CLINICAL STUDY PROTOCOL

A Phase 2a, Randomized, Double-Blind, Parallel-Group, Proof-of-Concept Study Evaluating the Safety, Tolerability, and Efficacy of OV101 in Fragile X Syndrome

PROTOCOL NUMBER OV101-17-001

Sponsor:	Ovid Therapeutics Inc. 1460 Broadway New York, NY 10036
Sponsor Contact:	[redacted]
Safety Monitor:	[redacted]
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Version of Protocol:	1.2 (Protocol Amendment 2)
Date of Protocol:	27 Mar 2019

CONFIDENTIAL

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

Declaration of Investigator

I have read and understood all sections of the protocol titled "A Phase 2a, Randomized, Double-Blind, Parallel-Group, Proof-of-Concept Study Evaluating the Safety, Tolerability, and Efficacy of OV101 in Fragile X Syndrome" and the accompanying investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with Final Protocol Version 1.21, dated 27 Mar 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:
OV101-17-001

Title:
A Phase 2a Randomized, Double-Blind, Parallel Group, Proof-of-Concept Study Evaluating the Safety, Tolerability, and Efficacy of OV101 in Fragile X Syndrome

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

Study Phase:
Phase 2a

Study Sites:
Approximately 8 sites in the United States and approximately 1 site in Israel

Indication:
Fragile X syndrome

Rationale:
Ovid Therapeutics Inc. is developing OV101 (gaboxadol) for the treatment of rare genetic disorders that are associated with severe developmental and behavioral challenges, such as Angelman syndrome and Fragile X syndrome (FXS). Gaboxadol was initially developed for the treatment of insomnia by H. Lundbeck A/S and Merck, but its development was discontinued in 2007 for clinical and commercial reasons. Extensive nonclinical and clinical data were generated during the initial stages of development, including data from exposure to gaboxadol in more than 4300 adult subjects with insomnia and approximately 500 adult subjects in non–insomnia-related studies.

Fragile X syndrome is the most common inherited form of intellectual disability, with a prevalence of 1 in 4000 males and 1 in 8000 females. It is also the most common known genetic cause of autism; approximately 25% to 30% of individuals with FXS meet the full diagnostic criteria for autism, and approximately 5% of children with autism carry the fragile X mutation. Males with FXS have moderate to severe intellectual disability, and females with FXS range from normal to moderate impairment.

Individuals with FXS are at increased risk for a range of behavioral problems that may limit their academic performance, adaptive function, daily living skills, and social interactions. Anxiety is the most common behavioral problem in individuals with FXS, with specific symptoms of shyness, social anxiety, hyperarousal, and stereotypic behavior such as hand flapping and hand biting. Aggressive behaviors in male individuals with FXS are also common and may lead to injuries to caregivers, peers, or friends. Attention-deficit/hyperactivity disorder symptoms (overarousal, hyperactivity, distractibility, and

impulsivity) may also be noted. Individuals with FXS can experience problems in one or more of these behavior domains. There is a wide range of variability in symptoms, although they tend to be more severe in males than in females.

Current behavior therapy treatments include speech therapy, physical therapy, occupational therapy, and educational resources. Current treatments with medications target only the behavioral phenotypes and not 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. The mechanism of action of OV101 is unique among GABAergic agents, including benzodiazepines, zolpidem and other zolpidem-like drugs, neurosteroids, and drugs that act on GABA metabolism or uptake.

The use of OV101 for treatment of individuals with FXS is based on studies in a relevant mouse model of the disease, the *Fmr1* knockout (KO) mouse, which lacks the fragile X mental retardation protein due to a disruption in its *FMR1* gene. *Fmr1* KO mice have decreased GABA synthesis, decreased presynaptic GABA release, and decreased extrasynaptic levels of GABA, resulting in decreased tonic inhibition. OV101 was shown to restore tonic inhibition in the amygdala, reduce sensory hypersensitivity and motor hyperactivity, and improve pre-pulse inhibition (signal to noise ratio) in *Fmr1* KO mice. Cogram et al recently presented data that showed full normalization of abnormal repetitive, social, and anxiety-like behaviors with OV101 in another FXS KO mouse model, the *Fmr1* KO2 mouse. Taken together, these data support the potential of OV101 to treat the core behavioral deficits noted in individuals with FXS. Importantly, the ability of OV101 to potentiate tonic inhibition is unlike any other GABAergic agent, including benzodiazepines, zolpidem, other zolpidem-like drugs, neurosteroids, and drugs that act on GABA metabolism or uptake.

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.

The purpose of this study is to investigate the safety, tolerability, and exploratory efficacy of treatment by oral administration of OV101 at doses of 5 mg/day (5 mg once a day [QD]), 10 mg/day (5 mg twice a day [BID]), or 15 mg/day (5 mg three times a day [TID]) in adolescent and adult male subjects with FXS. The 12-week, randomized, double-blind, parallel-group, proof-of-concept study design will inform OV101 clinical development and the design of future studies in FXS.

Objectives:

Primary Objectives:

- To evaluate the safety and tolerability of OV101 over 12 weeks of treatment across different daily dosing regimens in adolescent and adult male subjects with FXS

Secondary Objectives:

- To evaluate changes in behavior during 12 weeks of treatment with OV101 across different daily dosing regimens in adolescent and adult male subjects with FXS

Exploratory Objectives**:**

- To evaluate changes in sleep, adaptive functioning, and quality of life across different daily dosing regimens of OV101 treatment over 12 weeks in adolescent and adult male subjects with FXS
- [redacted]
- To explore the relationships among study endpoints (eg, behavior, sleep), where appropriate
- [redacted]

Study Population:

Inclusion criteria:

1. Is male and 13 to 22 years old (inclusive) at the time of informed consent.
2. Has a diagnosis of FXS with a confirmed *FMR1* full mutation (≥200 CGG repeats). The diagnosis must be confirmed by genetic testing prior to subject randomization.
3. Has a Clinical Global Impression-Severity score of 4 (moderately ill) or greater at screening.
4. Is currently being treated with no more than 3 anti-epileptic and/or psychoactive medications, including those prescribed off-label to address behavioral conditions. Any concomitant medication, including anti-epileptic and/or behavioral medications, supplements, and special diets, must be at a stable dose for at least 4 weeks before randomization and must be maintained at that dose throughout the duration of the study.

5. Has a legally acceptable representative (LAR)/caregiver capable of providing informed consent and able to attend all scheduled study visits, oversee the administration of study drug, and provide feedback regarding the subject's behavior and other symptoms as described in the protocol.
6. Provide assent to the protocol (to the extent possible and in accordance with local institutional review board and regulatory requirements) and have an LAR/caregiver who will provide written informed consent. Subjects providing assent must do so at the same visit as LAR/caregiver written informed consent is provided.
7. Is able to attend all scheduled study visits and willing and capable of performing the required study assessments.
8. Is able to ingest the study drug capsules (including sprinkling capsule contents onto 1 spoon of applesauce or low-fat yogurt).
9. Has an intelligence quotient less than 75 as measured by the Stanford-Binet-5 at screening or a previously documented SB-5 measurement conducted within 6 months of the screening visit. For the site in Israel, please see Appendix for site-specific details regarding the IQ test.
10. Will agree to remain sexually abstinent from the first day of screening until 30 days after the last dose of study treatment.
11. Has LAR/caregivers who will agree not to post any of the subject's personal medical data related to the study or information related to the study on any website or social media site (eg, Facebook and Twitter) until they have been notified that the study is completed.

Exclusion criteria:

1. Has a concomitant disease (eg, gastrointestinal, renal, hepatic, endocrine, respiratory, or cardiovascular system disease) or 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 this study.
2. Has clinically significant lab abnormalities or vital signs at the time of screening (eg, alanine aminotransferase or aspartate aminotransferase >2.5 × upper limit of normal; total bilirubin or creatinine >1.5 × upper limit of normal). Re-testing of safety labs may be allowed after consultation with the medical monitor or designee.
3. Uses any GABAergic agent (eg, acamprosate, baclofen, vigabatrin, tiagabine, riluzole, benzodiazepines, and gabapentin) when used on a regular schedule. Benzodiazepines administered for situational anxiety (eg, for occasional procedures or events) are permitted.
4. Uses any cannabinoid derivatives.
5. Has a history of uncontrollable seizure disorder or seizure episodes within 6 months of screening or change in the anticonvulsant pharmacotherapy in the past 3 months.
6. Has a history of suicidal behavior or considered by the investigator to be at high risk of suicide.
7. Has any condition or there is any reason that, in the opinion of the investigator, makes

the subject unsuitable for enrollment

8. Is unable or does not have an LAR/caregiver able to comply with study requirements.
9. Has enrolled in any clinical trial or used of any investigational agent, device, and/or investigational procedure within the 30 days before screening or does so concurrently with this study.
10. Is a family member of the investigator or study site personnel.

Study Design:

This is a Phase 2a, randomized, double-blind, parallel-group study to evaluate the safety, tolerability, and efficacy of OV101 at 3 daily doses: 5 mg/day (5 mg QD), 10 mg/day (5 mg BID), and 15 mg/day (5 mg TID) in adolescent and adult male subjects with FXS. Subjects with a clinically and molecularly confirmed diagnosis of FXS will be eligible for inclusion in the study. The study will comprise a screening period of at least 1 week (to allow for actigraphs) and up to 3 weeks; a baseline visit on Day 1 for treatment randomization (enrollment), baseline assessments, and first dose of study drug; clinic visits for safety and efficacy assessments over a 12-week treatment period, including clinic visits at Week 2, Week 6, and Week 12 (end-of-treatment [EOT]); and an end-of-study (EOS) follow-up visit occurring any time between the ends of Week 16 and Week 18.

For each subject, after informed consent is obtained, screening assessments will be completed within the 3 weeks preceding Baseline. At Baseline, subjects 13 to 22 years old (inclusive) who meet all eligibility criteria will be enrolled on Day 1 in a 1:1 target ratio between adolescents (13 to17 years old, inclusive) and adults (18 to 22 years old, inclusive). A sufficient number of subjects will be enrolled to ensure that at least 30 evaluable subjects complete 12 weeks of treatment.

Subjects will be randomly assigned in a 1:1:1 ratio to 1 of 3 treatment groups (5 mg QD, 5 mg BID, and 5 mg TID), stratified by age group (adolescent/adult) to achieve balance among treatment arms. All subjects will take study drug TID (morning, afternoon, and evening), OV101 in the morning and OV101 or placebo in the afternoon and evening throughout the treatment period (including Baseline). There will not be any dose adjustments permitted during the study.

After random assignment at Baseline, subjects will receive the assigned package of blinded study treatment according to the treatment code for the first 6 weeks of treatment and will take their first dose of study drug at the clinic. They will receive another assigned package of study treatment at the Week 6 clinic visit.

Subjects (assisted by LAR/caregivers) will complete paper sleep diaries and wear actigraphs over the 7-day periods immediately preceding Baseline and the Week 2, Week 6, EOT, and EOS clinic visits. The Baseline, Week 2, Week 6, and EOT visits will be full-day clinic visits. Safety information will be collected during phone calls at the end of Weeks 1, 4, 8, and 10 (on Days 8, 29, 57, and 71, respectively), in addition to during every clinic visit (screening, Day 1, Week 2, Week 6, EOT, and EOS). At the investigator's discretion, subjects may be evaluated at unscheduled clinic visits for reasons related to subject safety. At unscheduled visits, subjects will be queried about AEs, changes in concomitant medications, and

suicidality, and safety laboratory assessments may be conducted. Periodic interim blinded review of safety data will be performed as part of routine pharmacovigilance activities.

Estimated Study Duration:

After informed consent is obtained, screening assessments will be conducted within the 3 weeks preceding Baseline, followed immediately by treatment for 12 weeks and a 4- to 6-week follow-up period, for a maximum duration of individual subject participation of 21 weeks.

Efficacy Assessments:

Efficacy assessments will include the Aberrant Behavior Checklist–Community; the Anxiety, Depression, and Mood Scales; the Repetitive Behavior Scale–Revised; the Conners3rd Edition; the Short Sensory Profile–2; the Pediatric Sleep Clinical Global Impressions (Severity and Improvement) scales; Children's Sleep Habits Questionnaire; a 7-day sleep diary; the Behavior Assessment System for Children, 3rd Edition Parenting Relationship Questionnaire; Parent Global Impressions (Severity and Improvement) scales; the Pediatric Quality of Life Inventory; a top 3 concerns visual analog scale; the Vineland Adaptive Behavior Scale–3rd Edition; Clinical Global Impressions (Severity and Improvement) scales; 7-day actigraphy; a computerized measurement of cognition using the Test of Attentional Performance for Children; the Repeatable Battery for the Assessment of Neuropsychological Status; [redacted]

[redacted]

Safety Assessments:

All subjects who receive study drug will be evaluated for study drug safety and tolerability. Assessments will include: frequency and severity of treatment-emergent adverse events (TEAEs) and serious adverse events (including TEAEs leading to discontinuation), standardized clinical assessment of suicidality, clinical laboratory evaluations, and vital sign measurements.

Study Drug, Dosage, and Route of Administration:

Subjects will be assigned to receive 1 of 3 daily doses of OV101: 5 mg/day, 10 mg/day, or 15 mg/day. Subjects will take all doses orally (assisted by an LAR/caregiver, if necessary), TID (morning, afternoon, evening) at approximately the same times each day, for the duration of the 12-week treatment period.

OV101 Treatment Group	Morning Dose	Afternoon Dose	Evening Dose
5 mg/day	5-mg OV101 capsule	Placebo capsule	Placebo capsule
10 mg/day	5-mg OV101 capsule	Placebo capsule	5-mg OV101 capsule
15 mg/day	5-mg OV101 capsule	5-mg OV101 capsule	5-mg OV101 capsule

The morning and afternoon doses should be taken with food, and the afternoon dose should be taken at least 6 hours after the morning dose. The evening dose should be taken 30 minutes before bedtime. Capsules may be opened and the contents sprinkled onto 1 teaspoon of low-fat semi-liquid food (eg, 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 specifically how each capsule was taken (eg, swallowed whole or taken in 1 teaspoon of food).

Placebo capsules will be identical in appearance to the capsules containing OV101 and have the same excipient ingredients but will not contain OV101. Study drug will be supplied as 5-mg capsules of OV101 and matching placebo capsules in bottles. Bottles will have "Morning," "Afternoon," or "Evening" printed on their labels. Each LAR/caregiver will receive a 6-week supply of capsules in a package containing 1 "Morning" bottle, 1 "Afternoon" bottle, and 1 "Evening" bottle at the baseline (Day 1) visit and at the Week 6 visit.

Sample Size:

A sufficient number of subjects (36 estimated) will be enrolled to ensure that 30 evaluable subjects complete 12 weeks of treatment. Subjects will be randomly assigned to the 3 OV101 total daily dosing regimens in a 1:1:1 ratio.

The main emphasis in reporting the data will be on descriptive statistics and estimation with 95% CIs. For the objective of estimating the overall subject incidence of TEAEs (for the 3 OV101 total daily dose arms combined), a true incidence of 20% would be estimated with a 13.9% precision (half-width of the 2-sided 95% CI assuming N = 30).

Analysis Sets:

The randomized analysis set will be used for summaries of subject disposition, demographics, and other baseline characteristics. The safety analysis set (all subjects who receive at least 1 dose of study drug) will be used for the analysis of all safety parameters, analyzed according to treatment received. The full analysis set (all subjects who receive at least 1 dose of study drug and have at least 1 postbaseline efficacy evaluation) will be used for analysis of all efficacy parameters, analyzed according to randomized treatment. The modified full analysis set may be used for exploratory modelling of selected efficacy variables, in addition to the full analysis set.

Statistical Methods:

Descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum) will be presented for continuous variables and their changes from baseline. In addition, 95% CIs for the mean change from baseline will be provided for continuous variables. Graphical displays will be utilized to investigate trends over time and dose and the relationship between

certain variables and differences between age groups.

Ordinal variables with sufficient numerical categories (eg, 7-point scales of Parent Global Impressions-Severity and Clinical Global Impressions-Severity) and subscale total scores from questionnaires will be treated as continuous variables.

Categorical (not treated as continuous) endpoints (including adverse event incidence and binary endpoints) will be summarized by frequency and percentage. Frequencies and percentages will be presented for the shifts in these categories (eg, low to normal, low to high, high to low) from baseline to each post-treatment assessment time point for scales with categorical variables. If there are missing values, the number missing will be presented (as a category), but without a percentage. All data collected will be included in by-subject data listings.

All adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and will be classified by MedDRA system organ class (SOC) and preferred term (PT). The number and percentage of subjects who experience at least1 TEAE and the number and percentage of subjects who experience at least 1 TEAE within each specific SOC and PT will be presented by daily dosing regimen and overall. The number of TEAEs (event incidence) will also be summarized within each SOC and PT. The Wilson 95% CIs will be displayed for the proportion of subjects experiencing TEAEs as a total across the 3 dosing regimens.

Descriptive statistics for efficacy variables at each time point will be displayed by daily dosing regimen and overall. Post-hoc exploratory modelling may be conducted on selected variables using the full analysis set (and modified full analysis set, as required).

[redacted]

Version and Date of Protocol:

Version 1.2, 27 March 2019

List of Abbreviations

Abbreviation	Definition
ABC-C	Aberrant Behavior Checklist-Community
ADAMS	Anxiety, Depression, and Mood Scales
AE	adverse event
AS	Angelman syndrome
BASC-3 PRQ	Behavior Assessment System for Children, 3rd Edition, Parenting Relationship Questionnaire
BID	twice a day
CFR	Code of Federal Regulations
CGG	cytosine-guanine-guanine
CGI	Clinical Global Impressions
CGI-I	Clinical Global Impressions-Improvement
CGI-S	Clinical Global Impressions-Severity
Conners 3	Conners 3rd Edition
CSHQ	Children's Sleep Habits Questionnaire
CSR	clinical study report
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
eCRF	electronic case report form
EDC	electronic data capture
[redacted]	[redacted]
EOS	end of study
EOT	end of treatment
[redacted]	[redacted]
FAS	full-analysis set
FDA	US Food and Drug Administration
FMRP	fragile X mental retardation protein
FXS	fragile X syndrome
GABA	gamma-aminobutyric acid
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Council for Harmonisation
IQ	intelligence quotient

Abbreviation	Definition
IRB	institutional review board
IWRS	interactive web response system
KABC	Kaufman Assessment Battery for Children
KiTAP	Test of Attentional Performance for Children
KO	Knockout
LAR	legally acceptable representative
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified full-analysis set
MMRM	Mixed Model with Repeated Measures
PD	pharmacodynamic(s)
PedsQL	Pediatric Quality of Life Inventory
PGI-I	Parent Global Impressions-Improvement
PGI-S	Parent Global Impressions-Severity
[redacted]	[redacted]
PT	preferred term
QD	once a day
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RBS-R	Repetitive Behavior Scale-Revised
SAE	serious adverse event
SB-5	Stanford-Binet-5
SOC	system organ class
SOL	sleep onset latency
TEAE	treatment-emergent adverse event
TID	3 times a day
TST	total sleep time
VABS-3	Vineland Adaptive Behavior Scale, 3rd Edition
WASO	wake time after sleep onset
WISC	Wechsler Intelligence Scale for Children
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

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, such as Angelman syndrome (AS) and Fragile X syndrome (FXS). Gaboxadol was initially developed for the treatment of insomnia by H. Lundbeck A/S and Merck, but its development was discontinued in 2007 for clinical and commercial reasons. Extensive nonclinical and clinical data were generated during the initial stages of development by Lundbeck/Merck, including data from exposure to gaboxadol in more than 4300 adult subjects with insomnia and approximately 500 adult subjects in non–insomnia-related studies. Details of the Lundbeck/Merck program, including both the nonclinical program and the clinical program, are found in the investigator's brochure (Ovid Therapeutics Inc. 2017). Unless otherwise indicated, the source for the information in this introduction is the investigator's brochure.

1.1 Background on Fragile X Syndrome (FXS)

Fragile X syndrome is the most common inherited form of intellectual disability, with a prevalence of 1 in 4000 males and 1 in 8000 females (Crawford et al 2001). It is also the most common known genetic cause of autism; approximately 25% to 30% of individuals with FXS meet the full diagnostic criteria for autism, and approximately 5% of children with autism carry the fragile X mutation (Hall et al 2008; Harris et al 2008). Males with FXS have moderate to severe intellectual disability, and females with FXS range from normal to moderate impairment (Hagerman et al 2010).

The primary molecular basis underlying FXS is a reduced expression level or lack of fragile X mental retardation protein (FMRP). Reduced or absent FMRP is most commonly caused by an increased number of trinucleotide cytosine-guanine-guanine (CGG) repeats in the 5' untranslated region of *FMR1* on the X chromosome. The increased number of CGG repeats results in hypermethylation of DNA regions where a cytosine nucleotide is followed by a guanine nucleotide, which ultimately prevents transcription and leads to either partial or full silencing of gene expression. The full mutation, defined as over 200 CGG repeats that result in the absence of FMRP, is responsible for the symptoms of FXS. In contrast to the full mutation, the premutation (defined as 55 to 200 CGG repeats) leads to enhanced production of *FMR1* messenger RNA (mRNA; 2 to 8 times the normal levels) (Kenneson et al 2001). Enhanced mRNA production can lead to clinical features in premutation carriers that do not

occur in individuals with full mutation FXS, including fragile X–associated primary ovarian insufficiency and fragile X−associated tremor/ataxia syndrome (Tassone et al 2000).

Understanding the effects of the fragile X mutation on brain development and function has been facilitated by genetically engineered animal models that recapitulate the human phenotype of FXS. The best established animal model is the *Fmr1* knockout (KO) mouse (Bakker et al 1994). An RNA-binding protein, FMRP modulates the dendritic localization and translation of several hundred mRNA ligands (Fernández et al 2013). In the *FMR1* KO mouse, the absence of FMRP leads to excessive protein synthesis downstream of signaling pathways coupled to group I metabotropic glutamate receptors (mGluRs), in particular mGluR5. Inhibition of mGluR5 and downstream signaling has been shown to correct a wide array of disease phenotypes in animal models of FXS (Bhakar et al 2012). Glutamatergic transmission is under tight regulation by gamma-aminobutyric acid (GABA)-ergic inhibition, and deficiencies in GABA-mediated inhibitory neurotransmission have been identified in the hippocampus, striatum, somatosensory cortex, and amygdala of *Fmr1* KO mice (D'Hulst and Kooy 2007). The most consistent neurochemical change in the *Fmr1* KO mouse is impaired GABAergic neurotransmission, and this dysfunction has been implicated in many of the symptoms of FXS, including anxiety, autism-like behavior, epilepsy, and cognitive impairment. Specifically, GABAergic tonic inhibition is believed to underlie many of these symptoms and may, therefore, be an effective novel target for therapeutic treatment of FXS (Gantois et al 2006; Olmos-Serrano et al 2010; Martin et al 2014). Use of GABA agonists has been suggested as a therapeutic strategy for FXS (Olmos-Serrano et al 2010; Braat and Kooy 2015).

1.2 Clinical Manifestation of FXS

Individuals with FXS are at increased risk for a range of behavioral problems that may limit their academic performance, adaptive function, daily living skills, and social interactions. Anxiety is the most common behavioral problem in individuals with FXS, with specific symptoms of shyness, social anxiety, hyperarousal, and stereotypic behavior such as hand flapping and hand biting. Aggressive behaviors in male individuals with FXS are also common and may lead to injuries to caregivers, peers, or friends (Wheeler et al 2016). Attention-deficit/hyperactivity disorder symptoms (overarousal, hyperactivity, distractibility, and impulsivity) may also be noted. Individuals with FXS can experience problems in one or

more of these behavior domains. There is a wide range of variability in symptoms, although they tend to be more severe in males than in females (Hagerman 2002).

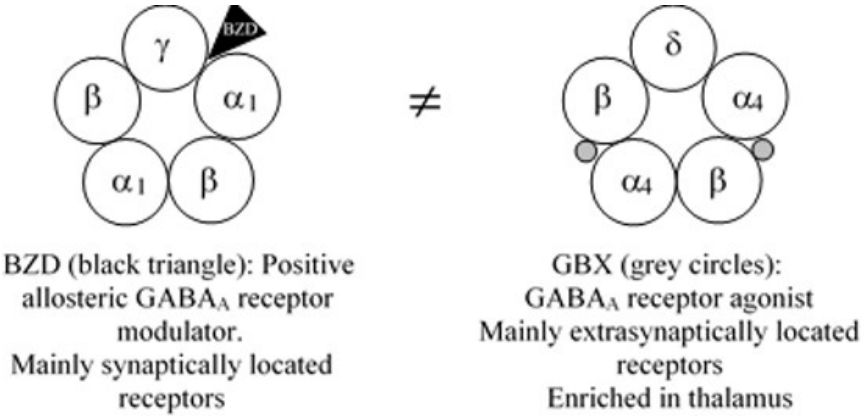
Disordered sleep is a phenotype noted in animal models of FXS, and parents typically report sleep problems for their children with FXS (Zhang et al 2008). Studies have estimated that 31% to 77% of individuals with FXS have sleep problems (Kronk et al 2010). Children with FXS typically experience shorter sleep duration, more difficulties settling into sleep, and increased wake time after sleep onset (WASO) than unaffected children (Gould et al 2000; Richdale 2003).

Current behavior therapy treatments include speech therapy, physical therapy, occupational therapy, and educational resources. Current treatments with medications target only the behavioral phenotypes and not the underlying brain deficits (Hagerman et al 2009).

1.3 Background on OV101

OV101 (gaboxadol) or 4,5,6,7-tetrahydroisoxazolo-[5,4-c]pyridin-3-ol (THIP) was synthesized in the late 1970s and has since been used in nonclinical studies as a $GABA_A$ receptor agonist. More than 1000 publications and reports, including several clinical studies in scientific journals, are available. OV101 is the first highly selective, extrasynaptic GABA receptor agonist that binds as an orthosteric agonist to the α4- and δ-containing subunit of extrasynaptic GABA receptors (Figure 1–1).

Figure 1–1 Main Sites of Action of OV101, Benzodiazepine, and Novel Benzodiazepine-Like Compounds



Abbreviations: BZD, benzodiazepine and benzodiazepine-like compounds; GABA, gamma-aminobutyric acid; GBX, OV101 (gaboxadol).

The affinity of OV101 is 1 to 3 orders of magnitude greater for extrasynaptic receptors containing the δ subunit than for the αβγ-containing $GABA_A$ receptors that are mainly located within the synaptic junction and are the site of the highest modulatory effects of most benzodiazepines and benzodiazepine-like compounds (eg, zolpidem). In vitro binding studies have shown that gaboxadol binds selectively to the extrasynaptic α4δ-containing $GABA_A$ receptor subpopulation and possesses no significant affinities for other target receptors in the central and peripheral nervous system. Conversely, the presence of α_4 or δ subunits in the GABA receptor confers insensitivity to benzodiazepines. The mechanism of action of OV101 is unique among GABAergic agents, including benzodiazepines, zolpidem and other zolpidem-like drugs, neurosteroids, and drugs that act on GABA metabolism or uptake.
In vivo and in vitro studies have shown that neither benzodiazepines nor alcohol potentiate the activity of OV101, and in contrast to benzodiazepine receptor agonists, no withdrawal effects were observed in animals after chronic dosing with OV101. In drug discrimination studies, rats and baboons trained to respond to benzodiazepines did not respond to OV101. Furthermore, OV101 did not show abuse potential in baboons trained to self-inject cocaine.

[redacted]

1.4 Clinical Experience with OV101

OV101 was generally safe and well tolerated in all Phase 2 and 3 studies that included more than 4300 subjects with insomnia (aged 18 to 64 years) who were administered doses up to 15 mg (20 mg in one early Phase 2 study). In adult subjects, the most common adverse events (AEs) that occurred more frequently in OV101-treated subjects than in subjects on placebo were dizziness, nausea, vomiting, somnolence, and headache. Most AEs were of mild to moderate intensity. Generally, tolerability was better in male subjects than in female subjects, most likely due to the lower body weight of females.

OV101 administration in the morning was safe at all doses (Study 99096). In healthy young men, doses up to 20 mg were well tolerated when given alone as single morning doses for 5 days. In young women, a 15 mg morning dose was not well tolerated or was tolerated with considerable discomfort from Day 2 onwards. An evening dose of 15 mg was well tolerated in young women and women above 55 years for 3 consecutive days. The AEs with the highest incidences in this study were dizziness, nausea, headache, and somnolence. The majority of AEs had a rapid onset (within 1 to 2 hours postdose) and resolved after the drug was discontinued.

Safety data from Study 11336 showed that 30 mg and 45 mg OV101 in women and 45 mg OV101 in men was not tolerated based on their history of hypnotic/sedative abuse or other drug abuse. This is contrary to previous experience with the same doses in healthy volunteers. These findings suggest that a history of hypnotic/sedative abuse or other drug abuse decreases the tolerability of supratherapeutic doses of gaboxadol. Adverse events that were associated with lack of tolerability included psychiatric events such as agitation, dissociation, hallucinations, disorientation, and anxiety.

Approximately 500 subjects were exposed to OV101 in clinical studies in non−insomnia-related development. The safety and tolerability profile of OV101 in the non−insomnia-related studies was similar to that in sleep disorder studies. In general, the AEs were dose related, with no AEs reported at the 5-mg dose and only mild AEs reported for the 10-mg dose of OV101.

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 (Roth et al 2010).

Currently, OV101 is being investigated by Ovid for AS and FXS. Results from Study OV101-16-001 indicated that a 5-mg dose administered in the morning was well tolerated in subjects 13 to 17 years of age with either FXS or AS. One subject experienced 2 nonserious AEs (flushing, considered to be related to study drug, and injection site bruising, considered to be unrelated to study drug) that were mild in intensity.

OV101 has been studied in a 12-week Phase 2 safety and efficacy study in 88 subjects (adults and adolescents aged 13 to 49 years) with AS. Fifty-eight subjects were treated with OV101 either once-daily (15 mg at bedtime) or twice-daily (10 mg in the morning, 15 mg at bedtime), and 29 patients were treated with placebo. Treatment discontinuations due to AEs were low (placebo, 1; OV101 once-daily, 0; OV101 twice-daily, 3). The most frequent AEs across all treatment groups were vomiting, somnolence, irritability, aggression, pyrexia, and upper respiratory infection. The AEs associated with OV101 treatment were similar to placebo treatment, with the majority of AEs being mild. Events occurring in >5% (2 or more patients) compared to placebo in either treatment arm included pyrexia, rash, seizure, enuresis, and myoclonic epilepsy. Two subjects had a SAE of seizure, both of whom had a previous history of seizures: 1 subject in the once-daily dose group, deemed unrelated to study drug, and treatment was continued; 1 subject in the twice-daily dose group, deemed as possibly related to study drug, and treatment was discontinued. Please see the investigator brochure for additional information on the study in AS and the benefit risk profile.

[redacted]

[redacted]

1.6 Study Rationale and the Role of GABA in FXS

There is a high unmet medical need for effective therapies targeting the behavior deficits in FXS. Current approaches to psychopharmacological treatment (eg, stimulants, mood stabilizers, and anxiolytics) for FXS are symptom targeted to manage difficult behaviors without regard to the underlying pathophysiology. There is currently no drug approved for the treatment of FXS.

The use of OV101 for treatment of individuals with FXS is based on studies in a relevant mouse model of the disease, the *Fmr1* KO mouse, which lacks FMRP due to a disruption in its *FMR1* gene. *Fmr1* KO mice have decreased GABA synthesis, decreased presynaptic GABA release, and decreased extrasynaptic levels of GABA, resulting in decreased tonic inhibition. OV101 was shown to restore tonic inhibition in the amygdala, reduce sensory hypersensitivity and motor hyperactivity, and improve pre-pulse inhibition (signal to noise ratio) in *Fmr1* KO mice (Olmos-Serrano et al 2010; Olmos-Serrano et al 2011; Martin et al 2014). Cogram et al recently presented data that showed full normalization of abnormal repetitive, social, and anxiety-like behaviors with OV101 in another FXS KO mouse model, the *Fmr1* KO2 mouse (Cogram et al 2017). Taken together, these data support the potential of OV101 to treat the core behavioral deficits noted in individuals with FXS. Importantly, the ability of OV101 to potentiate tonic inhibition is unlike any other GABAergic agent, including benzodiazepines, zolpidem, other zolpidem-like drugs, neurosteroids, and drugs that act on GABA metabolism or uptake.

In addition to these data on presynaptic dysfunction, additional studies support the potential of OV101 in FXS. Chronic treatment in mice resulted in both an increase in hippocampal neurogenesis and improved performance in several cognitive tasks (Whissell et al 2013). Moreover, OV101 has shown anticonvulsant/anti-epileptic activity in several animal models (Kristensen et al 2003; Sun et al 2013; Medrihan et al 2015).

This study will enroll only male subjects with FXS. FXS is more common in males, and males are more severely affected than females (likely because females have an additional X chromosome). Thus, the FXS phenotype in male subjects is expected to be more homogeneous than in female subjects, thus leading to a more homogeneous treatment response in this early Phase 2 study than would be likely if both male and female subjects were enrolled.

The purpose of this study is to investigate the safety, tolerability, and exploratory efficacy of treatment by oral administration of OV101 at doses of 5 mg/day (5 mg once a day [QD]), 10 mg/day (5 mg twice a day [BID]), or 15 mg/day (5 mg three times a day [TID]) in adolescent and adult male subjects with FXS. The 12-week, randomized, double-blind, parallel-group, proof-of-concept study design will inform OV101 clinical development and the design of future studies in FXS.

2 Study Objectives

2.1 Primary Objectives

- To evaluate the safety and tolerability of OV101 over 12 weeks of treatment across different daily dosing regimens in adolescent and adult male subjects with FXS

2.2 Secondary Objectives

- To evaluate changes in behavior during 12 weeks of treatment with OV101 across different daily dosing regimens in adolescent and adult male subjects with FXS

2.3 Exploratory Objectives

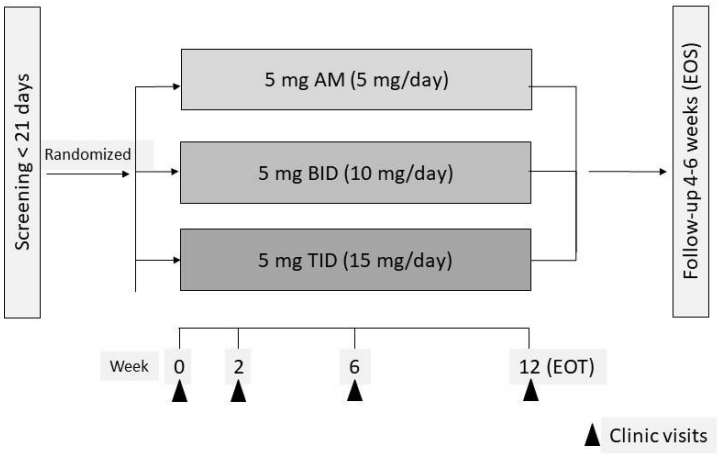
- To evaluate changes in sleep, adaptive functioning, and quality of life across different daily dosing regimens of OV101 treatment over 12 weeks in adolescent and adult male subjects with FXS
- [redacted]
- To explore the relationships among study endpoints (eg, behavior, sleep), where appropriate
- [redacted]

3 Investigational Plan

3.1 Study Design

This is a Phase 2a, randomized, double-blind, parallel-group study to evaluate the safety, tolerability, and efficacy of OV101 at 3 daily doses: 5 mg/day (5 mg QD), 10 mg/day (5 mg BID), and 15 mg/day (5 mg TID) in adolescent and adult male subjects with FXS. Subjects with a clinically and molecularly confirmed diagnosis of FXS will be eligible for inclusion in the study (Section 4.1). The study will comprise a screening period of at least 1 week (to allow for actigraphs) and up to 3 weeks; a baseline visit on Day 1 for treatment randomization (enrollment), baseline assessments, and first dose of study drug; clinic visits for safety and efficacy assessments over a 12-week treatment period, including clinic visits at Week 2, Week 6, and Week 12 (end-of-treatment [EOT]); and an end-of-study (EOS) follow-up visit occurring any time between the ends of Week 16 and Week 18 (Figure 3–1). The schedule of activities for this study is fully presented in Table 6-1.

Figure 3–1 Study Schematic



Abbreviations: AM, morning dose only; BID, twice a day; EOS, end of study; EOT, end of treatment; TID, 3 times a day.

For each subject, after informed consent is obtained (Section 9.3), screening assessments will be completed within the 3 weeks preceding Baseline. At Baseline, subjects 13 to 22 years old (inclusive) who meet all eligibility criteria (Section 4.1) will be enrolled on Day 1 in a 1:1 target ratio between adolescents (13 to17 years old, inclusive) and adults (18 to 22 years old, inclusive). A sufficient number of subjects will be enrolled to ensure that at least 30 evaluable subjects complete 12 weeks of treatment.

Subjects will be randomly assigned in a 1:1:1 ratio to 1 of 3 treatment groups (5 mg QD, 5 mg BID, and 5 mg TID), stratified by age group (adolescent/adult) to achieve balance among treatment arms. There is no placebo group in this study. All subjects will take study drug TID (morning, afternoon, and evening), OV101 in the morning and OV101 or placebo in the afternoon and evening throughout the treatment period (including Baseline), as described in Section 5.2 and Section 5.4.1. There will not be any dose adjustments permitted during the study.

After random assignment at Baseline, subjects will receive the assigned package of blinded study treatment according to the treatment code for the first 6 weeks of treatment and will take their first dose of study drug at the clinic. They will receive another assigned package of study treatment at the Week 6 clinic visit.

Each subject (assisted by a legally acceptable representative [LAR]/caregiver) will complete paper sleep diaries and wear actigraphs over the 7-day periods immediately preceding Baseline and the Week 2, Week 6, EOT, and EOS clinic visits. The Baseline, Week 2, Week 6, and EOT visits will be full-day clinic visits.

For each subject, after informed consent is obtained, the maximum duration of individual subject participation will be 21 weeks. A subject will have completed the study when he completes the EOS visit. The end of the study is defined as the date when the last subject completes his last visit (includes follow-up visit).

Safety information will be collected during phone calls at the end of Weeks 1, 4, 8, and 10 (on Days 8, 29, 57, and 71, respectively), in addition to during every clinic visit (screening, baseline, Week 2, Week 6, EOT, and EOS). At the investigator’s discretion, subjects may be evaluated at unscheduled clinic visits for reasons related to subject safety. At unscheduled visits, subjects will be queried about AEs, changes in concomitant medications, and suicidality, and safety laboratory assessments may be conducted. Periodic interim blinded

review of safety data will be performed as part of routine pharmacovigilance activities. No interim statistical analysis is planned.

Activities during each period of the study are described by study visit in Section 6.1 and are presented in greater detail in the workbooks for caregiver/clinician/subject assessments.

3.1.1 Rationale of Dose Selection

The total daily doses to be administered in the present study range from 5 mg/day to 15 mg/day, which are within the dose range previously found to be well tolerated in adult subjects. [redacted] Therefore, OV101 exposure in the present study in adolescent male subjects is expected to be comparable to the exposure range previously studied across the Phase 1, 2, and 3 studies that evaluated OV101 in adult subjects with insomnia.

Daily doses of 5 mg/day, 10 mg/day, and 15 mg/day will be evaluated with 3 dosing regimens: OV101 5 mg QD (morning), BID, and TID. [redacted]

After the last dose of study drug during the treatment period (at the EOT clinic visit) there will be no tapering of OV101 dosing, as no withdrawal effects have been observed in previous clinical studies.

4 Subject Selection and Withdrawal Criteria

4.1 Selection of Study Population

Subjects will be enrolled at approximately 8 sites in the United States and approximately 1 site in Israel, with a goal of having 30 subjects complete 12 weeks of treatment. Subjects will be assigned to study treatment only if they meet all of the 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, 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 of the following criteria to be enrolled in this study.

1. Is male and 13 to 22 years old (inclusive) at the time of informed consent.
2. Has a diagnosis of FXS with a confirmed *FMR1* full mutation (≥200 CGG repeats). The diagnosis must be confirmed by genetic testing prior to subject randomization.
3. Has a Clinical Global Impression-Severity (CGI-S) score of 4 (moderately ill) or greater at screening.
4. Is currently being treated with no more than 3 anti-epileptic and/or psychoactive medications, including those prescribed off-label to address behavioral conditions. Any concomitant medication, including anti-epileptic and/or behavioral medications, supplements, and special diets, must be at a stable dose for at least 4 weeks before screening and must be maintained at that dose throughout the duration of the study.
5. Has an LAR/caregiver capable of providing informed consent and able to attend all scheduled study visits, oversee the administration of study drug, and provide feedback regarding the subject's behavior and other symptoms as described in the protocol.
6. Provide assent to the protocol (to the extent possible and in accordance with local institutional review board [IRB] and regulatory requirements) and have an LAR/caregiver who will provide written informed consent. Subjects providing assent must do so at the same visit as LAR/caregiver written informed consent is provided.

7. Is able to attend all scheduled study visits and willing and capable of performing the required study assessments.
8. Is able to ingest the study drug capsules (including sprinkling capsule contents onto 1 spoon of applesauce or low-fat yogurt).
9. Has an intelligence quotient (IQ) less than 75 as measured by the Stanford-Binet-5 (SB-5) at screening or a previously documented SB-5 measurement conducted within 6 months of the screening visit. For the site in Israel, please see Appendix for site-specific details regarding the IQ test.
10. Will agree to remain sexually abstinent from the first day of screening until 30 days after the last dose of study treatment.
11. Has LAR/caregivers who will agree not to post any of the subject's personal medical data related to the study or information related to the study on any website or social media site (eg, Facebook and Twitter) until they have been notified that the study is completed.

4.1.2 Exclusion Criteria

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

1. Has a concomitant disease (eg, gastrointestinal, renal, hepatic, endocrine, respiratory, or cardiovascular system disease) or 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 this study.
2. Has clinically significant lab abnormalities or vital signs at the time of screening (eg, alanine aminotransferase or aspartate aminotransferase >2.5 × upper limit of normal; total bilirubin or creatinine >1.5 × upper limit of normal). Re-testing of safety labs may be allowed after consultation with the medical monitor or designee.
3. Uses any GABAergic agent (eg, acamprosate, baclofen, vigabatrin, tiagabine, riluzole, benzodiazepines, and gabapentin) on a regular schedule. Benzodiazepines administered for situational anxiety (eg, for occasional procedures or events) are permitted.
4. Uses any cannabinoid derivatives.

5. Has a history of uncontrollable seizure disorder or seizure episodes within 6 months of screening or change in the anticonvulsant pharmacotherapy in the past 3 months.
6. Has a history of suicidal behavior or considered by the investigator to be at high risk of suicide.
7. Has any condition or there is any reason that, in the opinion of the investigator, makes the subject unsuitable for enrollment.
8. Is unable or does not have an LAR/caregiver able to comply with study requirements.
9. Has enrolled in any clinical trial or used any investigational agent, device, and/or investigational procedure within the 30 days before screening or does so concurrently with this study.
10. Is a family member of the investigator or study site personnel.

4.2 Discontinuation of Subjects From Study Treatment and the Study

Discontinuation of a subject from treatment early (before Week 12) for any reason will initiate procedures for discontinuation of the subject from the study, including EOT and EOS visits (Section 3.1). For subjects for whom study treatment is stopped early (before Week 12), an EOT visit should be conducted within 2 weeks after the last day of study medication. After completing the EOT visit, an EOS visit should be completed within 4 to 6 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 visit.

4.2.1 Reasons for Withdrawal/Discontinuation

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

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 serious AE (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 30 evaluable subjects complete 12 weeks of treatment.

Subjects who fail to satisfy all inclusion and exclusion criteria at screening may be rescreened 1 additional time at the discretion of the medical monitor or his designee.

5 Study Treatments

5.1 Method of Assigning Subjects to Treatment Groups

Subjects who meet all eligibility criteria will be randomly assigned at Baseline to the 5 mg/day, 10 mg/day, or 15 mg/day OV101 treatment group in a 1:1:1 allocation ratio. It is anticipated that approximately 36 male subjects will be enrolled (to obtain 30 evaluable subjects), while maintaining a 1:1 target ratio between adolescents (13 to17 years old, inclusive) and adults (18 to 22 years old, inclusive). The randomization schedule will be stratified by age (13 to 17, inclusive; 18 to 22, inclusive). It will also use an appropriate block size, which will not be revealed.

An interactive web response system (IWRS) will be used to administer the randomization schedule. [redacted] 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 Treatments Administered

Subjects will take all doses orally (assisted by an LAR/caregiver, if necessary) TID (morning, afternoon, evening), at approximately the same times each day, for the duration of the 12-week treatment period. The morning and afternoon doses should be taken with light low-fat food (a glass of low-fat milk would qualify as food), and the afternoon dose should be taken at least 6 hours after the morning dose. The evening dose should be taken 30 minutes before bedtime. Capsules may be opened and the contents sprinkled onto 1 teaspoon of low-fat semiliquid food (eg, 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 specifically how each capsule was taken (eg, swallowed whole or taken in 1 teaspoon of semiliquid food).

5.3 Description of Study Drug

OV101 is formulated as the monohydrate form (4,5,6,7-tetrahydro-isoxazolo[5,4-c]-pyridin-3-ol, monohydrate) in a white size 2 capsule. The capsule contains 5.645 mg of OV101 monohydrate, which corresponds to 5.0 mg of OV101 (Table 5-1).

[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.

[redacted] will manufacture the OV101 and placebo capsules.

5.4 Management of Clinical Supplies

Bulk capsules, both active and placebo, will be shipped to [redacted] will package and label blinded kits. [redacted] will ship the blinded kits directly to each study site according to instructions from the IWRS.

5.4.1 Study Drug Packaging and Storage

Study drug will be supplied as 5-mg capsules of OV101 and matching placebo capsules in bottles. Bottles will have "Morning," "Afternoon," or "Evening" printed on their labels, which will be tinted specific colors for the morning, afternoon, and evening doses. Each LAR/caregiver will receive a 6-week supply of capsules in a package containing 1 "Morning" bottle, 1 "Afternoon" bottle, and 1 "Evening" bottle at the baseline visit and at the Week 6 visit.

Study drug will be packaged to enable administration for each treatment group regimen (Table 5-2).

Table 5-2 Treatment Group Regimens

Treatment Group	Morning Dose	Afternoon Dose	Evening Dose
5 mg/day OV101	5-mg OV101 capsule	Placebo capsule	Placebo capsule
10 mg/day OV101	5-mg OV101 capsule	Placebo capsule	5-mg OV101 capsule
15 mg/day OV101	5-mg OV101 capsule	5-mg OV101 capsule	5-mg OV101 capsule

A clinical label will be affixed to the outside of each bottle and each package of 3 bottles. The label will specify the sponsor name (Ovid Therapeutics Inc.); subject number; protocol number; bottle number (based on randomization); number of capsules (each bottle); "Morning," "Afternoon," or "Evening"; and "Take as directed." Bottles and study treatment will be distributed by unique subject numbers and bottle numbers as designated by the IWRS, and bottle quantities will be supplied to each study center in accordance with the IWRS. The recommended storage conditions and expiry date (where required) will be stated on the product label. At the study site, study drug must be stored in a secure area (eg, a locked cabinet), protected from moisture, and kept at a controlled room temperature, 59°F to 77°F.

Subjects and LAR/caregivers must keep all study drugs in the original bottles.

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.

5.4.3 Other Supplies

Actigraphs [redacted] Section 6.3.3.1) will be supplied to study sites by [redacted] will be responsible for device maintenance during the study and device retrieval at the end of the study.

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 associated with a SAE must be promptly reported to the [redacted] (Section 6.6.1.5). Overdoses without signs or symptoms do not need to be recorded as AEs; any AEs associated with the overdose should be reported on the relevant AE/SAE sections in the eCRF.

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 each clinic visit 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

The most likely symptomatic medication error will be overdose (Section 5.5.1).

5.6 Blinding

The study will be performed in a double-blind manner, 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.

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. In the event that the blind needs to be broken because of a medical emergency, 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 the IWRS. 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.

5.7 Treatment Compliance

Subject compliance will be determined by comparing the capsule counts of returned study drug bottles at Week 6 and EOT to the capsule count of study drug dispensed. The number of capsules remaining will be tracked and recorded by individual bottle (labeled "Morning," "Afternoon," or "Evening"). The LAR/caregiver will be questioned as to the reason(s) why remaining capsules have not been administered (eg, forgot, subject refused, subject had side effects so parent decided to give a drug holiday), and the approximate date and time of any missed doses will 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 (eg, speech therapy, physical therapy, occupational therapy) for 4 weeks before screening and should remain on the stable regimens until after the EOS visit. Additionally, unless required to treat AEs, there should be no new medications or changes to concomitant medications, 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 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 (eg, acamprosate, baclofen, vigabatrin, tiagabine, riluzole, benzodiazepines, 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.

Use of cannabinoid derivatives is prohibited during the course of the study.

Use of other investigational agents is prohibited during the course of the study.

5.8.2 Restrictions

Any concomitant medication, including anti-epileptic and/or behavioral medications, supplements, and special diets, must be at a stable dose for at least 4 weeks before screening and must be maintained throughout the duration of the study.

Each subject may be treated concurrently with no more than 3 anti-epileptic and/or psychoactive medications, including those prescribed off-label to address behavioral conditions.

Benzodiazepines administered for situational anxiety (eg, for occasional procedures or events) are permitted. Subjects should not consume alcohol during the course of the study.

6 Study Assessments and Procedures

The schedule of activities by clinic visit for this study is presented in Table 6-1. Detailed instructions for the conduct of study assessments and procedures will be provided in the workbooks for caregiver/clinician/subject assessments.

Table 6-1 Schedule of Activities by Clinic Visit

Visit Name	Screening	Baseline	Phone 1	Week 2	Phone 4	Week 6	Phone 8	Phone 10	EOT	EOS
Window (days)	–[a]	–	±2	±3	±2	±3	±2	±2	±3	+14
Day[b]	–21 to 1	1	8	15	29	43	57	71	85	113
Week	–	0	1	2	4	6	8	10	12	16[c]
Obtain informed consent and assent	X									
Verify inclusion/exclusion criteria	X	X								
Obtain medical history	X	X[d]								
Conduct clinical assessment[e] for FXS	X									
Stanford-Binet-5 or previous SB-5 documentation[f]	X									
Review for DSM-5 autism spectrum disorder criteria	X									
Molecular FXS Test[g]	X									
[redacted]		X		X		X			X	
[redacted]		X				X			X	
Clinical assessment of suicidality	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X[d]		X		X			X	X
Vital signs	X	X		X		X			X	X
Clinical laboratory tests	X	X[d]		X		X			X	
Randomization assignment		X								
Adverse event inquiry	X	X	X	X	X	X	X	X	X	X
Concomitant medication inquiry	X	X[d]	X	X	X	X	X	X	X	X
Dispense medication diary		X				X				
Review/collect medication diary, assess compliance				X		X			X	
Dispense study drug		X				X				
Collect unused study drug						X			X	

Visit Name	Screening	Baseline	Phone 1	Week 2	Phone 4	Week 6	Phone 8	Phone 10	EOT	EOS
Window (days)	**–[a]**	**–**	**±2**	**±3**	**±2**	**±3**	**±2**	**±2**	**±3**	**+14**
Day[b]	**–21 to 1**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**113**
Week	**–**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**16[c]**
Caregiver-Completed Measures										
Aberrant Behavior Checklist-Community		X		X		X			X	X
Anxiety, Depression, and Mood Scales		X		X		X			X	X
Repetitive Behavior Scale-Revised		X		X		X			X	X
Conners 3rd Edition	X (LF)	X (SF)		X (SF)		X (SF)			X (SF)	X (SF)
Short Sensory Profile-2		X		X		X			X	X
Children's Sleep Habits Questionnaire		X		X		X			X	X
Sleep diary issued[h]	X	X		X		X			X	
Sleep diary collected and reviewed		X		X		X			X	X
BASC-3 Parenting Relationship Questionnaire	X	X				X			X	
Parent Global Impressions-Severity	X	X		X		X			X	X
Parent Global Impressions -Improvement				X		X			X	X
Pediatric Quality of Life Inventory		X				X			X	X
Clinician-Completed Measures										
Pediatric Sleep CGI structured sleep history	X[i]	X[j]		X[j]		X[j]			X[j]	X[j]
Pediatric Sleep CGI-Severity	X	X		X		X			X	X
Pediatric Sleep CGI-Improvement		X		X		X			X	X
Caregiver top 3 concerns visual analog scale		X		X		X			X	X
Vineland Adaptive Behavior Scale, 3rd Edition		X				X			X	
CGI-Severity	X	X		X		X			X	X
CGI-Improvement				X		X			X	X

Visit Name	Screening	Baseline	Phone 1	Week 2	Phone 4	Week 6	Phone 8	Phone 10	EOT	EOS
Window (days)	**–[a]**	**–**	**±2**	**±3**	**±2**	**±3**	**±2**	**±2**	**±3**	**+14**
Day[b]	**–21 to 1**	**1**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**113**
Week	**–**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**16[c]**
Subject-Completed Measures										
Actigraph issued	X	X		X		X			X	
Actigraph and actigraphy data collected[k]		X		X		X			X	X
KiTAP	X	X				X			X	X
RBANS	X	X				X			X	X
[redacted]		X				X			X	

Abbreviations: BASC-3, Behavior Assessment System for Children, 3rd Edition; CGI, clinical global impressions; DSM-V, Diagnostic and Statistical Manual of Mental Disorders; EOS, end of study; EOT, end of treatment; FXS, fragile X syndrome; KiTAP, Test of Attentional Performance for Children; LF, long form; [redacted] RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SF, short form.

Note: At the investigator's discretion, subjects may be evaluated at unscheduled clinic visits for reasons related to subject safety. At unscheduled visits, subjects will be queried about AEs, changes in concomitant medications, and suicidality, and safety laboratory assessments may be conducted.

[a] Screening is to be conducted for up to 21 days (inclusive) before Day 1; subjects who meet all entry criteria can be randomly assigned at any time during the screening period.

[b] There is no Day 0. The screening period can start up to 21 days before Day 1.

[c] The EOS visit may occur 4 to 6 weeks after the EOT visit, between the end of Week 16 and the end of Week 18 for subjects who do not stop treatment early.

[d] If the screening and baseline visits can be completed within 10 days, the following procedures do not need to be repeated at the baseline visit: medical history, physical examination, clinical laboratory tests and determination of concomitant medications.

[e] Signs and symptoms of FXS.

[f] For the site in Israel, please see Appendix for site-specific details regarding the IQ test.

[g] Only if no written evidence for molecular diagnosis is available in the subject's records.

[h] The sleep diary is to be completed over the 7-day periods immediately preceding Day 1 and the Week 2, Week 6, EOT, and EOS clinic visits; a calendar will be issued to ensure that the diary information collection starts on the appropriate days.

[i] At the initial screening visit, the clinician will complete parts A, B, and C of the structured sleep history form.

[j] At clinic visits after the screening visit, the clinician will complete only part A of the structured sleep history form.

[k] The actigraph is to be worn and actigraphy data are to be collected for the 7-day periods immediately preceding Day 1 and the Week 2, Week 6, EOT, and EOS clinic visits; a calendar will be issued to ensure that the subject starts wearing the actigraph on the appropriate days.

6.1 Study Visits

After the screening period, each subject will be scheduled for 5 clinic visits and 4 phone visits (Table 6-1). At the investigator's discretion, subjects may be evaluated at unscheduled clinic visits for reasons related to subject safety. At unscheduled visits, subjects will be queried about AEs, changes in concomitant medications, and suicidality, and safety laboratory assessments may be conducted.

6.1.1 Screening Period

All subjects will be screened for participation in the study up to 21 days before Baseline, when the first dose will be administered. Subjects who meet all entry criteria can be randomly assigned at any time during the screening period.

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

During the screening period, the investigator will determine whether the LAR/caregiver and subject are able to complete all questionnaires and assessments that require their contributions and will also assess their ability to comply with study procedures. Screening of siblings will require approval from the medical monitor or his designee.

For those subjects without documentation of a molecularly confirmed diagnosis of FXS, blood samples will be obtained during the screening period to confirm the molecular diagnosis of FXS.

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

The LAR/caregiver will be provided with a sleep diary for documenting the subject's sleep and 1 wearable actigraph (Section 6.3.3) to document daily and nocturnal activities and sleep pattern. The subject will wear the actigraphy device and the LAR/caregiver will record data

in the sleep diary for at least 7 days before each study visit. A calendar reminder will also be provided for starting actigraph use and recording data in the sleep diary.

A subject who does not meet the inclusion criteria or who meets an exclusion criterion will be considered a screen failure. Whether rescreening is acceptable will be discussed with the medical monitor. Rescreening may be allowed under circumstances in which the subject passed screening but could not be randomly assigned within the 21-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 (Section 4.2.3).

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

6.1.2 Baseline Visit

Screened subjects will return to the study center for the baseline (Day 1) visit. The LAR/caregiver will bring the subject's completed sleep diary and actigraph, and study staff will manage the sleep diaries and actigraphs during the visit as detailed in Section 6.1.2.1. Prior to randomized assignment of study regimen, study center staff must confirm appropriate completion of the sleep diary, proper recording of the actigraph, and fulfilment of all eligibility criteria (Section 4.1).

Subjects who meet all eligibility criteria will be randomly assigned to treatment at Baseline as described in Section 5.1. After assignment at Baseline, subjects/caregivers will receive the IWRS-assigned package of blinded study treatment according to the treatment code for the first 6 weeks of treatment.

The following schedule of activities should be observed for subjects at the baseline visit:

1. Subject should eat a light low-fat breakfast (eg , cereal with low-fat milk, bagel with low-fat cream cheese, low-fat yogurt) before coming to the clinic.

2. Study staff conduct the following assessments that involve subject participation, in the following order: Test of Attentional Performance for Children (KiTAP), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and [redacted]

3. Morning dose is administered in the clinic (study staff will record time and date). On all clinic visit days, the morning dose must be administered before noon.
4. [redacted]
5. Subject optionally eats a light low-fat snack.
6. [redacted]

Subject vital sign measurements, urine sampling, [redacted] can be completed at any time during the visit. The LAR/caregiver questionnaires and investigator/study staff queries of the LAR/caregiver concerning AEs, concomitant medications, and subject suicidality (Section 6.8) can also be completed at any time during the visit.

The subject and his LAR/caregiver will be expected to complete the Baseline dosing (afternoon and evening doses) and continue study drug administration for the remainder of the study.

Details of the order of activities and instructions for assessments are provided in the workbooks for caregiver/clinician/subject assessments.

Screening and baseline assessments must be performed within a 21-day period. If the screening and baseline visits can be completed within 10 days, the following assessments do not need to be repeated at the baseline visit: medical history, physical examination, clinical laboratory tests, and determination of concomitant medications.

6.1.2.1 Management of Sleep Diary and Actigraph

6.1.2.1.1 Sleep Diary

Study staff will collect the sleep diary for recording in the eCRF and will review the sleep diary for completeness. If quality issues are detected, study staff will again instruct the LAR/caregiver in the proper use of the sleep diary.

A new sleep diary will be issued to the LAR/caregiver for use in the 7-day period preceding the Week 2 clinic visit. A calendar reminder will also be provided for the start of sleep diary assessments.

6.1.2.1.2 Actigraph

Study staff will upload data from the subject's actigraph as described in the study manual and will review the quality of the data. If quality issues are detected, study staff will review proper use of the actigraph with the LAR/caregiver. Study staff will issue a fully charged, reset actigraph to the LAR/caregiver, including new hospital bands (if needed; Section 6.3.3), for use in the 7-day period preceding the Week 2 clinic visit. A calendar reminder will also be provided for the start of actigraph use.

Study staff will reset and recharge the actigraph received from the LAR/caregiver, and that reset and recharged actigraph will be issued for use by the next available subject and LAR/caregiver.

6.1.3 Phone Visits to Assess Safety

Safety information will be collected during phone calls at the end of Weeks 1, 4, 8, and 10 (on Days 8, 29, 57, and 71, respectively). The LAR/caregivers will be queried about AEs, concomitant medications, and subject suicidality (Section 6.8).

6.1.4 Week 2 Clinic Visit

The subject will arrive at the clinic without having taken his morning dose of study medication, and study staff will record the actual date and time of his last previous dose of study drug. The subject's LAR/caregiver will bring the study medication to the clinic and the morning dose will be administered at the clinic. The subject's LAR/caregiver will bring the subject's completed sleep diary and actigraph, and study staff will manage the sleep diary and actigraph during the visit as detailed in Section 6.1.4.1.

The following schedule of activities should be observed for subjects at the Week 2 clinic visits:

1. Subject should have fasted overnight before coming to the clinic.

2. Morning dose is administered in the clinic (study staff will record time and date). On all clinic visit days, the morning dose must be administered before noon.
3. [redacted]
4. Subject should eat a light low-fat breakfast (eg, cereal with low-fat milk, bagel with low-fat cream cheese, low-fat yogurt).
5. [redacted]

Subject vital sign measurements and urine sampling can be completed at any time during the visit. The LAR/caregiver questionnaires and investigator/study staff queries of the LAR/caregiver concerning AEs, concomitant medications, and subject suicidality (Section 6.8) can also be completed at any time during the visit. Any unacceptable tolerability of study drug assessed at this visit (eg, somnolence, dizziness, vomiting, or change in behavior) must be reported as an AE.

The subject and his LAR/caregiver will be expected to complete the dosing for the day of the Week 2 clinic visit (afternoon and evening doses) and continue study drug administration for the remainder of the treatment period.

Details of the order of activities and instructions for assessments at the Week 2 clinic visit are provided in the workbooks for caregiver/clinician/subject assessments.

6.1.4.1 Management of Sleep Diary and Actigraph

6.1.4.1.1 Sleep Diary

Study staff will collect, review, and issue a new sleep diary, as described for the baseline (Day 1) visit (Section 6.1.2.1.1).

6.1.4.1.2 Actigraph

Study staff will upload data and issue a new actigraph, as described for the baseline (Day 1) visit (Section 6.1.2.1.2).

6.1.5 Week 6 Clinic Visit

The subject will arrive at the clinic without having taken his morning dose of study medication, and study staff will record the actual date and time of his last previous dose of study drug. The subject's LAR/caregiver will bring the subject's original study drug bottles (containing any unused study drug) to be collected by the study staff. The LAR/caregivers will also bring the subject's completed sleep diary and actigraph, and study staff will manage sleep diaries and actigraphs during the visit as detailed in Section 6.1.5.1.

Based on the returned study drug, study staff will assess compliance and counsel the LAR/caregiver on proper administration of study drug, as needed. Study staff will enter the capsule counts for each bottle in the eCRF. Study staff will dispense (to the LAR/caregiver) the IWRS-assigned package of blinded study treatment for the subject's second 6 weeks of treatment.

The following schedule of activities should be observed for subjects at the Week 6 clinic visit:

1. Subject should have fasted overnight before coming to the clinic.
2. Morning dose is administered in the clinic (study staff will record time and date). On all clinic visit days, the morning dose must be administered before noon.
3. [redacted]
4. Subject should eat a light low-fat breakfast (eg, cereal with low-fat milk, bagel with low-fat cream cheese, low-fat yogurt).
5. Study staff conduct the following assessments that involve subject participation, in the following order: KiTAP), RBANS, [redacted]

[redacted]

Subject vital sign measurements, urine sampling, [redacted] can be completed at any time during the visit. The LAR/caregiver questionnaires and investigator/study staff queries of the LAR/caregiver concerning AEs,

concomitant medications, and subject suicidality (Section 6.8) can also be completed at any time during the visit. Any unacceptable tolerability of study drug assessed at this visit (eg, somnolence, dizziness, vomiting, or change in behavior) must be reported as an AE.

The subject and his LAR/caregiver will be expected to complete the dosing for the day of the Week 6 clinic visit (afternoon and evening doses) and continue study drug administration for the remainder of the treatment period.

Details of the order of activities and instructions for assessments at the Week 6 clinic visit are provided in the workbooks for caregiver/clinician/subject assessments.

6.1.5.1 Management of Sleep Diary and Actigraph

6.1.5.1.1 Sleep Diary

Study staff will collect, review, and issue a new sleep diary, as described for the baseline (Day 1) visit (Section 6.1.2.1.1).

6.1.5.1.2 Actigraph

Study staff will upload data and issue a new actigraph, as described for the baseline (Day 1) visit (Section 6.1.2.1.2).

6.1.6 End-of-Treatment Visit

The EOT visit is to be scheduled to occur at the end of Week 12. For subjects for whom study drug administration is stopped early (before Week 12), an EOT study visit should be conducted within 2 weeks after the last day of study medication.

The subject will arrive at the clinic without having taken his morning dose of study medication, and study staff will record the actual date and time of his last previous dose of study drug. The subject's LAR/caregiver will bring the subject's original study drug bottles (containing any unused study drug) to be collected by the study staff. Study staff will assess compliance with dosing instructions, entering the capsule count for each bottle in the eCRF.

The LAR/caregiver will also bring the subject's sleep diary and actigraph, and study staff will manage the sleep diary and actigraph during the visit as detailed in Section 6.1.6.1.

The following schedule of activities should be observed for subjects at the EOT clinic visit:

1. Subject should have fasted overnight before coming to the clinic.

2. Morning dose is a dministered in the clinic (study staff will record time and date). On all clinic visit days, the morning dose must be administered before noon.

3. [redacted]

4. Subject should eat a light low-fat breakfast (eg, cereal with low-fat milk, bagel with low-fat cream cheese, low-fat yogurt).

5. Study staff conduct the following assessments that involve subject participation, in the following order: KiTAP, RBANS, [redacted]

6. [redacted]

Subject vital sign measurements, urine sampling, and [redacted] can be completed at any time during the visit. The LAR/caregiver questionnaires and investigator/study staff queries of the LAR/caregiver concerning AEs, concomitant medications, and subject suicidality (Section 6.8) can also be completed at any time during the visit. Any unacceptable tolerability of study drug assessed at this visit (eg, somnolence, dizziness, vomiting, or change in behavior) must be reported as an AE.

Details of the order of activities and instructions for assessments at the EOT visit are provided in the workbooks for caregiver/clinician/subject assessments.

6.1.6.1 Management of Sleep Diary and Actigraph

6.1.6.1.1 Sleep Diary

Study staff will collect, review, and issue a new sleep diary, as described for the baseline (Day 1) visit (Section 6.1.2.1.1).

6.1.6.1.2 Actigraphs

Study staff will upload data and issue a new actigraph, as described for the baseline (Day 1) visit (Section 6.1.2.1.2).

6.1.7 End-of-Study Visit

[redacted] The EOS visit will be scheduled to be completed within 4 to 6 weeks after the subject completes the EOT study visit, any time between the ends of Week 16 and Week 18. For subjects for whom study drug administration is stopped early and an early EOT visit occurred, an EOS visit should be completed within 4 to 6 weeks after completing the early EOT study visit.

The subject's LAR/caregiver will bring the subject's sleep diary and actigraph (issued at the EOT clinic visit), and study staff will manage the sleep diary and actigraph during the visit as detailed in Section 6.1.7.1.

The following schedule of activities should be observed for subjects at the EOS clinic visit:

- Study staff conduct the following assessments that involve subject participation, in the following order: KiTAP and RBANS.

The LAR/caregiver questionnaires and investigator/study staff queries of the LAR/caregiver concerning AEs, concomitant medications, and subject suicidality (Section 6.8) can be completed at any time during the visit.

Details of the order of activities and instructions for assessments at the EOS clinic visit are provided in the workbooks for caregiver/clinician/subject assessments.

6.1.7.1 Management of Sleep Diary and Actigraph

6.1.7.1.1 Sleep Diary

Study staff will collect the sleep diary for recording in the eCRF.

6.1.7.1.2 Actigraph

Study staff will upload data from the subject's actigraph as described in the study manual.

Actigraphs collected at the EOS clinic visit will be reset and recharged for re-issue and use by the next available subject and LAR/caregiver.

6.2 Screening Assessments

6.2.1 Autism Spectrum Disorder

The investigator or qualified designee will review the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for autism spectrum disorder for each subject, specifically assessing social communication deficits and restricted/repetitive behaviors and interests.

6.2.2 Intelligence Quotient

The SB-5 will be completed only if needed at screening to document that the subject meets Inclusion Criterion 9, ie, the subject has an IQ less than 75. Standardized administration of the SB-5 begins by administering 2 routing subtests (1 from each of the verbal and nonverbal IQ domains) and using these routing subtest scores to determine the start points for the remaining verbal and nonverbal domains. Participants will be administered the complete SB-5 following standardized administration procedures [redacted] If a participant is not able to complete the entire SB-5, the abbreviated battery IQ will be calculated from the 2 routing subtests. The abbreviated battery IQ provides a quick estimate of 2 major cognitive factors: fluid reasoning and crystallized ability.

A previous SB-5 documentation (within the 6 months before the screening visit) can be used to qualify the subject as having an IQ less than 75.

For the site in Israel, please see Appendix for site-specific details regarding the IQ test.

6.3 Efficacy Assessments

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

Table 6-2 Efficacy Assessments by Domain and Participant Source

Domain	LAR/Caregiver Assessment	Clinician Assessment	Direct Subject Assessment
Behavior	• ABC-C • ADAMS • RBS-R • Conners 3rd Edition • Short Sensory Profile-2		
Sleep	• Children's Sleep Habit Questionnaire • Sleep diary	• Pediatric Sleep CGI scales and structured sleep history	• Actigraphy
Global functioning and quality of life	• BASC-3 PRQ • PGI scales • Pediatric Quality of Life Inventory	• Caregiver top 3 concerns visual analog scale • Vineland Adaptive Behavior Scale • CGI scales	
Cognitive measures			• KiTAP • RBANS [redacted]

Abbreviations: ABC-C, Aberrant Behavior Checklist-Community; ADAMS, Anxiety, Depression, and Mood Scale; BASC-3 PRQ, Behavior Assessment System for Children, 3rd Edition Parenting Relationship Questionnaire; CGI, clinical global impressions; [redacted] KiTAP, Test of Attentional Performance for Children; LAR, legally acceptable representative; PGI, parent global impressions; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; RBS-R, Repetitive Behavior Scale-Revised.

6.3.1 Caregiver Assessments

6.3.1.1 Aberrant Behavior Checklist-Community

The Aberrant Behavior Checklist-Community (ABC-C) is a 58-item questionnaire completed by the LAR/caregiver that assesses a wide range of behaviors, including irritability, lethargy/social withdrawal, inappropriate speech, hyperactivity, stereotypic behavior, and social avoidance. Each item is rated on a scale of 0 to 3 ("not at all a problem" to "the problem is severe in degree"). The ABC-C will be scored 2 ways: according to the original method used to assess a population with a variety of disabilities (Aman et al 1985) and according to a method adapted for FXS that has a 6-factor structure (Sansone et al 2012). In the 6-factor method, 1 factor is unchanged from the original scoring (inappropriate speech); 4

factors are modified (irritability, hyperactivity, lethargy/withdrawal, and stereotypy); and 1 new factor (social/avoidance) has been added.

6.3.1.2 Anxiety, Depression, and Mood Scales

The Anxiety, Depression, and Mood Scales (ADAMS) is a caregiver-completed report that screens comprehensively for anxiety and depression in persons with intellectual disability and consists of 28 items grouped into 5 subscales that assess the frequency and severity of manic/hyperactive behavior, depressed mood, social avoidance, general anxiety, and obsessive behavior (Esbensen et al 2003).

6.3.1.3 Repetitive Behavior Scale-Revised

The Repetitive Behavior Scale-Revised (RBS-R) is a caregiver-completed, 43-item questionnaire assessing a variety of repetitive behaviors with 6 behavior subscales: stereotyped, ritualistic, self-injurious, compulsive, restricted, and sameness (Bodfish et al 2000).

6.3.1.4 Conners 3rd Edition

The Conners 3rd Edition (Conners 3; North Tonawanda Multi-Health System, North Tonawanda, NY) is designed to assess attention deficit hyperactivity disorder, and it will be used to collect LAR/caregiver observations of subject behavior. The assessment of behavior in neurodevelopmental disorders, such as FXS, frequently relies upon proxy report. The long form of Conners 3 is needed to assess inconsistency (reporter reliability) and will be administered at Screening only. The short form of Conners 3 will be administered as an outcome assessment at the baseline, Week 2, Week 6, EOT, and EOS visits.

6.3.1.5 Short Sensory Profile-2

The Short Sensory Profile-2 is a caregiver questionnaire to evaluate a subject's sensory processing patterns in the context of home, school, and community-based activities (PsychCorp, San Antonio, TX).

6.3.1.6 Children's Sleep Habits Questionnaire

The Children's Sleep Habits Questionnaire (CSHQ) is a caregiver-completed assessment of sleep behaviors in children and adolescents (Owens et al 2000). The abbreviated version of

this questionnaire includes 33 items that assesses sleep habits and possible difficulties with sleep. The CSHQ should take 5 to 10 minutes to complete.

6.3.1.7 Sleep Diary

A paper sleep diary will be completed by each subject's LAR/caregiver, on behalf of the subject. Endpoints assessed by the sleep diary are presented in Section 7.3.1. The sleep diary will be completed each day during the 7 days immediately preceding each clinic visit after screening. The LAR/caregiver will continue to complete a sleep diary for a subject who is unable to tolerate wearing an actigraph (Section 6.3.3.1).

At each clinic visit when a sleep diary is issued (Table 6-1), a calendar will be issued to remind the LAR/caregiver when next to start recording data in the sleep diary. Sleep diaries will be collected at each clinic visit, starting with the baseline visit (Table 6-1).

6.3.1.8 Behavior Assessment System for Children, 3rd Edition

The Behavior Assessment System for Children, 3rd Edition, Parenting Relationship Questionnaire (BASC-3 PRQ) provides information on the relationship between a caregiver and a child across multiple dimensions (Pearson, New York, NY). It yields the following subscale scores: attachment, communication, discipline practices, involvement, parent confidence, satisfaction with school, and relation frustration. The questionnaire is written at a third grade level and also calculates a number of response validity scores, such as consistency and response pattern, to detect careless or exaggerated responding. It includes normative samples for both female and male raters that are closely matched to the US Census population estimates.

6.3.1.9 Parent Global Impressions Scales

The Parent Global Impressions-Severity (PGI-S) scale will be completed by the LAR/caregiver to assess the severity of symptoms, and the Parent Global Impressions-Improvement (PGI-I) scale will be used by the LAR/caregiver to assess improvement from baseline. The PGI-S has been adapted to capture specific characteristics commonly present in the FXS population.

6.3.1.10 Pediatric Quality of Life Inventory

The Pediatric Quality of Life Inventory (PedsQL) generic core scales and Multidimensional Fatigue Scale will be administered in this study (Varni et al 2004). The generic core scales include 23 items covering the domains of physical, emotional, social, and school functioning. The Multidimensional Fatigue Scale contains 18 items measuring general fatigue, sleep/rest fatigue, and cognitive fatigue.

6.3.2 Clinician Assessments

6.3.2.1 Structured Sleep History Form

On the initial screening visit, the clinician will complete parts A, B, and C of the structured sleep history form by interviewing the LAR/caregiver. The sleep history form is used by the clinician as a source document for completion of the Pediatric Sleep Clinical Global Impressions (Pediatric Sleep CGI) scales (Section 6.3.2.2). On all subsequent clinic visits starting with baseline, the clinician will complete only part A of the structured sleep history form. Part D of the structured sleep history form will not be used for this study.

6.3.2.2 Pediatric Sleep Clinical Global Impressions Scales

The Pediatric Sleep CGI scales were recently developed to measure pediatric insomnia in autism spectrum disorder and have been validated against the CSHQ and actigraphy (Malow et al 2016). The clinician will interview the LAR/caregiver for each subject to complete the structured sleep history form (Section 6.3.2.1) as an aid to the clinician completing the Pediatric Sleep CGI-Severity and Pediatric Sleep CGI-Improvement scales as scheduled (Table 6-1). Questions include the subject's ability to fall asleep and remain sleeping independently (ie, apart from LAR/caregivers); bedtime resistance; sleep onset delay; night awakening; LAR/caregiver satisfaction with their child's current sleep patterns; family functioning, as affected by their child's current sleep patterns; and clinician's overall concern with the child's sleep.

6.3.2.3 Caregiver Top 3 Concerns Visual Analog Scale

In Part 1 of the visual analog scale (VAS), LARs/caregivers will generate their top 3 concerns for the subject. The investigator will then map each LAR/caregiver-generated concern onto one FXS-specific domain (e.g. communication, activities of daily living, anxiety) to which each behavior or symptom applies. Part 2 of VAS will be used to rate FXS-specific domains,

including speech and communication, socialization, and cognition. The investigator will ask the LAR/caregiver to rate the behaviors in both Part 1 and 2, using a 10-cm VAS, with the descriptive anchors of “worst ever” and “best ever.”.

6.3.2.4 Vineland Adaptive Behavior Scale

The Vineland Adaptive Behavior Scale, 3rd Edition (VABS-3) caregiver interview form will be used to evaluate communication, socialization, and daily living skills of subjects to assess their overall adaptive functioning (PsychCorp, San Antonio, TX). This assessment is an interview of the caregiver by a trained qualified rater.

6.3.2.5 Clinical Global Impressions Scales

The CGI-S scale will be used by the investigator to assess the severity of symptoms, and the CGI-I scale will be used by investigators to assess improvement from baseline. The CGI-S has been adapted to capture specific characteristics commonly present in the FXS population. Both CGI-S and CGI-I will be conducted by a clinician with experience in FXS.

6.3.3 Direct Subject Assessments

6.3.3.1 Actigraphy

Actigraphy is a noninvasive method of monitoring human rest/activity cycles. A small actigraph unit is worn to measure daytime and sleep activity. The actigraph unit stores motion data by clock time, and the data must be uploaded to an actigraphy database for analysis.

Each subject will be provided a wearable actigraph unit (Actiwatch; Philips Respironics Inc, Murrysville, PA), preferably to be worn on the nondominant wrist. If the subject is not able to tolerate the Actiwatch on his wrist, he may wear it on his ankle. The Actiwatch can be attached with a hospital band if that makes it more acceptable for the subject. Once a body location is selected for attachment of the Actiwatch, every effort should be made to keep the location the same throughout the study. Severe sensory sensitivities exist in the study population, and it is anticipated that some subjects will not be able to tolerate wearing the device. Therefore, if a subject is not able to tolerate the Actiwatch and/or comply with the Actiwatch guidelines, he may continue to participate in the study. The Actiwatch will be worn during the 7 days immediately preceding each clinic visit after screening. It should be

worn continuously throughout the day and night for 7 consecutive days. The actigraphy data (Section 7.3.3) will be compared to the sleep diary data.

6.3.3.2 Test of Attentional Performance for Children

The KiTAP is an automated computer-based assessment of attentional performance developed and normed for a pediatric population. The KiTAP is suitable for assessment of function in individuals of various ages, including children, adolescents, and adults, with FXS (Knox et al 2012). The task displays an "enchanted castle" animation and measures 8 aspects of attention: alertness, distractibility, divided attention, flexibility, go/no-go, sustained attention, vigilance, and visual scanning.

6.3.3.3 Repeatable Battery for the Assessment of Neuropsychological Status

The RBANS provides a brief individually administered battery to assess cognitive function in individuals 12 years of age and older (Randolph et al 1998). The full battery consists of 12 subtests to assess immediate memory, visuospatial abilities, language, attention, and delayed memory. In this study, 6 subtests of the RBANS will be used: list learning (immediate memory), list recall (delayed memory), list recognition (delayed memory index), story memory (immediate memory index), story recall (delayed memory index), and picture naming (language index). Each subtest can be administered in 5 minutes or less.

6.3.3.4 [redacted]

[redacted]

[redacted]

[redacted]

6.6 Safety and Tolerability Assessments

All subjects who receive study drug will be evaluated for study drug safety and tolerability. Assessments will include the frequency and severity of treatment-emergent AEs (TEAEs) and SAEs (including TEAEs leading to discontinuation), standardized clinical assessment of suicidality, clinical laboratory evaluations, and vital sign measurements. Safety and tolerability assessments will be conducted according to the schedule presented in Table 6-1.

6.6.1 Adverse Events

6.6.1.1 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 their clinical significance.

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 randomization if any symptoms develop.

A TEAE is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

6.6.1.2 Serious Adverse Events

An SAE is defined as any event that meets one of the following criteria:

- Results in death
- Is immediately life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity not consistent with baseline level
- Is a congenital anomaly/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.

6.6.1.3 Eliciting and Documenting Adverse Events

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

At every clinic visit after informed consent and at all phone visits (Table 6-1), subjects 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 (eg, laboratory values, physical examination findings) or identified from the review of other documents (eg, 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.

6.6.1.4 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 (diagnosis, not symptoms)
- Time of onset
- Investigator-specified assessment of severity and relationship to study drug
- Time of resolution of the event
- Seriousness
- Any required treatment or evaluations
- Outcome

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

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

6.6.1.5 Reporting Serious Adverse Events

Investigators and other study center staff must immediately (ie, within 1 business day) inform [redacted] 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 must be faxed to the following number.

- [redacted]

Any AE that meets SAE criteria (Section 6.6.1.2) must be entered into the EDC system immediately (ie, within 1 business day) after site personnel first learn about the event. Once the qualifying SAE data are entered, [redacted] will be notified by an email alert, which will contain high-level safety information. Additional safety information will be obtained from the EDC system via applicable eCRF pages. If the EDC system is not available, the site should send a completed, manual, paper SAE report form to [redacted] by fax:

- [redacted]

When the EDC system is again available, the site must enter all applicable information into the EDC system. All supporting source information concerning the SAE (eg, hospital records) should be provided by fax.

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 a Sciformix safety specialist, or the site urgently needs to report an SAE or make [redacted] aware of an SAE, the safety hotline should be used:

- [redacted]

If a site makes an initial report of an SAE by the safety hotline, the site must subsequently enter all applicable information into the EDC system immediately thereafter.

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. 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 (ie, the subject or health care practitioner is unable to provide additional information or the subject is lost to follow-up). Serious AEs that occur more than 30 days after the last dose of study drug do not need to be reported unless the investigator considers them related to study drug.

6.6.1.6 Suspected Unexpected Serious Adverse Reactions

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

To determine the reporting requirements for single AE cases, the sponsor will assess the expectedness of these events using the gaboxadol investigator's brochure [redacted]

The sponsor will compare the severity of each suspected unexpected serious adverse reaction and the cumulative event frequency reported for the study with the severity and frequency reported in the investigator's brochure.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the sponsor as needed.

6.6.1.7 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 the onset and duration of each episode.

6.6.1.8 Assessment of Causality

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

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

Unrelated: This relationship suggests that there is no association between the study drug and the reported event.

Possible: This relationship suggests that treatment with the study drug caused or contributed to the AE, ie, 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.

6.6.1.9 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 to be stable.

6.6.2 Other Safety Assessments

Safety assessments other than AEs (Section 6.6.1) will include standardized clinical assessment of suicidality (Section 6.8), clinical laboratory evaluations (Section 6.9), and vital sign measurements.

6.6.2.1 Vital Sign Measurements

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

6.7 Monitoring Committees

An Internal Monitoring Committee and Scientific Oversight Committee agreement charter will document the roles, responsibilities, scope of activities, communication pathway, and time of meetings.

6.7.1 Internal Monitoring Committee

The Internal Monitoring Committee is a committee that will review unblinded safety and efficacy data when 30 evaluable subjects have completed the EOT visit. It will consist of responsible representatives from Ovid clinical science, clinical pharmacology, statistics, drug safety, and statistical programming.

6.7.2 Scientific Oversight Committee

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

6.8 Clinical Assessment of Suicidality

In accordance with the schedule in Table 6-1, the investigator will ask the subject's LAR/caregiver the following questions (and record the answers in the eCRF):

1. Suicidal ideation: Has the subject wished he were dead or wished he could go to sleep and not wake up?

2. Suicidal behavior: Has the subject made a suicide attempt? Has the subject done anything to harm himself?

3. Self-injurious behavior: Has the subject engaged in nonsuicidal self-injurious behavior?

If the investigator determines that any of these questions can be asked directly to the subject based on his ability to understand and respond to the questions, then those questions should be directed to the subject. If the answer to any of these 3 questions is "yes," then the investigator will further evaluate the suicidal risk of the subject.

6.9 Laboratory Analyses

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis), including those that worsen from baseline, that are considered to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as AEs or SAEs.

The following clinical analytes will be assessed:

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

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

Urinalysis (safety assessment): macroscopic (pH, specific gravity, glucose, protein, ketones, nitrates, blood) and microscopic, reported only if present (red blood cells/high-power field, white blood cells/high-power field, casts, epithelial cells, crystals, granulation).

[redacted]

6.10 Sample Collections

Blood and urine 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 Section 6.1 and the investigator's study manual, according to the schedule of activities (Table 6-1). Samples for hematology, clinical chemistry, or urinalysis will be used only for the evaluation of safety and tolerability.

[redacted]

Blood samples will be collected for clinical laboratory safety assessments, [redacted]

The maximum volume of blood to be collected per subject over the course of the study is estimated to be less than 140 mL.

7 Statistical and Analytical Plan

7.1 Primary Safety Endpoints

Treatment-emergent AEs, treatment-related TEAEs, TEAEs leading to study discontinuation, and SAEs will be evaluated as primary safety endpoints.

7.2 Secondary Efficacy Endpoints

The efficacy parameters of the continuous secondary endpoints will be the mean changes from baseline in ABC-C total and subscale scores; in ABC-C factor score for FXS; in the ADAMS subscale scores; in the RBS-R total and subscale scores; in Conners 3 subscale scores; in the Short Sensory Profile-2 total and subscale scores; and in the CGI-S and CGI-I scores.

7.3 Exploratory Efficacy Endpoints

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

7.3.1 Caregiver-Completed Endpoints

- Change from baseline in the BASC-3 PRQ subscale scores
- Change from baseline in PGI-S and PGI-I scores
- Change from baseline in PedsQL total and subscale scores
- Change from baseline in the CHSQ total and subscale scores
- Change from baseline in sleep diary parameters, including how long it took the subject to fall asleep (sleep onset latency [SOL]), the amount of time the subject was awake during the night (WASO), the total amount of sleep obtained (total sleep time [TST]), and daytime sleepiness, defined as duration of napping in the daytime.

7.3.2 Clinician-Completed Endpoints

- Change from baseline in top 3 concerns visual analog scale
- Change from baseline in the VABS-3 overall composite and subscale scores

- Change from baseline in Pediatric Sleep CGI-Severity and Pediatric Sleep CGI-Improvement scores

7.3.3 Direct Subject Assessment Endpoints

- Actigraphy parameters for sleep, including SOL, WASO, sleep fragmentation, number of nocturnal awakenings, TST, sleep efficiency, and daily activity level.
- Mean change from baseline in KiTAP subtest scores
- Mean change from baseline in RBANS subtest scores

[redacted]

7.5 Sample Size Calculations

A sufficient number of subjects (36 estimated) will be enrolled to ensure that 30 evaluable subjects complete 12 weeks of treatment. Subjects will be randomly assigned to the 3 OV101 total daily dosing regimens in a 1:1:1 ratio, stratified by age group (adolescents/adults), with a target ratio of 1:1 between adolescents and adults.

The main emphasis in reporting the data will be on descriptive statistics and estimation with 95% CIs.

For the objective of estimating the overall subject incidence of TEAEs (for the 3 OV101 total daily dose arms combined), the precision varies with true incidence, eg, a true incidence of 20% would be estimated with a 13.9% precision (half-width of the 2-sided 95% CI, assuming N = 30). Table 7-1 contains the estimated precision for different incidence rates, using the Wilson method of calculating a confidence interval for a binomial proportion.

Table 7-1 Incidence Rates and Corresponding Precision

True TEAE Incidence Rate	10%	13.3%	20%	23.3%	30%
Expected n with a TEAE (N=30)	3	4	6	7	9
Expected proportion, p	0.100	0.133	0.200	0.233	0.300
95% CI	(3.5%, 25.6%)	(5.3%, 29.7%)	(9.5%, 37.3%)	(11.8%, 40.9%)	(16.7%, 47.9%)
Precision (half-width of CI)	11.1%	12.2%	13.9%	14.6%	15.6%

Note: All CIs are 2-sided and 95% CIs are calculated using Wilson's method.

Abbreviations: n, number of subjects observed; N, total number of evaluable subjects in the study (all treatment groups); TEAE, treatment-emergent adverse event.

7.6 Analysis Sets

The following analysis sets are defined:

Randomized Analysis Set: The randomized analysis set will consist of all randomly assigned subjects.

Full-Analysis Set (FAS): The FAS will consist of all randomly assigned subjects who receive at least 1 dose of study drug and have at least 1 postbaseline efficacy assessment. Following the intent-to-treat principle, subjects will be analyzed according to the treatment they are assigned to at randomization, regardless of compliance or any deviations from the study protocol.

Modified Full-Analysis Set (mFAS): The mFAS will consist of all subjects in FAS, excluding data after a subject discontinues treatment or commences treatment with a prohibited medication.

Safety Set: The safety set will consist of all subjects who receive at least 1 dose of study drug. All analyses using the safety set will group subjects according to treatment actually received.

The randomized analysis set will be used for summaries of subject disposition, demographics, and other baseline characteristics. All safety evaluations will be carried out on the safety set. All efficacy evaluations will be carried out on the FAS. The mFAS may be used for exploratory modelling of selected efficacy variables, in addition to the FAS.

7.7 Description of Subgroups to be Analyzed

Scatter plots of data will distinguish the age groups (adolescent/adult) with different symbols to allow visual assessment of the consistency of data between these groupings. In addition, listings of all data will identify the age group of each subject. In the case of an endpoint that is further analyzed through the Mixed Model with Repeated Measures (MMRM; Section 7.8.5) and for which differences between age groups are apparent, an age by time by treatment interaction may be included in the model in order to present estimates for each age group separately (in addition to overall).

Additional subgroup statistical analyses may be performed, as detailed in a separate statistical analysis plan.

7.8 Statistical Analysis Methodology

The detailed methodology for the summary and statistical analyses of the data collected in this study will be documented in a separate statistical analysis plan. This document may modify the plans outlined in the protocol; however, any major modifications of the endpoint definitions and/or their analyses will also be reflected in a protocol amendment.

All statistical analyses will be performed using SAS software Version 9.3 or higher.

Descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum) will be presented for continuous variables and their changes from baseline. In addition, 95% CIs for the mean change from baseline will be provided for continuous variables. Graphical displays will be utilized to investigate trends over time and dose and the relationship between certain variables and differences between age groups.

Ordinal variables with sufficient numerical categories (eg, 7-point scales of PGI-S and CGI-S) and subscale total scores from questionnaires will be treated as continuous variables.

Categorical (not treated as continuous) endpoints (including AE incidence and binary endpoints) will be summarized by frequency and percentage. Frequencies and percentages will be presented for the shifts in these categories (eg, low to normal, low to high, high to low) from baseline to each post-treatment assessment time point for scales with categorical variables. If there are missing values, the number missing will be presented (as a category), but without a percentage. All data collected will be included in by-subject data listings.

7.8.1 Safety Analyses

All safety analysis will be performed on the safety set.

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

The number and percentage of subjects who experience at least 1 TEAE and the number and percentage of subjects who experience at least 1 TEAE within each specific SOC and PT will be presented by daily dosing regimen and overall. The number of TEAEs (event incidence) will also be summarized within each SOC and PT.

The Wilson 95% CIs will be displayed for the proportion of subjects experiencing TEAEs as a total across the 3 dosing regimens.

Treatment-related AEs will be identified as those that are at least possibly related to investigational product based on the investigator's assessment. The number and percentage of subjects reporting SAEs, TEAEs, and AEs leading to study continuation will also be summarized by MedDRA SOC and PT.

For each SOC and each PT, a subject will be counted only once for subject-incidence tabulations. For summaries of severe or treatment-related AEs, for a given subject, the highest severity or relationship for a specific PT will be considered. Adverse events with missing start dates will be considered treatment emergent.

Number and percentage of deaths will be tabulated by primary SOC and PT.

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

Shift tables for laboratory parameters will be presented to show the change of normality from baseline to each postbaseline visit. For each continuous laboratory parameter, results will be categorized as low, normal, or high based on the laboratory reference ranges. Frequencies and percentages will be presented for the shifts in these categories (eg, low to normal, low to high, high to low) from baseline to each post-treatment assessment time point.

Tables and graphical displays (eg, scatter plots of baseline versus worst postbaseline values) of key safety parameters may be generated to better understand the study drug safety profile.

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

Abnormal findings in physical examinations will be listed.

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

7.8.2 Analysis of Secondary Efficacy Endpoints

Descriptive statistics for efficacy variables at each time point will be displayed by daily dosing regimen and overall. Post-hoc exploratory modelling may be conducted on selected variables (Section 7.8.5) using the FAS (and mFAS, as required).

7.8.3 Analyses of Exploratory Endpoints

Exploratory endpoints will be analyzed using the same methods as used for the secondary efficacy endpoints. Post-hoc exploratory modelling may be conducted on selected variables (Section 7.8.5) using the FAS (and mFAS as required).

[redacted]

[redacted]

7.8.5 Exploratory Modelling

Post-hoc exploratory modelling may be conducted on selected variables using an MMRM to further investigate any trends evident in the descriptive statistics and to inform a future study.

In case of post-hoc exploratory modelling, the MMRM analysis will be performed on the change from baseline in the response variable with baseline as a covariate and fixed effects for daily dosing regimen, week, age group and week by daily dosing regimen interaction. An unstructured covariance structure will be assumed. From this model, the least squares mean change from baseline and the corresponding 95% CI will be presented for each daily dosing regimen and the total (all regimens) at each week. The least squares mean difference and the corresponding 95% CI will be presented for each pairwise comparison between the 3 daily dosing regimens at each week.

The least squares mean changes from baseline and corresponding 95% CIs will be plotted at each time point by daily dosing regimens.

In the case of a statistically significant age group main effect ($P<0.05$) in the MMRM or age effects deemed evident in descriptive statistics, the mean changes with 95% CI described above will be estimated for each age group separately as well as overall; this will be achieved by inclusion of an additional term (age by week by daily dosing regimen interaction) in the MMRM. In this case, these additional estimates and 95% CI will be tabulated and plotted.

7.8.6 Other Analyses

7.8.6.1 Demographics and Other Baseline Characteristics

Demographic and background information variables and subject disposition will be listed by subject and summarized using frequency distributions for categorical variables and descriptive statistics (ie, number of subjects, mean, SD, minimum, median, and maximum)

for continuous variables. Relevant medical history/current medical conditions will be summarized by SOC and PT of MedDRA.

Background information will consist of data collected in the molecular FXS testing, clinical assessment of FXS, DSM-5 criteria for autism spectrum disorder, and IQ.

The above analyses will be performed based on the randomized analysis set.

7.8.6.2 Drug Treatments

7.8.6.2.1 Study Drug

Using the safety set, duration (days) of exposure to study drug and treatment compliance will be listed by subject and summarized descriptively by daily dosing regimen. Frequency and percentages for subject disposition and reasons for discontinuation of study drug will be presented.

7.8.6.2.2 Prior and Concomitant Medications

Using the randomized analysis set, prior and concomitant medications will be listed by subject and summarized descriptively.

7.8.7 Interim Analyses

No interim statistical analysis will be performed. Periodic interim blinded review of safety data will be performed as part of routine pharmacovigilance activities.

8 Data Quality Assurance

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

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

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 sponsor policy. Such audits will require access to study records, documentation, and regulatory files. At all times, subject privacy will be of utmost importance and will be respected. Typically, sufficient notice will be given to the investigator to prepare for the visit.

In the event of an audit or inspection, the investigator (and institution) must agree to grant the auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss any findings or relevant issues. 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.

Responsibility for the accuracy, completeness, and reliability of the study data presented to the sponsor lies with the investigator generating the data.

8.1 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 documents including (but not restricted to) the following: laboratory reports, questionnaire results, sleep diaries, and computerized or otherwise automated assessments.

Investigative site personnel will enter subject data into [redacted] (the eCRF EDC program). The analysis data sets will be a combination of these data and data from other sources (eg, 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, eg, removing errors and inconsistencies in the data. There will be 100% source data verification. 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.

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

9 Ethics

9.1 Institutional Review Board(s)

Federal regulations and ICH guidelines require that approval be obtained from an IRB before participation of human subjects in research studies. Before study onset, the protocol, informed consent and 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 LAR/caregiver must be approved by the IRB. Documentation of all IRB approvals and of IRB 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 approvals should be signed by the IRB chairman or designee and must identify the IRB name and address, the clinical protocol by title or protocol number or both, all approved materials, 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. The investigator must promptly supply the sponsor or its designee, the IRB, 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 US Title 21 CFR Part 50 shall be obtained from each adult competent subject (or from the LAR/caregiver of a minor or adult of diminished mental capacity, as applicable) before the subject enters the study or any unusual or nonroutine procedure that involves risk to the subject is performed. For minors or adults of diminished mental capacity, an assent document will be presented and assent 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 informed consent form (ICF) is revised during the course of the study, all active participating subjects and LAR/caregivers (as applicable) must sign the revised forms.

[redacted]

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 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 the IRB.

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 course of the investigation 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 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 subinvestigator 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-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the 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 according to the timeline and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study site IRB 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 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 External Data Monitoring Committee

There will not be an external data monitoring committee for this study.

11.1.2 Monitoring of the Study

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

The study monitor will visit the investigator and study site at periodic intervals, in addition to maintaining necessary telephone and letter contact. The study 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.

11.1.3 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB 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 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 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 for review and approval, to the sponsor for agreement, and to 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 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 of deviations in writing by the monitor. The IRB 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 his last visit (includes follow-up visit).

11.4 Final Report

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

Where required by applicable regulatory requirements, an investigator signatory will be identified for 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 and their LAR/caregivers, as appropriate. The study results will be posted on publicly available clinical trial registers.

12 Reference List

Aman MG, Singh NN, Stewart AW, et al. Psychometric characteristics of the Aberrant Behavior Checklist. Am J Ment Defic. 1985;89(5):492-502.

Bakker CE, Verheij C., Willemsen R, et al; Dutch-Belgian Fragile X Consortium. *Fmr1* knockout mice: a model to study fragile X mental retardation. Cell. 1994;78(1):23-33.

Bhakar AL, Dölen G, Bear MF. The pathophysiology of fragile X (and what it teaches us about synapses). Annu Rev Neurosci. 2012;35:417-43.

Bodfish JW, Symons FJ, Parker DE, et al. Varieties of repetitive behavior in autism: comparisons to mental retardation. J Autism Dev Disord. 2000;30(3):237-43.

Braat S, Kooy RF. Insights into $GABA_A$ergic system deficits in fragile X syndrome lead to clinical trials. Neuropharmacology 2015;88: 48-54.

Cogram P, Deacon RJ, During MJ, et al. Gaboxadol normalizes behavioral abnormalities in a mouse model of fragile X syndrome. Poster presented at: 18th International Fragile X and Related Neurodevelopmental Disorders Workshop; 2017 Oct 12-16; Saint-Alexis-des-Monts, Quebec.

Crawford DC, Acuña JM, Sherman SL. *FMR1* and the fragile X syndrome: human genome epidemiology review. Genet Med. 2001;3(5):359-71.

D'Hulst C, Kooy RF. The $GABA_A$ receptor: a novel target for treatment of fragile X? Trends Neurosci. 2007;30(8):425-31.

Esbensen AJ, Rojahn J, Aman MG, et al. Reliability and validity of an assessment instrument for anxiety, depression, and mood among individuals with mental retardation. J Autism Dev Disord. 2003;33(6):617-29.

Ethridge LE, White SP, Mosconi MW, et al. Reduced habituation of auditory evoked potentials indicate cortical hyper-excitability in fragile X syndrome. Transl Psychiatry. 2016;6:e787.

Fernández E, Rajan N, Bagni C. The FMRP regulon: from targets to disease convergence. Front Neurosci. 2013;7:191.

Gantois I, Vandesompele J, Speleman F, et al. Expression profiling suggests underexpression of the $GABA_A$ receptor subunit δ in the fragile X knockout mouse model. Neurobiol Dis. 2006;21(2):346-57.

Gould EL, Loesch DZ, Martin MJ, et al. Melatonin profiles and sleep characteristics in boys with fragile X syndrome: a preliminary study. Am J Med Genet. 2000;95(4):307-15.

Hagerman R, Hoem G, Hagerman P. Fragile X and autism: intertwined at the molecular level leading to targeted treatments. Mol Autism. 2010;1:12.

Hagerman RJ. The physical and behavior phenotype. In: Hagerman RJ, Hagerman PJ, editors. Fragile X syndrome: diagnosis, treatment, and research. 3rd ed. Baltimore: Johns Hopkins University Press; 2002. p 3-109.

Hagerman RJ, Berry-Kravis E, Kaufmann WE, et al. Advances in the treatment of fragile X syndrome. Pediatrics. 2009;123(1):378-90.

Hall SS, Lightbody AA, Reiss AL. Compulsive, self-injurious, and autistic behavior in children and adolescents with fragile X syndrome. Am J Ment Retard. 2008;113(1):44-53.

Harris SW, Hessl D, Goodlin-Jones B, et al. Autism profiles of males with fragile X syndrome. Am J Ment Retard. 2008;113(6):427-38.

Kenneson A, Zhang F, Hagedorn CH, et al. Reduced FMRP and increased *FMR1* transcription is proportionally associated with CGG repeat number in intermediate-length and premutation carriers. Hum Mol Genet. 2001;10(14):1449-54.

Knox A, Schneider A, Abucayan F, et al. Feasibility, reliability, and clinical validity of the Test of Attentional Performance for Children (KiTAP) in fragile X syndrome (FXS). J Neurodev Disord. 2012;4:2.

Kristensen BW, Noraberg J, Zimmer J. The $GABA_A$ receptor agonist THIP is neuroprotective in organotypic hippocampal slice cultures. Brain Res. 2003;973(2):303-6.

Kronk R, Bishop EE, Raspa M, et al. Prevalence, nature, and correlates of sleep problems among children with fragile X syndrome based on a large scale parent survey. Sleep. 2010;33(5):679-87.

Malow BA, Connolly HV, Weiss SK, et al. The Pediatric Sleep Clinical Global Impressions Scale–a new tool to measure pediatric insomnia in autism spectrum disorders. J Dev Behav Pediatr. 2016;37(5):370-6.

Martin BS, Corbin JG, Huntsman, MM. Deficient tonic GABAergic conductance and synaptic balance in the fragile X syndrome amygdala. J Neurophysiol. 2014;112(4):890-902.

Medrihan L, Ferrea E, Greco B, et al. Asynchronous GABA release is a key determinant of tonic inhibition and controls neuronal excitability: a study in the synapsin II$^{-/-}$ mouse. Cereb Cortex. 2015;25(10):3356-68.

Olmos-Serrano JL, Corbin JG, Burns MP. The $GABA_A$ receptor agonist THIP ameliorates specific behavioral deficits in the mouse model of fragile X syndrome. Dev Neurosci. 2011;33(5):395-403.

Olmos-Serrano JL, Paluszkiewicz SM, Martin BS, et al. Defective GABAergic neurotransmission and pharmacological rescue of neuronal hyperexcitability in the amygdala in a mouse model of fragile X syndrome. J Neurosci. 2010;30(29):9929-38.

Ovid Therapeutics Inc. Gaboxadol (OV101). Investigator’s brochure, 2nd ed. New York (NY); 2017. 76 p.

Owens J, Spirito A, McGuinn M. The Children's Sleep Habits Questionnaire (CSHQ): psychometric properties of a survey instrument for school-aged children. Sleep. 2000;23(8):1-9.

Randolph C, Tierney MC, Mohr E, et al. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. J Clin Exp Neuropsychol. 1998;20(3):310-9.

Richdale AL. A descriptive analysis of sleep behaviour in children with fragile X. J Intellect Dev Disabil. 2003;28(2):135-44.

Roth T, Lines C, Vandormael K, et al. Effect of gaboxadol on patient-reported measures of sleep and waking function in patients with primary insomnia: results from two randomized, controlled, 3-month studies. J Clin Sleep Med. 2010;6(1):30-9.

Sansone SM, Widaman KF, Hall SS, et al. Psychometric study of the aberrant behavior checklist in fragile X syndrome and implications for targeted treatment. J Autism Dev Disord. 2012;42(7):1377-92.

Sun Y, Wu Z, Kong S, et al. Regulation of epileptiform activity by two distinct subtypes of extrasynaptic $GABA_A$ receptors. Mol Brain. 2013;6:21.

Tassone F, Hagerman RJ, Taylor AK, et al. Elevated levels of *FMR1* mRNA in carrier males: a new mechanism of involvement in the fragile-X syndrome. Am J Hum Genet. 2000;66(1):6-15.

Varni JW, Sherman SA, Burwinkle TM, et al. The PedsQL™ Family Impact Module: preliminary reliability and validity. Health Qual Life Outcomes. 2004;2:55.

Wheeler AC, Raspa M, Bishop E, et al. Aggression in fragile X syndrome. J Intellect Disabil Res. 2016;60(2):113-25.

Whissell PD, Rosenzweig S, Lecker I, et al. γ-Aminobutyric acid type A receptors that contain the δ subunit promote memory and neurogenesis in the dentate gyrus. Ann Neurol. 2013;74(4):611-21.

Zhang J, Fang Z, Jud C, et al. Fragile X-related proteins regulate mammalian circadian behavioral rhythms. Am J Hum Genet. 2008;83(1):43-52.

13 Appendix (Israel Site-Specific Instructions)

The SB-5, which is to be conducted at screening, is not available in Hebrew. Therefore, for the site in Israel, alternative IQ assessments such as the Wechsler Intelligence Scale for Children (WISC), Wechsler Preschool and Primary Scale of Intelligence (WPPSI), or Kaufman Assessment Battery for Children (KABC) may be used. It is important that the alternative IQ test yields a full scale IQ (with nonverbal and verbal scores). For example, the Leiter International Performance Scale is a nonverbal intelligence test and therefore, would not be an appropriate substitute of the SB-5.

An equivalent previously documented IQ measurement conducted within 3 years of the screening visit can be used to qualify the subject as having an IQ less than 75.