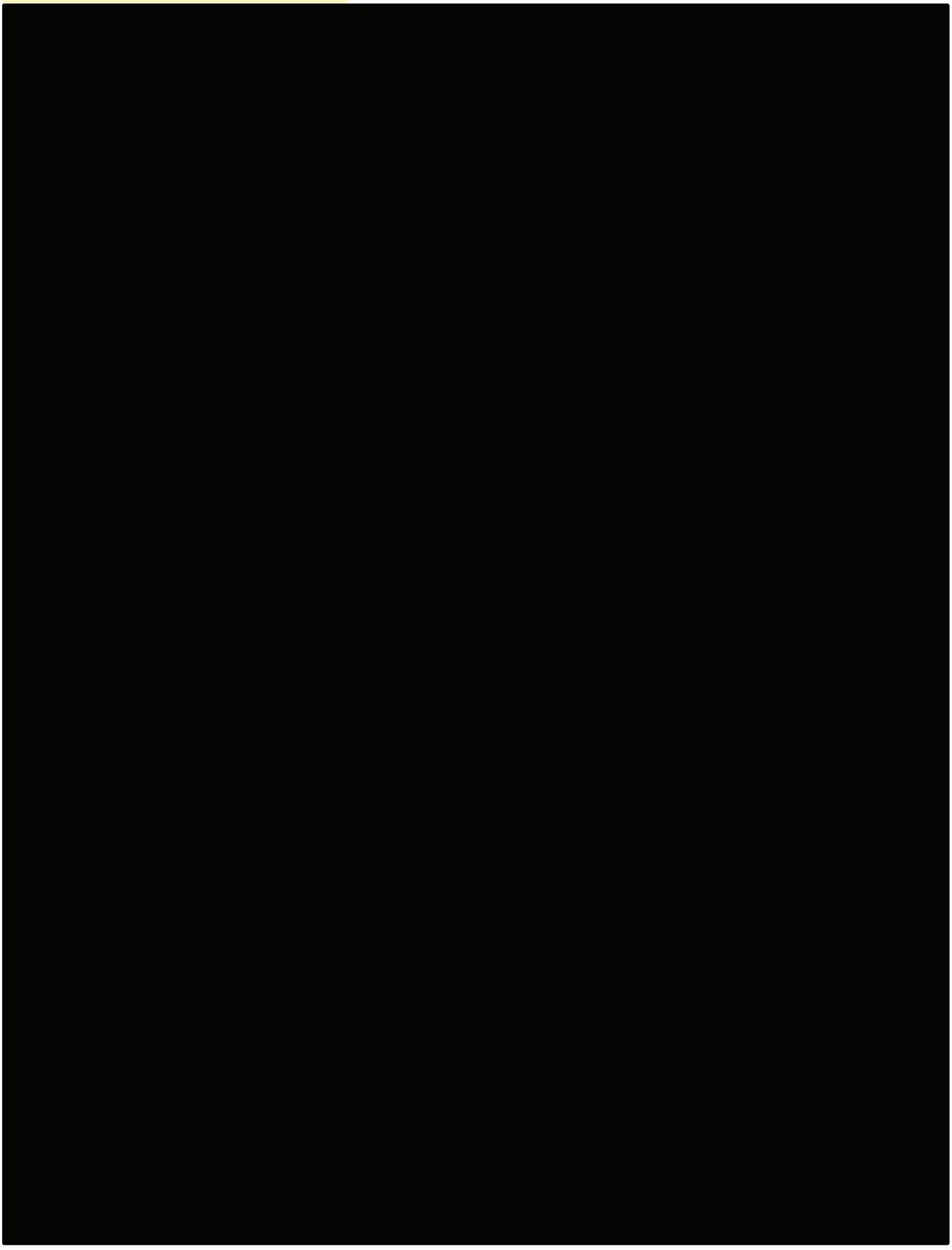
[redacted]

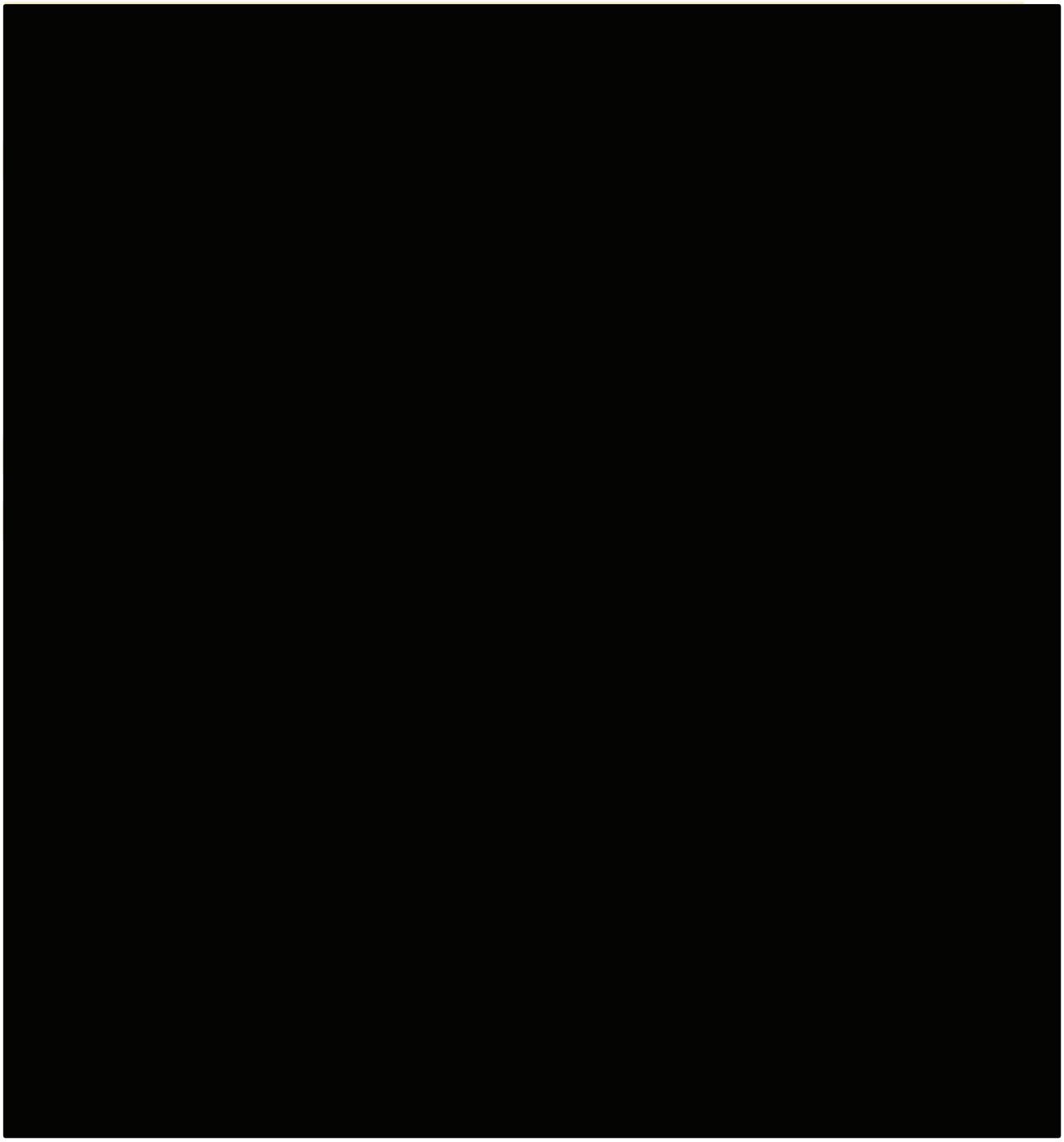
- VABS-3 assessment scores; change from baseline to Week 12
    - Communication domain and its subdomains
    - Socialization domain and its subdomains
    - Daily Living Skills domain and its subdomains
    - Motor Skills domain and its subdomains
    - Maladaptive Behavior domain and its subdomains
- The CGI-S-AS scores, change from baseline to Week 12.
    - The CGI-S-AS symptoms overall score
    - The CGI-S-AS domain scores
- The relationship between CGI-S-AS at baseline and CGI-I-AS at Week 12
- The relationship between each of CGI-S-AS domains at baseline and CGI-I-AS at Week 12

[redacted]

7.2.2 Safety Endpoints

- Incidence of AEs
- Change in clinical laboratory parameters from baseline to each post baseline assessment
- Shift in clinical laboratory parameters from baseline to each post baseline assessment
- Change in vital sign measurements from baseline to each post baseline assessment
- Shift in physical examination parameters from baseline to each post baseline assessment
- Change in suicidality assessment (ABC-I) from baseline to each postbaseline as assessed by ABC-I. The ABC-I will serve as a surrogate measure for suicidality
- Percent change in seizure frequency (expressed as a 28-day frequency) from baseline to each post baseline timepoint





7.4 Analysis Sets

The following analysis sets will only include subjects 4 to 12 years old (inclusive). The analysis for subjects 2 to 3 years old (inclusive) will be conducted separately.

The intent-to-treat set will consist of all subjects who are randomized, whether or not study drug is received. Subjects will be analyzed according to their randomized group

The full analysis set (FAS) will include all subjects who are randomized, receive at least 1 dose of study drug, and have at least 1 post baseline assessment of the primary efficacy endpoint. The FAS will be used for efficacy analyses based on the randomized treatment for each subject.

The per protocol set (PPS) is a subset of the FAS that includes subjects who complete the Week 12 visit and have no major protocol deviations that are deemed to impact efficacy. The PPS will be used for efficacy analyses based on the randomized treatment for each subject.

The safety set (SS) will consist of all subjects who are randomized and receive at least 1 dose of study drug and will be used for all safety analyses. The safety analyses will be based on the treatment that was actually administered to each subject.

[redacted]

7.5 Subject Disposition

The number of subjects screened and who failed screening will be displayed. The number and percentage of subjects who are randomized, dosed, withdrawn from the study (including reasons for withdrawal), and complete the study will be displayed by treatment group and overall for the intent-to-treat set. The number and percentage of randomized subjects in the SS, FAS, PPS, [redacted] data set will also be displayed by treatment group and overall.

The number of subjects screened, dosed, completed study, and withdrawn from the study will be summarized separately for subjects 2 to 3 years old (inclusive).

7.6 Demographic and Baseline Characteristics

Demographic characteristics include age at screening and at baseline, age group (randomization stratification variable: age at screening 4 to 8 years versus age 9 to 12 years), region (randomization stratification variable: US versus outside US), gender, race, ethnicity, study center, and country. Baseline characteristics include baseline body weight, height, body mass index (kg/m^2), and molecular diagnosis. All demographic and baseline characteristics data will be summarized descriptively by treatment group and overall for the SS.

Data for subjects 2 to 3 years old (inclusive) will be presented separately in listings.

7.7 Exposure and Compliance

Treatment compliance will be summarized by treatment group over the entire treatment period. Compliance rates during the treatment period will be derived using the following formula:

100× (Total number of capsules dispensed–Total number of capsules returned) / (Expected number of capsules)

The expected number of capsules to be taken is based on the date of first study drug dose and the date of last study drug dose, the subject's weight range band at screening that determines the number of capsules expected each study week, following the titration schedule (Section 5.1), and any dose down-titrations (Section 5.2.1). Compliance rates will be presented for the SS using summary statistics and percentage for the frequency distributions (0% to <20%, 20% to 40%, 40% to <60%, 60% to <80%, 80% to <100%, 100% to ≤120%) by treatment group and overall.

Data for subjects 2 to 3 years old (inclusive) will be presented separately in listings.

7.8 Efficacy Analyses

All efficacy analyses will be based on the FAS. Additionally, the analysis of the primary endpoint will be repeated on the PPS to assess the sensitivity of the results to major protocol violations. All efficacy variables will be summarized descriptively by treatment group and visit.

7.8.1 Primary Efficacy Analyses

The CGI-I-AS scale assessed by the clinician rater will be collected at the Week 6 and Week 12 visits. This is an ordinal variable with scores ranging from 1 (very much improved), to 4 (no change), to 7 (very much worse) which will be analyzed as a continuous outcome variable in these analyses.

An MMRM Analysis of Variance (ANOVA) model will be fitted using restricted maximum likelihood (REML) for CGI-I-AS with fixed effects for visit (Week 6 and Week 12), randomized treatment, the visit-by-treatment interaction, age group (randomization stratification variable: age 4 to 8 years versus age 9 to 12 years), and region (randomization stratification variable: US versus outside US). An unstructured within -subject covariance structure will be specified as the first choice, and if the model fails to converge, alternative covariance structures will be tested as detailed in the SAP. If a structured covariance is used, then a robust sandwich estimator will be utilized for estimating the variance of the treatment effect estimate. From the model, the Week 12 difference between least squared means of OV101 and placebo groups will be presented along with the corresponding 95% confidence interval and 2-sided *P* value.

As a sensitivity analysis for the assumption of normality, a Wilcoxon rank sum test will be used for treatment group comparison. The Hodges–Lehmann (Hodges and Lehmann 1963) estimate of

the median CGI-I-AS difference between OV101 and placebo groups, and its 95% confidence interval will be presented along with the 2-sided *P* value.

7.8.2 Key Secondary Efficacy Analyses

Generalized Estimating Equations (GEE) method will be used for the analysis of key secondary endpoints: CGI-I-AS response (at least minimally improved) and CGI-I-AS response (at least much improved). GEE models will include the response variable at each visit as the dependent variable, and fixed effects for visit (Week 6 and Week 12), randomized treatment, the visit-by-treatment interaction, age group (randomization stratification variable: age 4 to 8 years versus age 9 to 12 years), and region (randomization stratification variable: US versus outside US). An unstructured working correlation for the binary outcome variable will be assumed for the model parameter estimation, and if the model fails to converge, alternative covariance structures will be tested as detailed in the SAP. If there is no response in either treatment arm at the Week 6 visit, the GEE model will be substituted with a logistic regression for the Week 12 CGI-I-AS response variable with effects for the randomized treatment and the two randomization stratification variables. From the model (GEE or logistic regression, as appropriate), the Week 12 odds ratio will be presented along with the corresponding 95% confidence interval and 2-sided *P* value.

7.8.3 Other Secondary Analyses

The VABS-3 composite scores (Communications, Socialization, Daily Living Skills, Motor Skills, and Maladaptive Behavior domains) and scores of their subdomains will be assessed at baseline and Week 12 and analyzed as continuous outcome variables.

Change from baseline to Week 12 in each VABS-3 domain score and scores of their subdomains will be analyzed using an ANCOVA model with effects for randomized treatment, age group (randomization stratification variable: age 4 to 8 years versus age 9 to 12 years), region (randomization stratification variable: US versus outside US), and the corresponding baseline as a covariate. A test for a significant treatment-by-baseline interaction will be performed in a separate model (including the above terms plus the interaction term), using a 0.100 alpha level. If the treatment-by-baseline interaction is significant, then the ANCOVA assumptions are violated and an ANOVA model will be used instead. From the final model(s), the difference between least squared means of OV101 and placebo groups will be presented along with the corresponding 95% confidence intervals and 2-sided *P* values.

The CGI-S-AS Symptoms Overall and CGI-S-AS domains will be collected at baseline, Weeks 6, and 12, and will be treated as a continuous outcome variable. An MMRM ANCOVA methodology similar to the one described previously for [redacted] variables will be used to analyze the change from baseline in CGI-S-AS Symptoms Overall score and in scores of CGI-S-AS domains.

The relationships between CGI-S-AS Symptoms Overall score at baseline and CGI-I-AS at Week 12 will be explored. The relationships between each of CGI-S-AS domain scores at baseline and CGI-I-AS at Week 12 will also be explored.

[redacted]

7.8.5 Description of Subgroups to be Analyzed

Descriptive statistics will be presented separately by age group (randomization stratification variable: age 4 to 8 years versus age 9 to 12 years) for the primary endpoint and the two key secondary endpoints. Observed values will be reported by treatment group. The difference in means or proportions for OV101 versus placebo groups will also be presented with the corresponding 95% confidence intervals. Similar subgroup analysis will be conducted for region (US versus outside US).

If for a given endpoint, the results in the 2 subgroups appear different from a clinical perspective, the appropriate model (MMRM, GEE, or logistic) could be constructed as described above, including an age-by-treatment interaction term. This interaction term will be tested at alpha level of 0.10 to assess whether the treatment effects are statistically different for the 2 age subgroups.

7.9 Safety Analyses

All safety analyses will be based on the SS. Descriptive statistics will be used to summarize all safety endpoints by treatment group. Two-sided 95% CIs will be presented where meaningful. Data summaries will be displayed for incidence of AEs, clinical laboratory variables, vital signs, body weight and body mass index, physical examinations, clinical assessment of suicidality, and seizure diary data.

Unless otherwise specified below, safety data for subjects 2 to 3 years old (inclusive) will only be presented in listings and will be displayed in by-subject graphs, as appropriate.

7.9.1 Adverse Events

All TEAEs will be coded using MedDRA and will be summarized by MedDRA system organ class and preferred term and treatment group. Detailed listings of TEAEs, SAEs, related AEs, and discontinuations due to AEs will be provided.

The incidence of TEAEs, discontinuations due to TEAEs, drug-related, and serious TEAEs will be summarized. Incidence of TEAEs by severity and relationship to study drug will also be presented.

Incidence of TEAEs will be summarized separately for subjects 2 to 3 years old (inclusive).

7.9.2 Clinical Laboratory Tests

Changes from baseline to each post baseline visit with respect to clinical chemistry and hematology results will be summarized descriptively. Each laboratory parameter will be

classified as low, normal, or high relative to the parameter's reference range and will be summarized with shift tables. Listings of subjects with abnormal results will be provided.

7.9.3 Vital Signs and Physical Examinations

Vital signs (systolic and diastolic blood pressure, temperature, heart rate, and respiratory rate), weight, and body mass index will be summarized descriptively at baseline and all post baseline study visits by treatment group. Change from baseline to all post baseline study visits will be summarized descriptively by treatment group.

Physical examinations (general appearance; skin; head, ears, eyes, nose, and throat; neck; lymph nodes; chest (including lungs); heart; abdomen; extremities; nervous system; and musculoskeletal system) at baseline will be summarized. Shifts from baseline to post baseline study visits in each body system/site will be summarized by treatment group.

7.9.4 Suicidality

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

7.9.5 Seizure Diary Data

Seizure diary data will be summarized descriptively at baseline and all post baseline study visits by treatment group. Additionally, the seizure frequency (expressed as a 28-day frequency) will be calculated for the following study periods: Baseline (Screening to Day 1), Week 6 (Day 1 to Week 6 visit date), and Week 12 (Week 6 visit date + 1 to Week 12 visit date). Percent change in seizure frequency from baseline to all post baseline study visits also will be summarized descriptively by treatment group.

7.10 Other Analyses

7.10.1 Concomitant Medications

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) and will be summarized according to their WHO-DD Anatomic Therapeutic Chemical class level 4 and preferred drug name within Anatomic Therapeutic Chemical class level 4. The number and percentage of subjects who took at least 1 medication post baseline as well as the number and percentage of subjects who took each type of medication will be presented for each treatment group.

7.11 Interim Analyses

No interim analyses of efficacy data are planned for this study.

7.12 Statistical Testing and Significance Level

The primary analysis will be performed on the FAS and the PPS. However, the PPS analysis will only be considered a sensitivity analysis.

Inferential treatment comparison of the primary efficacy endpoint, CGI-I-AS at Week 12, will be conducted at the 0.050 level of significance using a 2-tailed test. If the null hypothesis of no

treatment difference for the primary endpoint is rejected, the alpha (0.05) will be passed to the significance testing for the key efficacy endpoints, CGI-I-AS response (at least minimally improved) at Week 12 and CGI-I-AS response (at least much improved) at Week 12, which will be tested using the corresponding 2-sided tests at 0.05 level of significance in a fixed sequence. If and only if the null hypothesis of no treatment difference based on CGI-I-AS response (at least minimally improved) is rejected at 0.05 level of significance, testing will continue and the null hypothesis of no treatment difference based on CGI-I-AS response (at least much improved) will be tested at 0.05 level of significance.

No formal statistical testing of other secondary endpoints will be performed. All *P* values presented for secondary and tertiary endpoints will be considered descriptive in nature.

7.13 Missing Data Handling and Sensitivity Analysis

The MMRM model used in the analysis of key efficacy endpoints implicitly adjusts for missing data. If missing data are 5% or more for the primary endpoint, a sensitivity analysis will be performed, with missing outcomes be imputed in the analysis models. Multiple imputation techniques will be used for imputation, under the assumption of data missing not at random. Additionally, a tipping point analysis will be performed. Details will be specified in the SAP.

Rules for imputation of missing dates for AEs and concomitant medications will be stated in the SAP.

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 study.

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, subject privacy will be of utmost importance and maintained. Typically, sufficient (minimum of 2 weeks) 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 subjects 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, [redacted] and computerized or otherwise automated assessments [redacted]

Investigative site staff will enter subject data into Medidata RAVE® (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 CD-ROM containing all its site specific eCRF data as entered into the EDC system for the study, including full discrepancy and audit history. Additionally, a CD-ROM copy of all the site's data from the study will be created and sent to the Sponsor for storage. [redacted] will maintain a duplicate CD-ROM copy for their records. In all cases, subject 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 subjects in research studies. Before study onset, the protocol, informed consent, assent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject or the subject'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 subjects.

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 Subject Information and Consent

A written informed consent in compliance with applicable regulatory authority regulations shall be obtained from the LAR/caregiver of a minor before the subject enters the study or any unusual or nonroutine procedure that involves risk to the subject is performed. For minors an assent document will be presented, and assent will be obtained before the subject 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 or her IRB for review and approval before the start of the study. If the ICF is revised during the study, all active participating subjects and LAR/caregivers (as applicable) must sign the revised forms.

Before recruitment and enrollment, each prospective subject's LAR/caregiver and subject (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 subject understand the implications of participating in the study, the LAR/caregiver and subject 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 subjects, 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 subject 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 subject 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 subject (or the subject'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 the Sponsor nor [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 the Sponsor nor [redacted] is financially responsible for further treatment of the subject'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.
- Curriculum vitae for the investigator and each sub investigator listed on Form FDA 1572.
- 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 and assent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject 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 subjects 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 investigational product. 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

11.1 Monitoring

11.1.1 Independent Data Monitoring Committee

An IDMC will monitor the study (Section 6.5): it will include 3 independent representatives including a chairperson, a pediatric epileptologist, and a biostatistician. The IDMC charter includes the details for the IDMC including responsibilities, qualifications, and key processes. The IDMC responsibilities will include (but are not limited to) the following:

- Staged Enrollment Review Meetings. Subject assignment to treatment will be stratified and staged by age and gated by the IDMC via the evaluation of sentry subjects (Section 5.1). No age cohort may begin treatment without IDMC review of tolerability [redacted] in sentry subjects in the previous older cohort.
- Meet periodically to review aggregate and individual subject data related to safety, data integrity, and overall conduct of the trial.
- Work with the Independent Statistical Center to determine the data presentations (tables, listings, and figures) that are necessary for the IDMC to monitor study conduct and safety.
- Review and evaluate the content of all data presentations received before each IDMC Meeting.
- Contribute to closed session reviews and recommendations.

11.1.2 Clinical Trial Steering Committee

The CTSC will include approximately 5 independent representatives, including a chairperson, representatives with relevant expertise in pediatric psychiatry, pediatric epileptology, pediatric neurology and psychology, and a parent of a child with AS. In addition, 2 Sponsor representatives will be included on the CTSC. The CTSC responsibilities will include (but are not limited to) the following:

- Conduct interim review of the trial's progress including updated data on recruitment and data quality.
- Review recommendations of the IDMC including but not limited to:

- Safety issues which may suggest risk to currently enrolled or future subjects
- Recommendations to modify or terminate the trial if, following review of the data, there are safety or efficacy concerns.

- Monitor compliance with IDMC recommendations.
- Monitor recruitment data and accrual within relevant subsets, screen failures, dropouts, and losses to follow-up overall and by study site.
- Monitor compliance with the protocol and protocol violations by subjects and investigators.
- Advise on protocol modifications suggested by investigators or Sponsors (e.g., amendments to inclusion criteria, trial endpoints, or sample size).
- Monitor planned sample size assumptions.
- Monitor continuing appropriateness of subject information.
- Assess the impact and relevance of external evidence.

11.1.3 Monitoring of the Study

The clinical monitor, as a representative of the Sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals, in addition to maintaining necessary telephone and letter contact. The 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 personnel.

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.

11.1.4 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 and [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 subject, 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 subjects can be enrolled into an amended protocol.

11.2.2 Protocol Deviations

The investigator or designee must document and explain in the subject'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 subjects 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 subject or investigator that results in a significant, additional risk to the subject. Significant deviations can include nonadherence to inclusion or exclusion criteria, or nonadherence to FDA regulations or ICH GCP guidelines, and will lead to the subject 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 subject 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 agencies as required by the applicable regulatory requirements. 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 subjects, 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 subjects, ensure continuation of study conduct, and preserve the integrity of the study, in case of a general public health crisis or pandemic such as COVID-19. This addendum addresses situations in which scheduled in person clinic visits are not feasible due to local, regional or national restrictions.

Specifically, the addendum aims to ensure:

- Continued safe study conduct and participation of existing patients
- Uninterrupted supply of study treatment
- 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 subjects 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 subject participation in the NEPTUNE study:

Guidance for subjects scheduled to undergo study screening

- **For subjects 4-12 years old who are unable to attend a clinic visit in person**
    - Remote screening via telehealth and/or telephone may be performed at the discretion of the Principal Investigator. The choice of telehealth platform is the Principal Investigator's discretion but must be consistent with local policies and standard practice. The requirements for data protection, must be adhered to.
    - Informed Consent may be sent to the subject either electronically (pdf format) or by mail prior to the scheduled screening visit
    - Informed consent can be performed via telehealth or telephone during the screening visit and documented in the source document with the date and time of the verbal consent. Wet ink signature on ICF should be returned to the site via courier.

- **For remote screening**
    - Site must ensure that subject has access to a weighing scale, for determination of weight band assignment
    - Screening visit clinical labs may be performed at a local laboratory. Reference ranges must be documented
    - Home visits may be conducted by a trained mobile healthcare professional to perform study assessments e.g. vital signs, body weight assessment, clinical lab draws, review/collection of study materials
    - Instructions should be provided verbally or in writing to the caregiver

    - Copies of Seizure [redacted] forms should be sent to caregiver. Electronic copies may be provided if caregivers can make physical copies.
    - Pre-paid envelopes will be provided to support the shipping of the diaries
    - Update EDC as soon as possible to allow planning of IP shipment
    - Notify Sponsor/CRA to plan support with shipment arrangement
- **For subjects 2-3 years old**
    - Screening shall be performed on-site. If pandemic restrictions preclude on-site visits, then screening of subjects 2-3 yrs old shall be placed on a temporary hold until permissible under local and investigative site's guidelines
    - Informed Consent may be sent to the subject either electronically (pdf format) or by mail prior to the scheduled screening visit. The signed consent should be returned by the subject to the site and appropriately filed. If Informed Consent is completed remotely, a wet ink signature on ICF should be returned to the site via courier.

Guidance for subjects scheduled for Randomization/Baseline Visit

- Randomization visits can only occur when patients can physically be present on-site
- If the baseline visit cannot be conducted within 28 days of screening, it should be captured as a protocol deviation due to pandemic restrictions but do not automatically screen fail the subject. IWRS and EDC will not automatically screen fail subjects in this case
- Every attempt should be made to follow procedures at the randomization visit as per study protocol. Any deviation should be appropriately documented and reported to each site's IRBs/ECs per their reporting guidelines
- Additional instructions pertaining to the randomization visit will be provided for subjects who are still in the screening phase when pandemic restrictions are scaled back, and subjects are able to attend clinic visits in person

[redacted]

- Seizure [redacted] diaries must be collected and reviewed as per protocol procedures and Epilepsy Consortium instructions including SIF and DRF forms. Physical/electronic PDF copies of diaries (including medication diary) should be provided in preparation of week 6 and week 12 visits
- Preprinted shipment labels and envelopes should be provided to caregivers to receive diaries
- Upon retrieval of diaries, EDC should be updated accordingly

Guidance for established subjects completing Week 6 Study Visit

- Schedule the visit as close as possible to Week 6 date to allow time to ship IP.
- When on-site visits are not feasible, remote assessment of the CGI-I-AS, CGI-S-AS, VABS3, and other PROs) may be performed via your institution-approved (HIPAA compliant) telehealth system. Telehealth assessments must be consistent with local policies and standards. The requirements for data protection of Personal Health Information (PHI) must be adhered to.
- In the absence of a telehealth system, a remote assessment is to be completed by utilizing a unified communication software such as Skype, Microsoft Teams or Zoom
- Provide a script to a local lab as required per clinical labs per protocol
- 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
- If the site visits become possible/permissible at any point between Week 6 and Week 12, the subject should be scheduled for an on-site, unscheduled visit prior to week 12 time point and all safety assessments should be completed at this visit
- IP with kit number will be assigned to each subject. Where allowed, a preferred courier will be assigned to pick up and deliver the IP to subject. [redacted]

Guidance established subjects completing Week 12 Study Visit

- Whenever possible, all week 12 visits should be completed onsite
- If an onsite visit is not possible, a remote visit should be completed to collect assessments via telehealth system. A unified communication software such as Skype, Microsoft Teams or

Zoom may be utilized unless prohibited by local guidelines. Telehealth assessments must be consistent with local policies and standards. The requirements for data protection, must be adhered to.

- Provide a script to a local lab for clinical labs required per protocol
- 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
- For subjects intending to immediately transition into ELARA, the week 12 (NEPTUNE EOT) visit may be considered as ELARA Baseline if ELARA protocol criteria are met.
- Unused IP should be shipped back to site for reconciliation.

[redacted]

- Ensure subject diaries are collected and reviewed appropriately.
- If any patient is enrolling into the ELARA study immediately after week 12 visit, EOS week 14 visit (over the phone) should be completed prior to enrollment into ELARA

If at any time during the conduct of the NEPTUNE study /a subject 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.