1. TITLE PAGE

PROTOCOL

A Phase 2 Angelman Syndrome Clinical Trial: A Randomized, Double-blind, Safety and Efficacy Study of Gaboxadol (Short Name: STARS)

Protocol No:	OV101-15-001
Investigational Product:	Gaboxadol (OV101)
Indication:	Angelman syndrome (AS)
Sponsor:	Ovid Therapeutics Inc. 1460 Broadway New York, NY 10036 USA
Sponsor Signatory and Medical Lead:	[redacted] Ovid Therapeutics Inc.
Steering Committee Meeting Chair:	[redacted]
Development Phase:	Phase 2
Date of the Protocol:	24 Oct 2017
Version of the Protocol:	4.0 (Amendment 3)

Ovid Therapeutics Inc.

1460 Broadway

New York, NY 10036

2. TABLE OF CONTENTS

List of Tables

List of Figures

List of Appendices

Not applicable

3. SPONSOR INFORMATION

Ovid Therapeutics Inc. is the Sponsor of this study.

Ovid Therapeutics Inc.

1460 Broadway

New York, NY 10036

For urgent medical issues that require the study's Medical Director be contacted, please refer to the contact list for complete contact information.

Ovid Therapeutics Inc. may transfer any or all if its study-related responsibilities to contract research organization and other third parties; however, Ovid retains overall accountability for these activities.

4. SIGNATURE PAGES

SPONSOR SIGNATURE PAGE

PROTOCOL

A Phase 2 Angelman Syndrome Clinical Trial: A Randomized, Double-blind, Safety and Efficacy Study of Gaboxadol (Short Name: STARS)

Protocol No: OV101-15-001

[redacted]

10/25/2017
Date (day/month/year)

5. GENERAL INFORMATION

PROTOCOL

A Phase 2 Angelman Syndrome Clinical Trial: A Randomized, Double-blind, Safety and Efficacy Study of Gaboxadol (Short Name: STARS)

Protocol No: OV101-15-001

Sponsor:	Ovid Therapeutics Inc. 1460 Broadway New York, NY 10036 USA
Clinical Research Organization:	[redacted]
Sponsor Medical Lead and Signatory	[redacted]
Steering Committee Meeting Chair:	[redacted]

[redacted]

The Medical Monitor must be contacted in the event of any urgent safety issues.

Ovid Therapeutics Inc. is transferring responsibilities as outlined in the Transfer of Obligations document.

6. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABC-C	Aberrant Behavior Checklist – Community
[redacted]	[redacted]
AE	Adverse event
AS	Angelman syndrome
[redacted]	[redacted]
ß-hCG	beta-Human chorionic gonadotrophin
BID	Twice daily
[redacted]	[redacted]
CGI-I	Clinical Global Impression – Improvement
CGI-S	Clinical Global Impression – Severity
[redacted]	[redacted]
CI	Confidence interval
COA	Clinical outcomes assessment
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
eCRF	Electronic case report form
EEG	Electroencephalogram
[redacted]	[redacted]
FAS	Full analysis set
FDA	Food and Drug Administration
FXS	Fragile X syndrome
GABA	Gamma-aminobutyric acid
GCP	Good clinical practice
ICF	Informed consent form
ICH	International Conference on Harmonization
IRB	Institutional review board
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary of Regulatory Activities
MM	Medical Monitor
[redacted]	[redacted]
MMRM	Mixed model repeated measures
[redacted]	[redacted]

[redacted]	[redacted]
PT	Preferred term
QD	Once daily
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
[redacted]	[redacted]
[redacted]	[redacted]
SOC	System organ class
SOL	Sleep onset latency
SOP	Standard operating procedure
SS	Safety analysis set
TEAE	Treatment-emergent adverse event
TST	Total sleep time
UBE3A/Ube3a	Ubiquitin protein ligase E3A
ULN	Upper limit of normal
USA	United States of America
WASO	Wake after sleep onset

7. STUDY SYNOPSIS

Name of Sponsor/Company:
Ovid Therapeutics Inc.

Name of Investigational Product:
OV101 (gaboxadol)

Name of Active Ingredient:
OV101 (gaboxadol)

Protocol Number:
OV101-15-001

Title of Study:
A Phase 2 Angelman Syndrome Clinical Trial: A Randomized, Double-Blind, Safety and Efficacy Study of Gaboxadol (Short Name: STARS)

Version Number:
Protocol Version 4.0

Study Indication:
Angelman syndrome (AS)

Study Rationale

OV101 (gaboxadol) is being evaluated in Phase 2 studies of subjects with AS. This rare neuro-genetic disorder occurs in approximately 1 in every 15,000 live births and manifests as several distinct characteristics. Consistent clinical findings range in severity and include developmental delay, movement and/or balance disorder, and tremulous movement of limbs. Perhaps the most unique behavioral characteristic is the combination of a happy demeanor, smiling, and frequent bouts of laughter. Moreover, these individuals possess an easily excitable personality exhibited by hand-flapping or waving movements. Finally, these individuals suffer from motor dysfunction related to gait and balance, severe disruptions in sleep, impairments in speech, and frequent seizures with characteristic abnormal electroencephalogram (EEG) patterns. Individuals with AS will require life-long care.

OV101 is the first highly selective extrasynaptic gamma-aminobutyric acid (GABA) receptor agonist that binds to the α4 and δ-subunit containing extrasynaptic GABA receptors as an orthosteric agonist and may restore the deficit in tonic inhibition that has been associated with AS. This is unlike any other GABAergic agent, including benzodiazepines, zolpidem and other Z-drugs, neurosteroids and drugs that act on GABA metabolism or uptake. Further, in a mouse model of AS, gaboxadol was shown to restore tonic inhibition in UBE3A-deficient cerebellar neurons and correct motor abnormalities in UBE3A-deficient mice.

These results suggest that OV101 may alleviate the motor dysfunction observed in individuals with AS. These potential effects on tonic inhibition may impact motor function in people with AS.

Previous Phase 2 and 3 studies in subjects with primary insomnia suggest OV101 is effective in restoring classical sleep parameters and slow-wave sleep, resulting in an improvement in the quality and restorative effects of sleep. One study using a transient insomnia model involving 100 subjects showed that administration of OV101 resulted in statistically significant improvements on both sleep induction and sleep maintenance. More importantly, these effects were achieved without the risk of drug dependence.

[redacted]

[redacted]

Since the targeted study population may not be compliant with certain study assessments, the highest possible level of flexibility will be applied to the schedule of assessments at each study center visit, thus minimizing the risk of missing or confounded data, while data reliability is maintained.

Phase of Development:
Phase 2

Study Design:
Multicenter, randomized, parallel (3-arm), double-blind, placebo-controlled

Study Location:
Approximately 15 specialized centers across the United States of America and 1 specialized site in Israel

Principal Investigator:
[redacted]

Study Period (first subject first visit to database lock):
1.5 year

Estimated date of first subject first visit:
1st Quarter 2017

Estimated date last subject last visit:
2nd Quarter 2018

Study Objectives and Endpoints:

The primary objective of the study is to evaluate the safety and tolerability of OV101 from Baseline to Week 6 and Week 12 in adolescent and adult subjects with AS across different dose levels and in 2 dosing schedules.

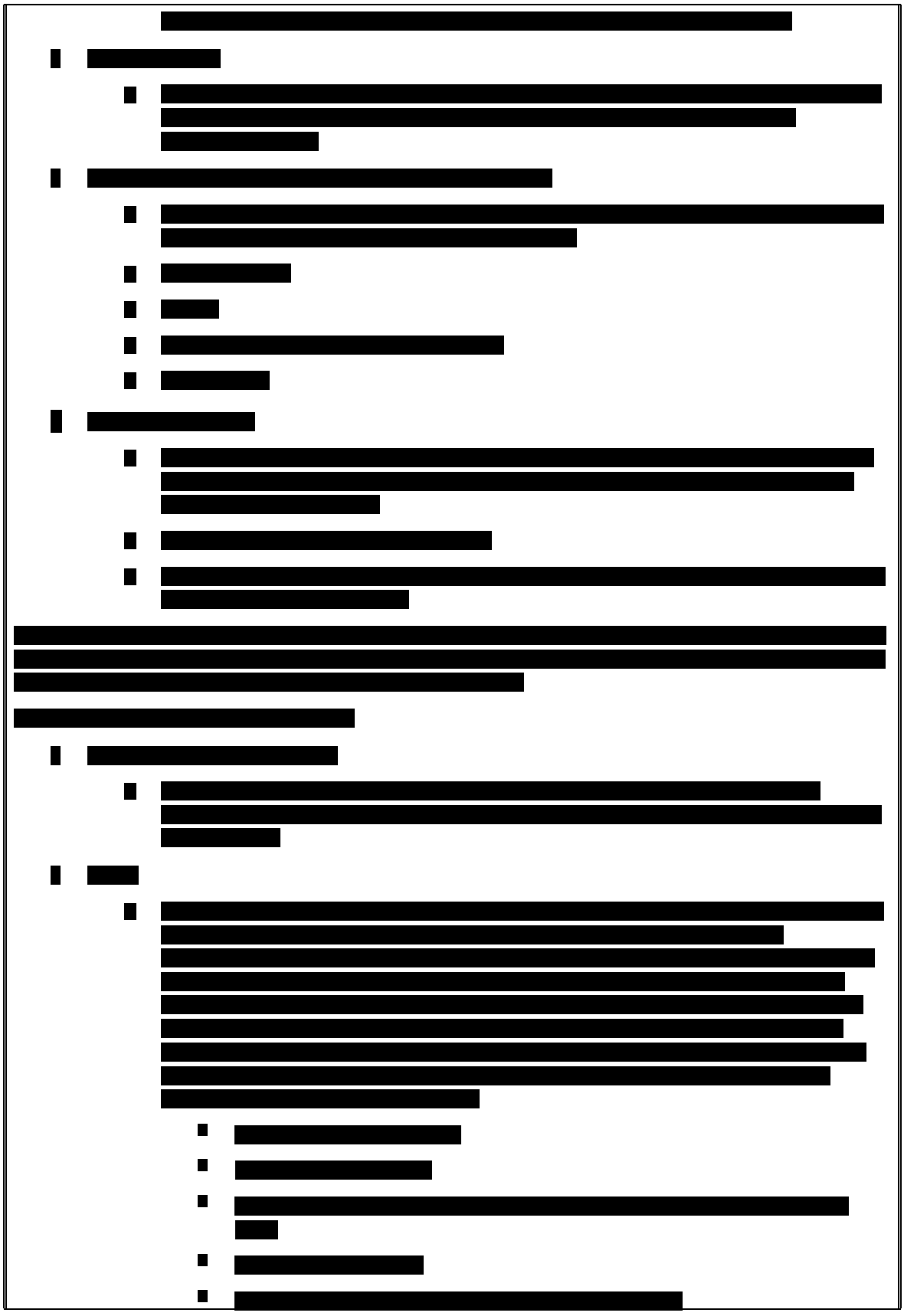
The following dosing schedules will be assessed against placebo:

- Once daily (QD): An evening dose titrated to the target dose of 15 mg unless not tolerated
- Twice daily (BID): Evening and morning doses titrated to the target doses of 15 mg evening dose and 10 mg morning dose unless not tolerated

The safety endpoints that relate to this objective are as follows:

- Frequency and severity of adverse events (AEs) and serious adverse events (SAEs)
- Vital signs (weight, blood pressure, heart rate, and temperature)
- Laboratory parameters (electrolytes, lipids, glucose, hepatic, renal and pancreatic function tests, and hematology). It is in the discretion of the study center staff to apply local best practices to obtain a blood sample from the subject
- Irritability will be assessed using the Aberrant Behavior Checklist – Community (ABC-C) in an attempt to assess suicidality
- EEG
- Caregivers will maintain an electronic seizure diary. Any clinically important changes, including changes in seizure medication, will be reported as a safety event
- Physical Exam findings

[redacted]



[redacted]

All safety and efficacy assessments will be performed as indicated in the schedule of assessments (Table S2). Assessments such as laboratory sampling and EEG should be done towards the end of a visit to minimize any confounding impact on subject performance. Options to perform these safety assessments away from the study center prior to the study center visit will be assessed in collaboration with study center staff and approved by the Medical Monitor case by case, if required.

Additional biomarker samples will be acquired from all subjects for whom the caregiver provides a separate informed consent for purification of DNA and plasma, to allow for identification of secondary pathogenic variants and metabolic profiles.

Number of subjects (planned):

Approximately 75 subjects will be enrolled. At the completion of the study, there will be approximately 25 subjects in each of the 3 treatment groups: 1) single evening dose 2) morning and evening dose, and 3) placebo.

Sample size calculations for this study are based on the objective of estimating AE rates within each active treatment group. The sample size of 25 subjects per group provides sufficient precision for estimation of incidence of common AEs. For example, a 2-sided 95% confidence interval (CI) for a true incidence of 25% will estimate that incidence with a 17% precision (half-width of the 95% CI).

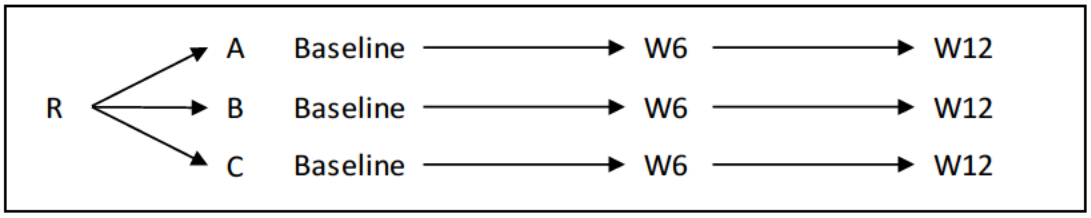
While the expected enrollment is 25 subjects per treatment group, if enrollment expectations are not realized, the sample size may be as low as 20 subjects per group. A sample size of 20 subjects per group provides sufficient precision for estimation of incidence of common AEs. For example, a 2-sided 95% CI for the true incidence of 25% will estimate that incidence with 19% precision.

[redacted]

Methodology:

All subjects will receive a morning dose (either OV101 or placebo) and an evening dose (either OV101 or placebo) during the entire duration of treatment. The 2 dosing schedules of OV101 will be assessed; a single evening dose (QD): based on what was previously clinically assessed in the treatment of sleep disorder; Schedule A) and a morning plus evening dose (Schedule B: BID) designed to provide a more sustained exposure. Schedule C is morning and evening placebo. All subjects will be up-titrated to the

target dose unless this target dose is not tolerated (for titration conventions see below). All subjects will receive treatment for a maximum of 12 weeks at their highest tolerated dose.



Investigational Product and Packaging:

OV101 is supplied as 5 mg capsules, and matching placebo capsules, in bottles. Bottles will have "Morning" or "Evening" printed on their labels. Caregiver will receive a sufficient number of capsules in 1 bottle "Morning" and 1 bottle "Evening" at Baseline and at Week 6 Interim visits.

Depending on the allocated treatment group, the "Morning"/"Evening" bottles will contain:

- Group A (QD): Morning – Placebo/Evening – OV101
- Group B (BID): Morning – OV101/Evening – OV101
- Group C (Placebo): Morning – Placebo/Evening – Placebo

Justification of dose range:

The evening dose was selected based on the safety and efficacy data from all studies conducted by Merck/H. Lundbeck A/S in the indication of insomnia (reference to IND 64,567 from H. Lundbeck A/S).

The morning dose was selected based on a Phase 1 study in healthy volunteers, which determined that a 10 mg morning dose had a similar safety profile to placebo.

The doses of OV101 administered will be the same for adolescent and adult subjects. PK results from the adolescent PK study OV101-16-001 indicate that the PK profile of OV101 following a single 5 mg oral administration to adolescent male and female subjects with Fragile X syndrome (FXS) or AS is comparable to data with the same dose previously obtained from healthy young adult subjects. Therefore, OV101 exposure in the present study is anticipated to be consistent across adolescent and adult subjects. While the same target dosages are planned in adolescent and adult subjects, dosing may be individualized at the investigators discretion based on tolerability through up- and down-titrations as described in Section 12.1.3.

Titration conventions:

Doses will be progressively increased in 5 mg increments (OV101 or placebo) (Table S1) to a target of 15 mg (3 capsules) in the evening and 10 mg (2 capsules) in the morning for each subject, which will deliver the target dose of 15 mg OV101 as an evening dose in Schedules A and B, and 10 mg OV101 as a morning dose in Schedule B. Each dose-escalation will be performed after adequate tolerability has been assessed by caregiver and investigator during a phone visit. Unscheduled study center visits are optional at any time to confirm tolerability.

The decision to up- or down titrate will be at investigator's discretion and can be discussed with the Sponsor Medical Monitor (MM) or his/her delegate if necessary. The study center will document each titration step in the eCRF and in source documents. The AEs triggering any down-titration need to be recorded. The study center will provide the caregiver with written dosing instructions until the next titration step, via fax, e-mail, or during an unscheduled on-study center visit.

Treatment initiation

- Day 1: Treatment can start on any day during the week. The next up-titration will occur on Day 3. If the defined interval occurs during the weekend, a + 2 day window for next titration step is acceptable, but the investigator should consider scheduling the start of treatment appropriately to limit titration steps occurring during the weekend. All subjects will start with 1 capsule (OV101 or placebo) in the evening

Given the potential effects with food:

- For the morning dose, it is recommended that the study drug be given with or shortly after the morning meal
- For the evening dose, it is recommended that study drug be given within 30 minutes of scheduled bedtime

Target up-titration

- Day 3 (window + 2 days): If no AE related to the study drug is observed from the previous time point by caregiver and/or the investigator, another capsule (OV101 or placebo) is added in the evening
- Day 7 (window + 2 days): If no AE related to the study drug is observed from the previous time point by caregiver and/or the investigator, another capsule (OV101 or placebo) is added in the evening
- Day 10 (window + 2 days): If no AE related to the study drug is observed from the previous time point by caregiver and/or the investigator, another capsule (OV101 or placebo) is added in the morning
- Day 14 (window + 2 days): If no AE related to the study drug is observed from the previous time point by caregiver and/or the investigator, another capsule (OV101 or placebo) is added in the morning

Slowed up-titration

If tolerability does NOT allow immediate further dose-escalation at any of the above detailed days (3, 7, 10, or 14), but if that is possible at subsequent visit (e.g. Day 10 instead of Day 7), also such delayed up-titration will be acceptable. In such a case, the investigator will record up-titration data during the additional phone titrations calls. Any intolerability will be documented as an AE.

Down-titration

Modifications may be made per investigator judgment on urgent need or medical necessity. If tolerability is not acceptable (e.g. somnolence, dizziness, vomiting, or change in behavior) after a previous up-titration step or during the 12 weeks of treatment, the Investigator should discuss with the Sponsor MM or his/her delegate if necessary. Any such intolerability must be documented as an AE. Once a tolerable dose has been reached, it shall remain constant for the duration of the treatment period.

Ongoing treatment

- Day 14: Earliest day the target dose can be reached (10 mg [2 capsules] in the morning and 15 mg [3 capsules] in the evening): if so, dosing should be kept stable until the End of Treatment visit (Week 12) unless intolerability requires down-titration per the above described conventions

Treatment and Titration Schedule

Table S1 Study Titration Schedule

Schedule/Time		Days 1 to 2	Days 3 to 6	Days 7 to 9	Days 10 to 13	Day 14*
Schedule A	Evening	5 mg 1 Capsule	10 mg 2 Capsules	15 mg 3 Capsules	15 mg 3 Capsules	15 mg 3 Capsules

* To end-of-study treatment period

Diagnosis and main criteria for inclusion:

Adolescents and adults with a molecularly-confirmed diagnosis of AS will be eligible for inclusion in the study. After obtaining signed informed consent from the parent/caregiver (or legally authorized representative) and assent as appropriate from the potential subject, individuals with AS will begin the study by completing the screening procedures to confirm eligibility which will include clinical and laboratory evaluation as well as all measurements that will be used to assess exploratory efficacy (sleep, motor function, and behavior).

Those who do not consent to the gene-biomarker sampling will still be eligible to participate in the STARS study.

For those individuals not possessing documentation of a molecularly-confirmed AS diagnosis, DNA samples will be obtained during the screening period and subjected to methylation sensitive polymerase chain reaction amplification of a portion of the small nuclear ribonucleoprotein polypeptide N gene or *UBE3A* sequencing to confirm the diagnosis of AS.

If a subject needs a repeat lab or additional lab to confirm eligibility the screening period may be extended.

Inclusion Criteria

1. Age ≥ 13 years, ≤ 49 years at the time of informed consent
2. Molecular confirmation of AS
3. Receiving a stable dose of concomitant medications such as anti-epileptic medication, gabapentin, clonidine, melatonin, trazadone, supplements, and special diets for at least 4 weeks prior to Baseline, and able to maintain these throughout the duration of the study
4. Has a parent or caregiver capable of providing informed consent on behalf of the subject and able

to attend scheduled study visits to participate in all assessments described in the protocol

5. Able to attend scheduled study visits and be willing to perform the required clinical evaluations
6. Able to ingest the study drug
7. Caregivers must agree not to post any subject's personal medical data related to the study or information related to the study on any website or social media site (e.g. Facebook, Twitter, etc.) until the study is completed

Exclusion Criteria

1. Non-ambulatory subjects (e.g. requiring a wheelchair) not able to perform the assessments of Motor Ability/Function
2. Poorly controlled seizures defined as > 3 seizures lasting less than 3 minutes per week or > 1 seizure episode lasting more than 3 minutes per week or as per medical monitor judgment
3. Concomitant cardiovascular or respiratory diseases of a degree that would limit participation in the study
4. Concomitant disease (e.g., gastrointestinal, renal, hepatic, endocrine 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.
5. Any of the following laboratory abnormalities: total bilirubin >1.5 x upper limit of normal (ULN) (unless isolated Gilbert's syndrome), alanine aminotransferase or aspartate aminotransferase >2.5 x ULN; serum creatinine >1.2 x ULN; absolute neutrophil count <1.5 x 10^9/L, platelets < 80 x10^9/L, hemoglobin <80 g/L; TSH >1.25 x ULN or <0.8 x ULN.
6. Pregnancy
7. Women of child-bearing potential who are not using a double-barrier method of contraception (e.g. condoms plus oral contraceptives), with abstinence being an accepted method
8. Concomitant use of minocycline, levodopa, zolpidem, zaleplon, eszopiclone, ramelteon or benzodiazepines for sleep, as well as, cannabinoid derivatives, and any other use of any investigational agent, device, and/or investigational procedure 4 weeks prior to Baseline and during the study
9. Allergy to OV101 or any excipients
10. At increased risk of harming self and/or others based on investigator assessment
11. Any condition or reason that in the opinion of the investigator makes the subject unsuitable for enrollment
12. Inability of subject or caregiver to comply with study requirements

Study periods, duration of treatment and follow-up:

1. Screening (up to 28 days) if a subject needs a repeat lab or additional lab to confirm eligibility the screening period may be extended.
2. Baseline visit (Day 1); full day visit
3. Titration period (2 weeks); at least 4 titration phone visits during that period
4. Treatment until end of Week 12; at least 3 safety phone visits during that period
5. Interim; full day visit at Week 6
6. End of Treatment; full day visit at Week 12
7. Follow-up period; the study center will have 1 phone visit (2 weeks after End of Treatment) to capture information on any AEs which occur after the End of Treatment visit

Statistical methods for analysis:

Descriptive statistics will be used to summarize all primary and secondary endpoints as well as baseline variables, by treatment group. For continuous variables, n, number of missing values, mean, standard deviation, median, minimum, and maximum will be provided. For categorical variables, frequency and percentage will be presented for each category. The CIs will be provided where meaningful. All CIs will be 2-sided 95% CIs. All data collected during the study will be listed.

The primary endpoint is the incidence of treatment emergent adverse events (TEAE). The Safety Analysis Set (all subjects that received at least one dose of study drug) will be used for the analysis of the TEAEs. All AEs will be coded using the latest released version of Medical Dictionary of 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 least one TEAE as well as the number and percentage of subjects who experience at least one TEAE within each specific SOC and PT will be presented by treatment group.

[redacted]

Table S2 Schedule of Assessments

Visit Name	[redacted]	[redacted]	Unscheduled	Phone Titrate	Phone Safety	Interim	Phone Safety	End of Treatment	Follow-up Phone*
Window			Any Time	+2 Days	± 2 Days	± 3 Days	± 2 Days	+ 3 Days	± 2 Days
	D -28 to D 0	D 1	Any Time	D 3, 7, 10, 14	D 31	D 43	D 57, 71	D 84	D 98
Week		1				6		12	14
ICF and Assent (Separate for Caregiver and Subject)	X								
Inclusion/Exclusion Criteria	X	X							
Medical History	X	X							
Clinical Assessment†	X	X		X	X	X	X	X	X
Biomarker Plasma‡		X						X	
Biomarker DNA‡		X							
Molecular AS Test§	X								
Dose Titration				X	X#	X#	X#		
Physical Exam	X	X				X		X	
Vital Signs	X	X				X		X	
Clinical Laboratory Tests	X	X				X		X	
Serum Pregnancy Test**	X	X				X		X	
EEG		X						X	
Adverse Events	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X
Check Scales Completed by Clinician:									
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]	[redacted]								
[redacted]									
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[redacted]									
[redacted]									
eDiary of Sleep Pattern††	X	X				X		X	
eDiary of Seizure Activity††	X	X				X		X	

	eDiary of Medication Compliance††		X				X		X	
Check Other Assessments Completed										
	[redacted]		[redacted]						[redacted]	
	[redacted]		[redacted]				[redacted]		[redacted]	

Abbreviations: ABC-C = Aberrant Behavior Checklist – Community; ABC-C-Irritability Subscale = Aberrant Behavior Checklist – Community – Irritability Subscale; [redacted] D = day; EEG = Electroencephalogram; [redacted] ICF = Informed Consent Form; [redacted]

* Safety follow-up phone visit 2 weeks after End of Treatment.
† Signs and symptoms of the syndrome.
‡ Only if separate ICF was signed.
§ Only if no written evidence for molecular diagnosis in subject records available.
# Ongoing up-titration if target dose could not be reached until Day 14. Down-titration for non-tolerability should be discussed with the Sponsor MM or his/her delegates if necessary.
** For women of child-bearing potential.
†† Continuous use and documentation; [redacted]

8. INTRODUCTION

8.1 Background and Overview of Angelman Syndrome

Angelman syndrome (AS) is a rare neurogenetic disorder associated with the deletion of or mutation in the Ubiquitin Protein Ligase E3A gene (*UBE3A*). While expressed ubiquitously in the cells of other tissues, in neurons the paternal allele is preferentially silenced through the epigenetic process known as imprinting. Therefore, any alteration in the maternal copy of *UBE3A* results in the expression of the AS phenotype. The syndrome occurs in approximately 1 in every 15,000 live births and has several distinct characteristics. Clinical findings range in severity and may include developmental delay, movement and/or balance disorder, and tremulous movement of limbs. The most unique behavioral characteristic is the combination of a happy demeanor, smiling, and easily provoked. Moreover, these individuals possess a short attention span and an easily excitable personality exhibited by hand-flapping or waving movements. Finally, individuals with AS suffer from motor dysfunction related to gait and balance, severe disruptions in sleep, impairments in speech, anxiety, and frequent seizures with characteristic abnormal electroencephalogram (EEG) patterns[1].

Current Therapies for Angelman Syndrome

There are no current specific treatments for AS. Clinical management includes management of symptoms including anti-epileptic medications for seizure control and oftentimes medications for sleep or anxiety. Physical and occupational therapies, communication therapy, and behavioral therapies are important in allowing individuals with AS to reach their maximum developmental potential[2].

Pre-clinical Experience with OV101

Research has shown that absence (or dysfunction) of *UBE3A* results in an aberrant increase in the uptake of gamma-aminobutyric acid (GABA), which the main inhibitory neurotransmitter in the brain. OV101 is the first highly selective GABA receptor agonist that binds to the α4 and δ-containing $GABA_A$ receptors. These receptors mediate tonic inhibition and contribute to sleep maintenance. Further, in a mouse model of AS, gaboxadol was shown to restore tonic inhibition in *Ube3a*-deficient cerebellar neurons and correct motor abnormalities in *Ube3a*-deficient mice[3].

These results suggest that OV101 may alleviate the motor dysfunction observed in individuals with AS. Importantly, OV101's ability to potentiate tonic inhibition is unlike any other GABAergic agent, including benzodiazepines, zolpidem, other Z-drugs, neurosteroids, and drugs that act on GABA metabolism or uptake.

In addition to the data on presynaptic dysfunction leading to reduced tonic inhibition, there are additional studies which speak to the potential of OV101 in AS, including modulation of sleep and cognition domains that are impaired in AS subjects[4,5,6,7,8,9].

[redacted]

[redacted]

Pharmacokinetics

The pharmacokinetic profile of OV101 was similar whether administered in the morning or evening in the fasting state [redacted][11]. There were also no differences between morning and evening pharmacokinetics when OV101 was given with food. A high-fat meal just prior to OV101 administration in the morning or evening delayed absorption by 0.5 to 1 hours and decreased maximum concentration by approximately 30%, while exposure was practically unchanged compared with the fasting state.

Prior Clinical Experience

OV101 was generally safe and well tolerated in all Phase 2 and 3 studies in more than 4300 subjects with insomnia, in non-elderly adult subjects (aged 18 to 64 years) at doses up to 15 mg (in 1 early Phase 2 study up to 20 mg). In non-elderly adult subjects, the most common adverse events (AEs) occurring 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 than in female subjects.

OV101 administration in the morning was safe at all doses [redacted][12]. 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 tolerated with considerable discomfort from Day 2 and onwards. An evening dose of 15 mg was well tolerated in young women and women above 55 years for 3 consecutive days. Therefore, a 10 mg morning dose was chosen for this study. The AEs with the highest incidences were dizziness, nausea, headache, and somnolence. The majority of AEs had a rapid onset (within 1 to 2 hours post-dose) and resolved after the drug was discontinued.

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 seemed to be dose related, with no AEs reported for the 5 mg dose, and only mild AEs reported for the 10 mg dose of OV101.

8.2 Study Rationale

OV101 acts with high potency and efficacy at extrasynaptic α4 and δ-containing $GABA_A$ receptors which are not activated by benzodiazepines, or agents acting at the benzodiazepine binding site (such as zolpidem, zaleplon, indiplon, and zopiclone). These extrasynaptic δ receptors are thought to be involved in mechanisms underlying tonic inhibition and sleep maintenance. *In vivo* and *in vitro* studies have shown that neither alcohol nor benzodiazepines potentiate the activity of OV101. In contrast to benzodiazepine receptor agonists, no withdrawal effects with OV101 are seen after chronic dosing.

The possibility that OV101 may alleviate the motor dysfunction observed in individuals with AS and the ability of OV101 to potentiate tonic inhibition makes OV101 a candidate for potential treatment of people with AS.

Based on previous clinical experience, in this study OV101 will be titrated across different dose levels (15 mg evening dose and 10 mg morning dose) and in 3 dosing schedules for 12 weeks.

The morning dose was selected based on a Phase 1 study in healthy volunteers which determined that a 10 mg morning dose had a comparable safety profile compared to placebo. The evening dose was selected based on the safety and efficacy data obtained from all studies conducted by H. Lundbeck A/S and Merck in the indication of insomnia (reference to IND 64,567).

This Phase 2 study will assess the safety and tolerability of oral OV101 in adolescent and adult subjects with AS. In addition, multiple endpoints will be explored to identify the most appropriate efficacy outcome measures for future Phase 3 studies.

This includes all main AS symptom domains of gross and fine motor function, sleep, behavior, and health-related quality of life, with focus on motor ability and sleep. The impact on caregivers will also be assessed. Questionnaires, diaries, [redacted] will be used, complemented by more innovative outcome measures (gait analysis).

Testing may be extensive for some of the study subjects, so the highest possible level of flexibility will be applied to the schedule of assessments at each study center visit to minimize the risk of missing or confounded data, while maintaining data reliability.

This study will be conducted in compliance with the protocol and with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP). More information can be found in the Investigator's Brochure.[10]

9. STUDY OBJECTIVES AND ENDPOINTS

9.1 Primary Objectives

The primary objective of the study is to evaluate the safety and tolerability of OV101 from Baseline to Week 6 and Week 12 in adolescent and adult subjects with AS across different dose levels and in 2 dosing schedules.

The following dosing schedules will be assessed against placebo:

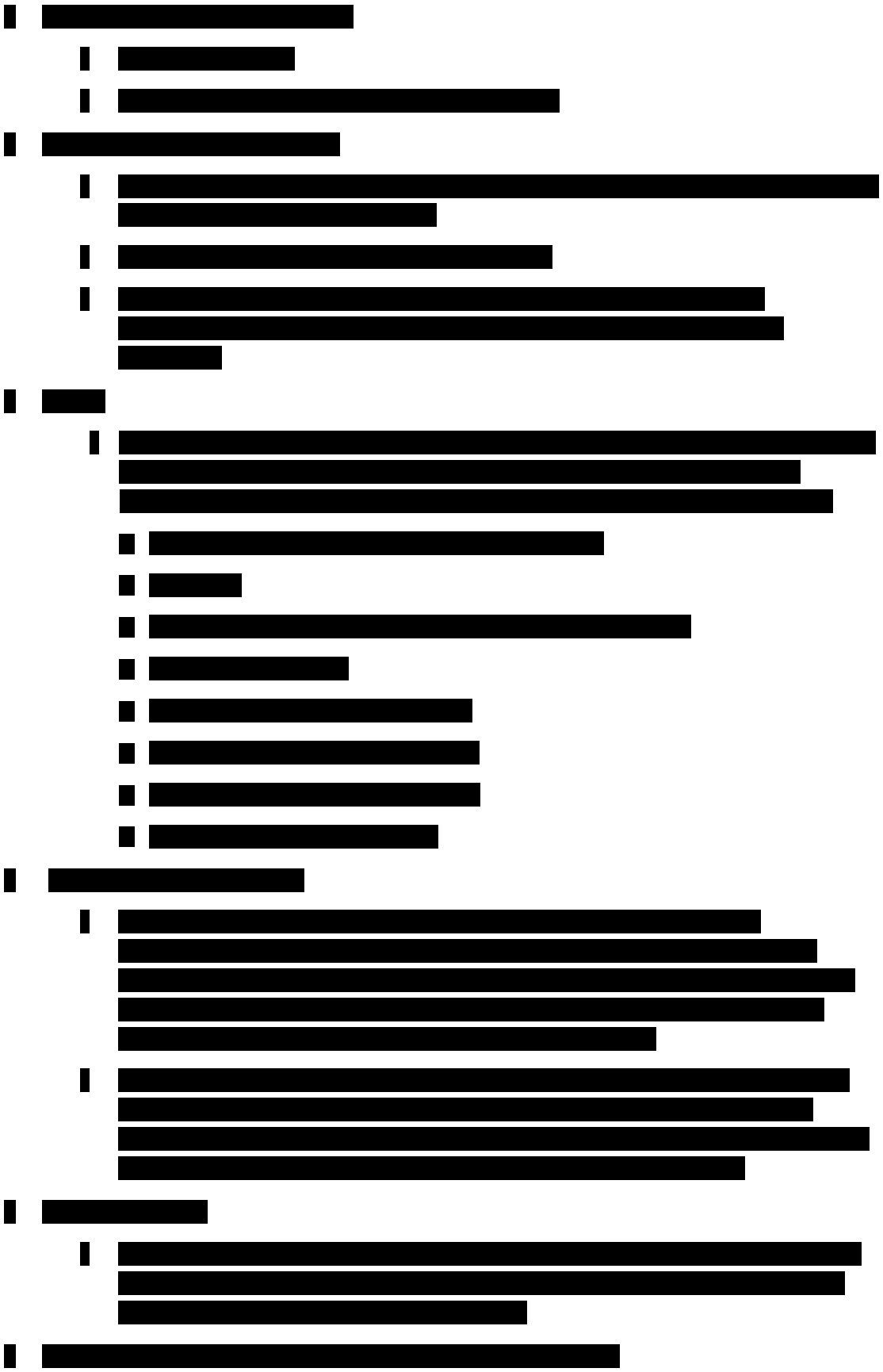
- Once daily (QD): An evening dose titrated to the target dose of 15 mg unless not tolerated
- Twice daily (BID): Evening and morning doses titrated to the target doses of 15 mg evening dose and 10 mg morning dose unless not tolerated

The safety endpoints that relate to this objective are as follows:

- Frequency and severity of AEs and serious adverse events (SAEs)
- Vital signs (weight, blood pressure, heart rate, and temperature)
- Laboratory parameters (electrolytes, lipids, glucose, renal, hepatic and pancreatic function tests, and hematology). It is in the discretion of the study center staff to apply the best local practices to obtain a blood sample from the subject. Laboratory sampling should be done towards the end of a visit to minimize any confounding impact on subject performance
- Irritability will be assessed using the Aberrant Behavior Checklist – Community (ABC-C), Irritability subscale as a surrogate measure for suicidality
- EEG
- Caregivers will maintain an electronic seizure diary. Any clinically important changes, including changes in seizure medication, will be reported as a safety event
- Physical Exam findings

9.2 Secondary Objective

[redacted]



[redacted]

9.3 Exploratory Objective

[redacted]

[redacted]

10. STUDY DESIGN

10.1 Overall Study Design and Plan

10.1.1 Description

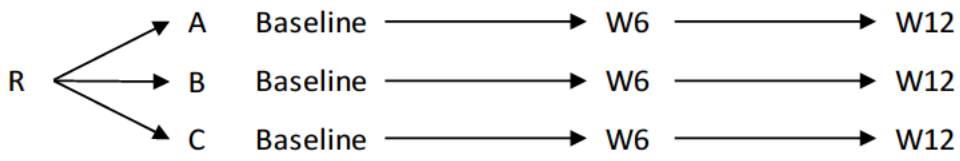
This is a multicenter, Phase 2, randomized, parallel (3 arm), double-blind, placebo-controlled study of OV101 in adolescent and adult subjects with AS. In addition, multiple efficacy endpoints will be assessed to identify the most appropriate and sensitive outcome measures for future efficacy studies. OV101 will be administered in 3 different dosing schedules (15 mg evening dose only [QD], or 15 mg evening dose plus 10 mg morning dose [BID], or placebo) for 12 weeks.

Approximately 75 subjects will be enrolled at approximately 15 study centers in the United States of America (USA) and 1 study center in Israel. At the completion of the study, there will be approximately 25 subjects in each of the 3 schedules: A) single evening dose, B) morning and evening dose, and C) placebo.

Adolescents and adults aged 13 to 49 years at the time of informed consent with a molecular confirmation of AS will be eligible for inclusion.

The study will comprise a screening visit; a baseline visit for treatment randomization; a titration period during which study treatment doses are progressively increased, which is part of the 12 weeks of treatment; a Week 6 visit for safety and efficacy assessments; a Week 12 visit for safety and efficacy assessments and End of Treatment visit procedures; and a 2 week telephone follow-up period to monitor safety. Figure 1 summarizes study design.

Figure 1: Study Design



Abbreviations: R = randomization; W = week

10.1.2 Schedule of Assessments

The schedule of assessments is presented in Table 1.

Table 1 Schedule of Assessments

Visit Name	Screening	[redacted]	[redacted]	[redacted]	[redacted] Safety	Interim	Phone Safety	End of Treatment	Follow-up Phone*
Window			Any Time	+2 Days	± 2 Days	± 3 Days	± 2 Days	+ 3 Days	± 2 Days
	D -28 to D 0	D 1	Any Time	D 3, 7, 10, 14	D 31	D 43	D 57, 71	D 84	D 98
Week		1				6		12	14
ICF and Assent (Separate for Caregiver and Subject)	X								
Inclusion/Exclusion Criteria	X	X							
Medical History	X	X							
Clinical Assessment†	X	X		X	X	X	X	X	X
Biomarker Plasma‡		X						X	
Biomarker DNA‡		X							
Molecular AS Test§	X								
Dose Titration				X	X#	X#	X#		
Physical Exam	X	X				X		X	
Vital Signs	X	X				X		X	
Clinical Laboratory Tests	X	X				X		X	
Serum Pregnancy Test**	X	X				X		X	
EEG		X						X	
Adverse Events	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X
Check Scales Completed by Clinician:									
CGI[redacted]		[redacted]				[redacted]		[redacted]	
[redacted]		[redacted]				[redacted]		[redacted]	
[redacted]		[redacted]						[redacted]	
[redacted]		[redacted]						[redacted]	
ABC-I (ABC-C Irritability Subscale)	See Caregiver ABC-C (Factor I) Score	X	X	X	X	X	X	X	X
Check Scales Completed by Caregiver:									
ABC-C	X	X				X		X	
[redacted]	[redacted]	[redacted]				[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]				[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]				[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]				[redacted]		[redacted]	
[redacted]		[redacted]				[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]				[redacted]		[redacted]	
[redacted]		[redacted]				[redacted]		[redacted]	
[redacted]		[redacted]						[redacted]	
eDiary of Sleep Pattern††	X	X				X		X	

	eDiary of Seizure Activity††	X	X				X		X	
	eDiary of Medication Compliance††		X				X		X	
Check Other Assessments Completed										
	[redacted]		[redacted]						[redacted]	
	[redacted]	[redacted]	[redacted]				[redacted]		[redacted]	

Abbreviations: ABC-C = Aberrant Behavior Checklist – Community; ABC-C-Irritability Subscale = Aberrant Behavior Checklist – Community – Irritability Subscale; [redacted]; AS = Angelman syndrome [redacted] CGI-I = Clinical Global Impression – Improvement; CGI-S = Clinical Global Impression – [redacted] D = day; EEG = Electroencephalogram; [redacted]

* Safety follow-up phone visit 2 weeks after End of Treatment.
† Signs and symptoms of the syndrome.
‡ Only if separate ICF was signed.
§ Only if no written evidence for molecular diagnosis in subject records available.
# Ongoing up-titration if target dose could not be reached until Day 14. Down-titration for non-tolerability should be discussed with the Sponsor MM or his/her delegates if necessary.
**For women of child-bearing potential.
††Continuous use and documentation [redacted] electronic subject reported outcomes data will be downloaded by study center staff at baseline, interim, and End of Treatment visits. [redacted]

10.1.3 Study Assessments

Section 14 details the individual assessments.

10.1.3.1 Screening Period (Day -28 to Day 0)

After obtaining a signed informed consent form (ICF) from the parent or legally authorized caregiver and assent as appropriate from the potential subject, individuals with AS will begin the study screening procedures for eligibility including clinical and laboratory evaluation and all measurements used for efficacy assessment (sleep, motor function, and behavior). 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 for non-verbal subjects.

Investigators will explain to caregivers the necessity to discontinue the intermittent use of sleep medication and not to introduce new medication during the study.

[redacted]

Study centers will request a subject registration and treatment code centrally generated by an Interactive Web Response System (IWRS) (Section 12.3). No subject may begin treatment prior to assignment of a unique identification number (registration) and randomization. Any subject identification numbers that are assigned will not be reused, even if the subject does not receive treatment.

Screening laboratory assessments will be performed.

Caregivers will also be asked to sign a separate ICF for the subject to provide an additional blood sample (1 tube) at Baseline (and on Day 84 [Section 10.1.3.2]) to permit purification of DNA and plasma to enable identification of secondary pathogenic gene variants and allow for metabolic profiling. Those not consenting to this will still be eligible for the main study.

All subjects will be screened for participation in the study up to 28 days prior to the first dose administration. Subjects who meet all criteria can be randomized at any time during the screening period. The screening assessments are listed in Table 1.

The caregiver will be provided with an e-Diary for documenting sleep and subject's seizures [redacted].

During the screening period, it will be determined by the Investigator whether or not the caregiver and subject are able to complete all questionnaires and assessments that require their contribution to assess their ability to comply with study procedures.

For those without documentation of a molecularly-confirmed diagnosis, blood samples will be obtained during the screening period and subjected to methylation sensitive polymerase chain reaction amplification of a portion of the small nuclear ribonucleoprotein polypeptide N gene and/or *UBE3A* gene sequencing to confirm the diagnosis of AS.

[redacted]

Screening and Baseline assessments must be performed within the 28-day period. If the subject can perform the Screening and Baseline visit within 5 days, the following assessments do not need to be repeated at the Baseline visit (medical history, clinical assessment, physical examination, clinical laboratory tests, serum pregnancy test, and concomitant medications).

Those not meeting the inclusion criteria or meeting an exclusion criterion will be considered a screen failure. It shall be discussed with Medical Monitor whether later rescreening is acceptable. Rescreening may be allowed under circumstances where the subject passed the screening but could not be randomized within the 28 day screening window due to logistical, personal or other unforeseeable reasons. Rescreening will only be allowed in cases where no safety risk is posed to the subject.

If a screening test result (lab or any other tests) is considered uncertain or abnormal, the test may be repeated to confirm the result after approval from the Medical Monitor. If a subject needs a repeat lab or additional lab to confirm eligibility the screening period may be extended.

10.1.3.2 Treatment Period (12 Weeks)

<u>Baseline Visit (Day 1; Full Day Visit)</u>

Eligible subjects will return to the study center for the Baseline (Day 1) visit. Caregivers will bring the e-Diary and wearables. Prior to randomization, study center staff must confirm proper recording of the wearables, appropriate completion of the e-Diary, and fulfilment of all selection criteria.

Subjects will be randomized on a 1:1:1 ratio according to the following dosing schedule:

- Schedule A: a single evening dose of OV101 (QD) plus morning placebo
- Schedule B: a morning plus evening dose of OV101 (BID)
- Schedule C: morning and evening placebo

- Subjects will receive the assigned package of blinded study treatment as per treatment code for the titration period and until the next scheduled visit at Week 6
- Baseline safety and efficacy assessments will be conducted

- Baseline laboratory assessments will be performed

[redacted]

The e-Diary will be kept by the caregiver throughout the study. It must be charged overnight each day by the caregiver. Study center staff shall remotely check data completeness at least once a week and contact caregiver if there is non-adherence, such as missing data.

Titration (Day 1 to Day 14)

Section 12.1.1 details the dosing schedule.

During the titration period (Day 1 to Day 14), doses progressively increase in 5 mg increments according to the titration schedule, allowing slower up- or down-titration if the OV101 or placebo treatment is not tolerated (Table 2) up to a target evening dose of 15 mg (3 capsules) in Schedules A and B, and up to a target morning dose of 10 mg (2 capsules) in Schedule B. Multiple phone visits are scheduled to confirm tolerability of study treatment. Each dose-escalation will be performed after adequate tolerability has been assessed by the caregiver and investigator during a phone visit. At any time, ad-hoc study center visits may occur to further assess drug safety. These should follow the script for phone visits.

If the target dose is not achieved at Day 14 (due to slowed titration based on intolerability), the up-titration can continue until the target dose or the maximum tolerated dose is reached. Additional phone visits to agree on next titration level will be performed. As a general guidance for investigators, for subjects undergoing a slowed titration regimen, the maximal tolerated dose for the duration of the study should be reached by Day 21.

Investigators will decide whether to up- or down-titrate based on subject symptomatology, which should be discussed with the Sponsor MM or his/her delegate as necessary. The study center will document each titration step in the electronic case report form (eCRF) and in source documents. The AEs triggering any slower- or down-titration will be recorded. Modifications may be made per investigator judgment based on urgent

need or medical necessity. If tolerability is not acceptable (e.g. somnolence, dizziness, vomiting, or change in behavior) after a previous up-titration step or during the course of the 12 weeks of treatment, the Investigator should discuss with the Sponsor MM or designee if necessary. Any such intolerability must be documented as an AE. Once a tolerable dose has been reached, it shall remain constant for the duration of the treatment period. The study center will provide the caregiver with written dosing instructions until the next titration step, by fax, e-mail, or during an unscheduled study center visit.

Treatment (Day 15 to Day 84); Until End of Week 12

If the target dose was not yet achieved at Day 14 (due to slowed titration based on intolerability), up-titration can continue until the target dose or the maximum tolerated dose is reached. Additional phone visits to agree on next titration level will be performed. As a general guidance for investigators, for subjects undergoing a slowed titration regimen, the maximal tolerated dose for the duration of the study should be reached by Day 21.

At Days 30 and 60 (±2 days) the caregiver will courier the wearables back to the study center, because battery life will come to an end around that time. Study center staff will upload and check data for any compliance or user errors. If errors are detected, the caregiver will be contacted to receive further instructions how to properly use the wearable. Study center staff will courier a new set of wearables to the caregiver.

Interim Visit (Week 6; Full Day Visit)

During the Week 6 visit (Day 43, window ±3 days); subjects will make an interim full day study center visit to for the following procedures:

- All scheduled safety and efficacy assessments will be conducted
- [redacted]
- Additional phone visits are scheduled to confirm tolerability of study drug
- If tolerability is not acceptable (e.g. somnolence, dizziness, vomiting, or change in behavior) after a previous up-titration step or during the course of the 12 weeks of

treatment, the Investigator should discuss with the Sponsor MM or designee if necessary. Any such non-tolerability must be reported as an AE.

End of Treatment (Week 12; Full Day Visit)

During the Week 12 visit (Day 84, window +3 days); subjects will make a final full day study center visit for the following procedures:

- Safety and efficacy assessments
- [redacted]
- Caregivers will bring the e-Diary to the study center. Any e-Diaries no longer required will be returned to the [redacted] at or before study center closure
- Subjects will be asked to volunteer an additional tube of blood to permit purification of DNA and plasma to enable identification of secondary pathogenic gene variants and allow for metabolic profiling
- The last dose of study drug should be taken the morning of the Day 84 visit if the subject is on the BID dosing regimen. After the last dose during the treatment period, downward titration of OV101 is not necessary given that in previous clinical studies with OV101, no withdrawal effects were observed after chronic dosing.

10.1.3.3 Follow-Up Period (Day 85 to 98)

During the follow-up period, the study center will have 1 phone visit (2 weeks after End of Treatment) to capture information on any AEs which occur after the End of Treatment visit, using the phone visit script.

10.1.3.4 Early Termination

The study may be terminated at an individual study center if it becomes apparent that subject enrollment is unsatisfactory with respect to quality and/or quantity. Study centers may also be closed if they prove to be unable to comply with the requirements of the protocol or GCP, or data recording is inaccurate and/or incomplete. If the study is terminated in an individual study center for any reason, the investigator must make every effort to follow-up all subjects as planned according to the protocol. Replacement of study centers is allowed and new study centers may be initiated. An initiative for study center closure or study termination can be taken at any time either by Ovid Therapeutics

Inc. or by the investigator, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

See Section 13 for early withdrawal from study. For early withdrawal, subject should follow Week 12 study visit schedule of assessment for safety measure which include medical history, clinical assessment, ABC-C irritability subscale, physical examination, clinical lab test, serum pregnancy test, concomitant medications. Efficacy assessments do not need to be completed.

10.2 Discussion of Study Design

Neither the investigators nor the subjects will be aware of the treatment assignments, to minimize any subjective or unrecognized bias in reporting. Placebo will be used as the comparator.

Based on the potential reproductive effects observed in pre-clinical studies, pre-menopausal females who have a positive pregnancy test at the screening or baseline visits, or those who are not able to use an effective method of contraception (with abstinence being an accepted method), will be excluded from the study.

Pre-clinical and clinical data suggest that the doses prescribed in this study will likely be therapeutically relevant and well-tolerated.

A variety of scales will be employed for the exploratory assessment of safety and exploratory efficacy endpoints (Section 13).

10.3 Risk/Benefit Assessment

In adult subjects, the most common AEs occurring more frequently in OV101-treated subjects than in subjects on placebo have been dizziness, nausea, vomiting, somnolence, and headache. Most AEs have been mild to moderate severity. OV101 is generally tolerated better by males than females and has been generally safe and well tolerated in Phase 2 and 3 insomnia studies in adult subjects at doses up to 15 mg and in the elderly at doses up to 10 mg.

OV101 is rapidly absorbed and eliminated when given orally at doses of 10 to 40 mg. The maximum plasma concentration is reached after half to 1 hour, the elimination half-life is approximately 1.5 hours and there is no evidence of accumulation after 5 days of multiple dosing. Pharmacokinetic data from the adolescent PK study OV101-16-001 with a single 5 mg oral administration to adolescent male and female subjects with FXS or AS suggest the exposure of OV101 is comparable to young adult subjects given the same dose. The dosing recommendation for adolescents in this study is therefore the same as for adults.

Close monitoring of safety will be conducted throughout this study.

11. SELECTION OF SUBJECTS

11.1 Diagnosis and Main Criteria for Inclusion:

Adolescents and adults with a molecularly-confirmed diagnosis of AS will be eligible for inclusion in the study. See Section 10.1.3.1 for testing of individuals who do not have documentation of diagnosis.

After obtaining signed informed consent from the legally authorized representative (e.g. parent or caregiver) and assent as appropriate from the potential subject, an individual with AS will begin the study screening procedures to confirm eligibility. The screening procedures to confirm eligibility will include clinical and laboratory evaluation as well as all measurements to assess exploratory efficacy (sleep, motor function, and behavior).

Those who do not consent to the gene biomarker sampling will still be eligible to participate in the STARS study.

[redacted]

For those individuals not possessing documentation of a molecularly confirmed AS diagnosis, DNA samples will be obtained during the screening period to confirm the diagnosis of AS.

If a subject needs a repeat lab or additional lab to confirm eligibility the screening period may be extended.

11.2 Inclusion Criteria

A subject will be eligible for enrollment in the study if ALL of the following criteria apply:

1. Age ≥ 13 years, ≤ 49 years at the time of informed consent
2. Molecular confirmation of AS
3. Receiving a stable dose of concomitant medications such as anti-epileptic medication, gabapentin, clonidine, melatonin, trazadone, supplements, special diets for at least 4 weeks prior to Baseline; and able to maintain these throughout the duration of the study
4. Has a parent or caregiver capable of providing informed consent on behalf of the subject and able to attend scheduled study visits to participate in all assessments described in the protocol
5. Able to attend scheduled study visits and be willing to perform the required clinical evaluations
6. Able to ingest the study drug

7. Caregivers must agree not to post any subject's personal medical data related to the study or information related to the study on any website or social media site (e.g. Facebook, Twitter, etc.) until the study is completed

11.3 Exclusion Criteria

A subject will NOT be eligible for this study if any of the following criteria apply:

1. Non-ambulatory subjects (e.g. requiring a wheelchair) not able to perform the assessments of Motor Ability/Function
2. Poorly controlled seizures defined as > 3 seizures lasting less than 3 minutes per week or > 1 seizure episode lasting more than 3 minutes per week or as per medical monitor judgment
3. Concomitant cardiovascular or respiratory diseases of a degree that would limit participation in the study
4. Concomitant disease (e.g., gastrointestinal, renal, hepatic, endocrine 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
5. Any of the following laboratory abnormalities: total bilirubin >1.5 x upper limit of normal (ULN) (unless isolated Gilbert's syndrome), alanine aminotransferase or aspartate aminotransferase >2.5 x ULN; serum creatinine >1.2 x ULN; absolute neutrophil count <1.5 x 10^9/L, platelets < 80 x10^9/L, hemoglobin <80 g/L; TSH >1.25 x ULN or <0.8 x ULN
6. Pregnancy
7. Women of child-bearing potential who are not using a double-barrier method of contraception (e.g. condoms plus oral contraceptives), with abstinence being an accepted method
8. Concomitant use of minocycline, levodopa, zolpidem, zaleplon, eszopiclone, ramelteon or benzodiazepines for sleep, as well as, cannabinoid derivatives, and any other use of any investigational agent, device, and/or investigational procedure 4 weeks prior to Baseline and during the study
9. Allergy to OV101 or any excipients
10. At increased risk of harming self and/or others based on investigator assessment
11. Any condition or reason that in the opinion of the investigator, makes the subject unsuitable for enrollment
12. Inability of subject or caregiver to comply with study requirements

11.4 Withdrawal of Subjects

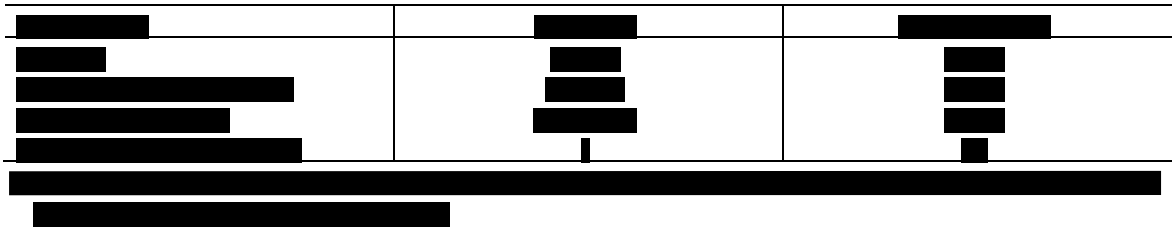
A subject may voluntarily withdraw at any time and for any reason. If a subject withdraws, at his or her request or at the request of his or her caregiver or legal representative, the reason(s) must be recorded on the relevant page of the subject's eCRF. Subjects who withdraw from the study prematurely should undergo all end-of-study assessments where possible. It is vital to obtain follow-up data on any subject withdrawn because of an AE. In any case, every effort must be made to undertake protocol-specified safety follow-up procedures. If a subject refuses to continue with study procedures, the reason for refusal should be fully documented in the subject's source document and recorded in the study specific eCRF. Subjects who withdraw from the study prior to completing the final follow-up visit may be replaced at the discretion of Ovid Therapeutics Inc.

12. TREATMENT OF SUBJECTS

12.1 Identity of Study Treatment(s)

12.1.1 OV101

[redacted]



12.1.2 Placebo

Placebo will be provided as a visually matching capsule, without active ingredient.

12.1.3 Administration of Study Treatments

OV101 will be supplied as a 5 mg capsule, and matching placebo, in bottles. The caregiver will receive a sufficient number of capsules in 1 bottle "Morning" and 1 bottle "Evening" at the baseline visit and at the Week 6 interim visit.

All subjects will receive a morning dose of OV101 or placebo and an evening dose of OV101 or placebo during the entire duration of treatment. Two dosing schedules of OV101 will be assessed; a single evening dose (Schedule A: QD) based on what was previously clinically assessed in the treatment of sleep disorder, and a morning plus evening dose (Schedule B: BID) designed to provide a more sustained exposure. Schedule C is morning and evening placebo (BID). All subjects will be up-titrated to the target dose unless this target dose is not tolerated (for titration conventions see below). All subjects will receive treatment for a maximum of 12 weeks at their highest tolerated dose. The last dose of study drug should be taken the morning of the Day 84 visit if the subject is on the BID dosing regimen.

Given the potential effects with food previously described:

- For the morning dose, it is recommended that the study drug be given with or shortly after the morning meal
- For the evening dose, it is recommended that study drug be given within 30 minutes of scheduled bedtime

The capsules can be opened and content added to one spoon of semi-liquid food (applesauce, pudding etc.). CAPSULE CONTENT CANNOT BE PLACED IN LIQUID. It must be documented specifically how the capsules were taken e.g. swallowed whole or taken in one spoon of applesauce or other food.

12.1.3.1 Titration Conventions

Doses will be progressively increased in 5 mg increments (OV101 or placebo) (Table 2) to a target of 15 mg (3 capsules) in the evening and 10 mg (2 capsules) in the morning for each subject which will deliver the target dose of 15 mg OV101 as an evening dose in Schedules A and B, and 10 mg OV101 as a morning dose in Schedule B. Each dose-escalation will be performed after adequate tolerability has been assessed by caregiver and investigator during a phone visit. Unscheduled study center visits are optional at any time to confirm tolerability.

The decision to up- or down-titrate will be at the investigator's discretion. The study center will document each titration step in the eCRF and in source documents. The AEs triggering any down-titration must be recorded. The study center will provide the caregiver with written dosing instructions until the next titration step, via fax, e-mail, or during an unscheduled on-study center visit.

Details for target up-titration, slowed titration, and down-titrations are provided in Sections 12.1.3.4, 12.1.3.5, and 12.1.3.6, respectively."

12.1.3.2 Titration Scheme

Table 2 summarizes the titration scheme.

Table 2 Study Titration Schedule

Schedule/Time	Days 1 to 2	Days 3 to 6	Days 7 to 9	Days 10 to 13	Day 14*
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* To end-of-study treatment period

12.1.3.3 Titration Initiation

Day 1: Treatment can start on any day during the week. The next up-titration will occur on Day 3. If the defined interval occurs during the weekend, a +2 day window for next titration step is acceptable, but the investigator should consider scheduling the start of treatment appropriately to limit titration steps occurring during the weekend. All subjects will start with 1 capsule (OV101 or placebo) in the evening.

12.1.3.4 Target Up-Titration

Day 3 (window + 2 days): If no AE related to study treatment is observed from the previous time point by caregiver and/or the investigator, another OV101 or placebo capsule is added in the evening.

Day 7 (window + 2 days): If no AE related to the study treatment is observed from the previous time point by caregiver and/or the investigator, another OV101 or placebo capsule is added in the evening.

Day 10 (window + 2 days): If no AE related to the study treatment is observed from the previous time point by caregiver and/or the investigator, another OV101 or placebo capsule is added in the morning.

Day 14 (window + 2 days): If no AE related to the study treatment is observed from the previous time point by caregiver and/or the investigator, another OV101 or placebo capsule is added in the morning.

12.1.3.5 Slowed Up-Titration

If tolerability does NOT allow immediate further dose-escalation at any of the above detailed days (3, 7, 10, or 14), but does at subsequent visit (e.g. Day 10 instead of Day 7), delayed up-titration will also be acceptable. In this case, the investigator will record up-titration data during the additional phone titrations calls. Any such intolerability must be documented as an AE.

12.1.3.6 Down-Titration

Modifications may be made per investigator judgment on urgent need or medical necessity. If tolerability is not acceptable (e.g. somnolence, dizziness, vomiting, or change in behavior) after a previous up-titration step or during the course of the 12 weeks of treatment, the Investigator should discuss with the Sponsor MM or his/her delegate if necessary. Any such intolerability must be documented as an AE. Once a tolerable dose has been reached, it shall remain constant for the duration of the treatment period.

12.1.3.7 Ongoing Treatment

Day 14: Earliest day the target dose can be reached (10 mg [2 capsules] in the morning and 15 mg [3 capsules] in the evening): if so, dosing should be kept stable until End of Treatment visit (Week 12) unless intolerability requires down-titration according to the above described conventions.

12.2 Study Treatment Packaging and Labeling

12.2.1 Packaging

OV101 will be supplied as a 5 mg capsule, and matching placebo, in 75 mL bottles containing 90 capsules for morning and 120 mL bottles containing 140 capsules for evening. The caregiver will receive a “Morning” bottle and an “Evening” bottle at Baseline and Week 6, respectively. Depending on the allocated treatment group, the “Morning” or “Evening” bottles will contain the following:

- Group A (QD): Morning – Placebo/Evening – OV101

- Group B (BID): Morning – OV101/Evening – OV101
- Group C (Placebo): Morning – Placebo/Evening – Placebo

12.2.2 Labeling

Bottles containing OV101 or matching placebo, will have color tinted labels marked "Morning" (yellow label) or "Evening" (blue label). Labels will include the Sponsor Name (Ovid Therapeutics Inc.), protocol number, bottle number (based on randomization), expiration date, number of capsules (each bottle), "Morning" or "Evening" and "Take as directed", as well as storage specifications. Each bottle will be labeled with an English and Spanish label. Bottles and study treatment will be distributed by unique bottle number as designated by the IWRS and bottle quantities will be supplied to each study center in accordance with IWRS.

12.2.3 Storage

Study treatment must be received by a designated person at the study center, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated staff have access. Study treatments are to be dispensed only in accordance with the protocol. The investigator is responsible for keeping accurate records of study treatment supplies received from Ovid Therapeutics Inc., the amount dispensed to and returned by the subjects, and the amount remaining at the conclusion of the study. Study treatment should be stored at ≤ 86°F.

12.3 Blinding and Randomization to Study Treatments

This is a double-blind, placebo-controlled study. Investigators, study staff, and study subjects will be blinded to the randomized study treatment assignments. Both randomization and blinding techniques will be used in this study to minimize bias. A computer-generated randomization schema will be centrally available via IWRS to all clinical centers that meet the requirements for participation in the study. The IWRS system can be accessed by individuals who have been issued a user ID and password, such as individuals at the study center or individuals from [redacted]

[redacted] Caregivers and investigators will also be asked at the End of Treatment visit whether they believe the subject was in an OV101 or placebo treatment arm.

12.4 Procedure for Breaking the Randomization Code

In most cases, study drug unblinding will not be necessary. In a medical emergency where knowledge of the subject's treatment assignment may influence the subject's clinical care, the investigator, and if applicable, designated personnel at [redacted] may access the subject's treatment assignment. The study center investigator and appropriate [redacted] project team members will be authorized to access the emergency unblinding functionality within the IWRS. The system will require the user to enter an authorization key number to complete the emergency unblinding transaction. The exact description of the treatment assigned to the individual subject then will be accessible. Emergency

unblinding can thus be made for any subject without affecting the double-blind nature of the study. Subject treatment information may only be accessed in the event of an emergency and out of necessity to know the identity of the allocated study drug to institute appropriate therapeutic management. The investigator should make every effort to discuss the rationale for emergency unblinding with the [redacted] Medical Monitor prior to unblinding the individual subject. Emergency unblinding should only be considered in situations where the knowledge of the treatment code has an impact on the planned treatment of the emergency. Once the randomization code is broken for a subject, he/she must be withdrawn from the study.

Should a situation arise where unblinding is urgently required (i.e. knowledge of treatment code is required to adequately manage a life-threatening situation), the investigator at that study center may perform immediate unblinding through IWRS without the need for communication with the [redacted] Medical Monitor.

In the event that emergency unblinding is performed, the investigator can view and must print the blinded confirmation document from IWRS. The investigator must record on the confirmation document printout the reason for the emergency unblinding, and sign the document. The confirmation document must then to be kept in a safe place until the end of the study. Once a randomization code has been broken, the investigator must inform the [redacted] Medical Monitor in writing within 24 hours. The investigator is strongly advised not to divulge the subject's treatment assignment to any individual not directly involved in managing the medical emergency, nor to personnel involved with the analysis and conduct of the study. The investigator can contact Ovid Therapeutics Inc. or their designee to discuss such situations without divulging subject's treatment assignment.

12.5 Subject Compliance

Study drug compliance will be assessed by the investigator and/or study center staff by recording capsule counts of study treatments from the previously dispensed capsules, separately for "Morning" and "Evening" bottles. The investigator and/or study center staff will also assess whether the subject has been given the capsules in the prescribed order. The total number of doses administered to each subject will be derived from dosing information recorded in the eCRF.

Caregivers must bring the bottles back at each study center visit. Any remaining capsules will be counted and recorded to assess compliance. Caregivers shall be questioned as to the reason why remaining capsules have not been administered (e.g. forgot because not part of routine, subject refused, subject had side effects so parent decided to give a drug holiday, couldn't open the bottle, down-titration recommended by doctor, etc.) and the approximate time of any missed doses.

12.6 Study Drug Accountability

Records shall be maintained of the delivery of study drugs to the study centers, the inventory at the study centers, the use by each subject and the return to Ovid Therapeutics Inc.

These records shall include dates, quantities, batch numbers, expiry dates and the unique code numbers assigned to the study drug and to the study subjects.

The investigator shall be responsible for ensuring that the records adequately document that the subjects were provided the doses specified in the protocol and that all study drug received from Ovid Therapeutics Inc. is reconciled. All randomization codes must be returned to Ovid Therapeutics Inc. at the end of the study.

After completion of the study, all unused study drug will be inventoried and returned to Ovid Therapeutics Inc. or as directed by them.

12.7 Concomitant Therapy

Medication other than those listed in the Exclusion Criteria (Section 11.3) that are given at stable dose for at least 4 weeks prior to Baseline (e.g. constant use of sleep or anti-epileptic medication) are acceptable, and must be documented in the eCRF.

Any changes in dose should be avoided during the study and, if felt necessary, be previously discussed with the Medical Monitor.

Medications that are not prohibited and considered necessary for the subject's safety and well-being may be given during the study at the discretion of the investigator and must be recorded in the appropriate sections of the eCRF.

All prior medications taken within 30 days and ongoing concomitant medication must be documented in the eCRF.

Subjects must be receiving a stable dose of concomitant medications, including anti-epileptic medication, gabapentin, clonidine, melatonin, trazadone, supplements, and special diets, for at least 4 weeks prior to Baseline, and be able to maintain these throughout the study. Modifications may be made per investigator judgment based on urgent need or medical necessity. Subjects with questions about allowed concomitant therapy should seek medical guidance from the investigator.

13. DISCONTINUATION OF STUDY TREATMENT OR WITHDRAWAL OF SUBJECTS FROM STUDY

13.1 Withdrawal/Discontinuation of Individual Subjects

The reasons for study drug discontinuation and/or subject withdrawal from the study must be recorded in the subject's eCRF. The investigator must notify Ovid Therapeutics Inc. and/or the Medical Monitor immediately when a subject has been discontinued/withdrawn due to an AE.

13.1.1 Withdrawal from the Study

Subjects or their caregiver may withdraw subjects from the study at any time for any reason without compromising the subject's medical care. The investigator may also withdraw subjects from the study.

Subjects who withdraw from the study prior to the End of Treatment visit should complete the procedures scheduled for that visit. The reason for subject withdrawal will be recorded in the eCRF.

Withdrawal of subjects for any reason should be discussed with the Medical Monitor.

13.1.2 Discontinuation of Study Drug

If it is necessary to discontinue the study drug earlier than planned, subjects should continue to be followed per protocol to capture safety and efficacy assessments for the duration of the study period if feasible.

The investigator may withdraw the subject from the study drug for the following reasons:

- Upon subject's or caregiver's request
- The subject or caregiver is unwilling or unable to adhere to the protocol-specified visits
- The subject experiences an intolerable AE
- During the study, the subject develops symptoms or conditions listed in the exclusion criteria
- Other medical reason, at the discretion of the investigator and/or the Medical Monitor

Subjects who discontinue the study due to an AE considered related to study drug should be followed until the event is resolved, considered stable, or the investigator determines the event is no longer clinically significant. Study drug discontinuation due to AEs considered not related to study drug will be followed until resolution.

13.2 Study Termination

The study, or any portion of it, may be terminated at any time for safety reasons including the occurrence of AEs or other findings suggesting unacceptable risk to subjects, administrative, or operational reasons. Study centers must promptly notify their IRB and initiate withdrawal procedures for participating subjects.

14. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

14.1 Efficacy Assessments

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

14.1.4 (Mal)adaptive Behaviors:

- The **Aberrant Behavior Checklist - Community (ABC-C)** is a rating scale that measures the severity of a range of problem behaviors commonly observed in individuals with intellectual and developmental disabilities[17]. It is completed by the caregiver. It is an empirically developed scale designed to measure psychiatric symptoms and behavioral disturbance exhibited by individuals across 5 domains with 58 items: irritability, agitation, and crying (15 items), lethargy, social withdrawal (16 items), stereotypy (7 items), hyperactivity/noncompliance (16 items), and inappropriate speech (4 items). Most individuals with AS are not able to communicate thoughts of suicidality, so subject irritability reported by the caregiver is being used as a surrogate measure of suicidality.
    - The ABC–C Irritability subscale will be used as an indicator for suicidality. The investigator will review the scale items with the caregiver at each scheduled time point. If grading worsens, the investigator must decide whether that indicates a suicidal ideation of the subject, and if so, must document it as an AE and closely monitor it until resolution. The ABC-C Irritability subscale will be used to assess risks of suicidality (safety variable). The Aberrant Behavior Checklist was developed for use with individuals living in institutions and residential settings. Revisions to the measure have made it more applicable for home and school settings; the commonly used measure is now the ABC-C version.
- [redacted]

14.1.5 Clinical Change:

Clinical Global Impressions (Severity [CGI-S] and Improvement [CGI-I] scales). Both scales will assess all sub-domains of AS (gross and fine motor ability, sleep, and adaptive behavior) and will be filled out by the caregiver and investigator. For the CGI-S, the rating should be relative to all people, including typically developing individuals in the community. This rating is based upon observed and reported symptoms, behavior, and function. The CGI-I rates total improvement compared to the subject's condition at baseline.

[redacted]

15. SAFETY ASSESSMENTS

Details for safety assessments are provided below. Details regarding the management of AEs are provided in Section 16.

15.1 Suicidality

Most individuals with AS are not able to communicate thoughts of suicidality, so subject irritability reported by the caregiver is being used as a surrogate measure of suicidality. The ABC–C Irritability subscale will be used as an indicator for suicidality. The investigator will review the scale items with the caregiver at each scheduled time point. If grading worsens, the investigator must decide whether that indicates a suicidal ideation of the subject, and if so, must document it as an AE and closely monitor it until resolution.

15.2 Physical Examination

A physical examination should be performed at each visit to evaluate the medical condition of the subject and detect any sign/symptom of AEs, and to perform all the procedures required per protocol.

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

15.3 Vital Signs

The following vital signs will be recorded during this study (this must include but not be limited to the measurement of changes in heart rate and blood pressure):

- Heart rate
- Blood pressure
- Body temperature
- Weight

15.4 Laboratory Assessments

Blood samples will be collected for routine clinical laboratory safety evaluations. Study center staff can apply the best local practices to obtain a blood sample in this population.

Additional laboratory safety evaluations will be performed at other times, if judged to be clinically appropriate, or if the ongoing review of the data suggests a more detailed assessment of laboratory safety evaluations is required. Any changes to the scheduled times of laboratory safety tests will be agreed with [redacted] and Ovid Therapeutics Inc. and documented. The investigator will perform a clinical assessment of all laboratory safety data.

Laboratory parameters include electrolytes, lipids, glucose, renal, hepatic and pancreatic function tests, and hematology. A serum pregnancy test will be done for female subjects at the times noted in Table 1.

Table 3 lists the clinical chemistry and hematology tests planned for this study.

Table 3 Clinical Chemistry and Hematology Tests

Clinical Chemistry	Hematology
Albumin	Basophils (absolute)
Alkaline phosphatase	Eosinophils (absolute)
Alanine aminotransferase	Lymphocytes (absolute)
Aspartate aminotransferase	Monocytes (absolute)
Bicarbonate	Neutrophils (absolute)
Calcium	Basophils
Chloride	Eosinophils
Cholesterol	Hematocrit
Creatine kinase	Hematology slide
Creatine, enzymatic	Hemoglobin
Direct bilirubin	Lymphocytes
Glucose, random, serum	Monocytes
High density lipoprotein cholesterol	Neutrophils
Indirect bilirubin	Platelets
Lactate dehydrogenase	Red blood cells
Low density lipoprotein cholesterol, calculated	White blood cells
Phosphorous	-
Potassium	-
Sodium	-
Total bilirubin	-
Total protein	-
Triglyceride	-
Urea (blood urea nitrogen)	-
Uric acid	-
Total cholesterol	-
Magnesium	-
Thyroid stimulating hormone	-

15.5 Electroencephalogram Assessments

EEG will be assessed as changes in background rhythms and the frequency of epileptiform discharges. Study centers will perform a routine EEG with local equipment. EEG should be done towards the end of a visit to minimize any confounding impact on subject performance. Standard protocol and montage will be followed as outlined in the separate EEG manual, including but not limited to resting and evoked stimuli. Placing of electrodes (if possible according to the international 10/20 system) must be documented. Recording should last about 10 minutes in the wake state, and if possible, recording should end with a nap period. Data will be collected in electronic format in European Data Format for centralized reading. An EEG manual will be provided.

15.6 Optional Biomarker Analysis

Additional biomarker samples will be acquired from all subjects for whom the caregiver provides separate informed consent for purification of DNA, and plasma, to allow for identification of secondary pathogenic variants and metabolic profiles.

Two tubes of blood will be collected at baseline for biomarker plasma and biomarker DNA and one tube of blood will be collected at End of Treatment (Day 84) for isolation biomarker plasma. DNA will be used to identify secondary pathogenic variants that may be present (e.g. microdeletions encompassing 2q21.3)[18] and plasma for quantification of metabolites (e.g. glutamic acid)[19]. This data will not be captured in the CSR.

16. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

The timing and frequency of safety assessments are described in Table 1 and Section 15.

16.1 Adverse Events

16.1.1 Definitions

The definitions for TEAEs, AEs, and SAEs are given below. The Principal Investigator is responsible for ensuring that all study center staff are familiar with the content of this section. Any AE experienced by the subject between the screening visit (Day -28) and up to completion of the follow-up period after the last administration of study drug (Day 98 follow-up phone visit) must be recorded on the eCRF, regardless of the severity of the event or its relationship to study treatment.

Adverse Event (AE)

An AE is defined as any untoward medical occurrence in a clinical investigation subject, administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Determination of whether an abnormal laboratory value meets the definition of an AE will be made by the investigator. Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result meets the criteria for an SAE
- A laboratory test result requires the subjects to receive specific corrective therapy
- A laboratory abnormality that the investigator considers to be clinically significant

Any intolerance that triggers a dose reduction during the titration period must be documented as an AE.

Treatment-Emergent Adverse Event (TEAE)

A treatment-emergent adverse event (TEAE) is defined as an AE with an onset that occurs after receiving study drug (AE start date ≥ first dose date) and within 30 days after receiving the last dose of study drug (AE start date minus last dose date ≤ 30), or an AE that occurs pre-treatment but worsens post treatment.

Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that at any dose:

- Results in death

- In the view of the investigator, places the subject at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongs existing hospitalization. Planned hospitalizations will NOT be reported as an SAE unless categorized as otherwise medically important
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is otherwise medically important: Important medical events that may not result in death, be life-threatening or require hospitalization may be considered a serious adverse drug experience, when based on appropriate medical judgment, they may jeopardize the subject or the subject may require medical or surgical intervention to prevent one of the outcomes listed in this definition

16.1.1.1 Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment, including hospitalization that is part of the study design will not be considered an SAE, even if the subject is hospitalized. The study center must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled prior to obtaining the informed consent to participate in the study
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the investigator between the informed consent and time of procedure or treatment
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission

16.1.1.2 Recording of Adverse Events

For the purposes of this study, any detrimental change in the subject's condition, from the screening visit (Day -28) and up to completion of the follow-up period after the last administration of study drug (Day 98 follow-up phone visit) should be considered an AE and must be recorded on the eCRF.

All SAEs and AEs will be recorded starting from the screening visit (Day -28).

All ongoing AEs should be followed up for 30 days after the last administration of study drug, with the exception of any ongoing study drug-related AEs, which should be followed until resolution, unless in the investigator's opinion, the AE is unlikely to resolve due to the subject's underlying disease. Any new SAEs occurring up to 28 days after the last administration of study drug (Day 98 follow-up phone visit) should be reported according to Section 16.1.1.6.

At any time after the follow-up visit, if an investigator learns of an SAE that can be reasonably related to study drug, he/she should promptly notify Ovid Therapeutics Inc.

The severity of AEs and SAEs will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, Version 4). Any AE not listed in the CTCAE will be graded as follows:

Severity Grade	Definition
1	Mild AE
2	Moderate AE
3	Severe or medically significant AE
4	Life-threatening AE
5	Death related to AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 16.1.1.

An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

16.1.1.3 Abnormal Laboratory Values/Vital Signs

Laboratory/vital sign abnormalities should be reported as AEs if any one of the following criteria is met:

- Any criterion for an SAE is fulfilled
- The laboratory/vital signs abnormality causes the subject to discontinue from the study treatment
- The laboratory/vital signs abnormality causes the subject to interrupt the study treatment
- The laboratory/vital signs abnormality causes the subject to modify the dose of study treatment
- The investigator believes that the abnormality should be reported as an AE
- If an abnormal laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom should be reported as an AE and the associated laboratory result or vital sign should be considered additional information that must be collected on the relevant eCRF

16.1.1.4 Deaths

Should a death occur within the study period or within 60 days after the last administration of study drug an AE form and an SAE form should be completed, detailing the AE that resulted in the death (death is an outcome, not an event). The SAE must be reported to the [redacted] Medical Monitor within 24 hours. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

16.1.1.5 Relationship to Study Treatment

The investigator will assess the causality/relationship between the study drug and the AE and record that assessment in the eCRF. The investigator should use medical judgment to determine whether there is a "reasonable causal relationship", including all relevant factors such as temporal course and latency, results from de-challenge or re-challenge, pattern of the reaction, known pharmacological properties of the product, and alternative explanations, such as other drugs, medical history, and concomitant diseases.

The expression "reasonable causal relationship" means to convey in general that there are facts (evidence) or arguments to suggest a causal relationship. Assessment will be documented on the AE and SAE form.

The relationship should be assessed according to the following criteria:

- No Reasonable Possibility: The relationship of the clinical event to the study drug makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.
    - None (intercurrent event): An event that is not and cannot be related to the study drug, such as subject is a passenger in a road traffic accident
    - Unlikely (remote): Relationship is not likely, such as a clinical event including laboratory test abnormality with temporal relationship to drug administration which makes a causal relationship improbable and in which other drugs, chemicals or underlying disease provide plausible explanations
- Reasonable Possibility: The relationship of the clinical event to the study drug makes a causal relationship possible, and other drugs, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.
    - Possible: Relationship may exist, but event could have been produced by the subject's condition or treatment or other cause
    - Probable: Relationship is likely, the AE abates upon discontinuation of study drug and cannot be due to the subject's condition
    - Definite: Strong relationship, the event abates upon discontinuation of study drug and, if applicable, re-appears upon repeat exposure

For the purposes of AE and SAE assessment, the causality criteria of Possible, Probable, and Definite are considered to represent a "reasonable causal relationship". Conversely, the causality criteria of None or Unlikely are not considered to meet this threshold.

For an AE to be a suspected study drug-related event there should be at least a reasonable possibility of a causal relationship between the study drug and the AE.

16.1.1.6 Reporting of Serious Adverse Events

Investigators and other study center staff must inform appropriate [redacted] representatives of any SAE that occurs (whether or not attributable to the study drug) in the study within 24 hours (i.e. immediately but no later than the end of the next business day) or when he

or she becomes aware of it. 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 within 24 hours:

[redacted]

In a study-related medical emergency situation, when assigned Medical Monitors for a study cannot be reached by a caller, an on-call Physician can be reached 24 hours per day, 7 days per week via the [redacted]

[redacted]

(chargeable telephone number allowing a global reach from both landlines and mobile phones)

[redacted]

On this internet page, a list of country-specific toll-free telephone numbers is provided. It should be noted that not all countries globally have access to toll-free numbers as indicated on the "24/7 Medical Help Desk" index. Countries without toll-free numbers need to dial the chargeable number as indicated above. Furthermore, toll-free numbers are not available from mobile phones.

The [redacted] will work with the investigator to compile all the necessary information and ensure that the appropriate Ovid Therapeutics Inc. representative receives a report within one day (24 hours) for all fatal and life-threatening cases and within 5 days for all other SAEs.

Follow-up information on SAEs must also be reported by the investigator within the same time frames.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to [redacted] within one day as described above. For a non-serious AE that become serious but which is not fatal or life-threatening a report should be received within 5 days.

The following variables will be recorded for each AE: verbatim/AE description, time and date for AE start and stop, maximum intensity, seriousness, causality rating, whether or not the AE caused the subject to discontinue, and the outcome.

All SAEs have to be reported, whether or not considered causally related to the investigational product or to the study procedures. All SAEs will be recorded in the eCRF. The investigator is responsible for informing the Ethics Committee of the SAE as per local requirements. The investigator should report to [redacted], who will forward the report to the appropriate Ovid Therapeutics Inc. representative.

16.1.2 Overdose

An overdose is any dose of study treatment administered to a subject or taken by a subject that exceeds the dose assigned to the subject according to the protocol. Overdoses are not considered AEs and should not be recorded as an AE on the eCRF; however, all overdoses must be recorded on the overdose form and faxed to the [redacted] Safety Group within 24 hours of the study center becoming aware of the overdose. An overdose must be reported to the [redacted] Safety Group even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded. If an overdose results in an SAE, both the SAE and overdose forms must be faxed to the [redacted] Safety Group. If no AE is observed, this should be clearly stated in the report.

16.1.3 Pregnancy

Females of child-bearing potential (not surgically sterile) will undergo serum beta-human chorionic gonadotrophin (ß-hCG) pregnancy test at the times shown in Table 1. Any female subject with a positive pregnancy test result at Screening or Baseline must be excluded from the study. A serum ß-hCG pregnancy test must be performed if any woman is suspected of becoming pregnant during the study.

If pregnancy occurs, study drug must be discontinued immediately. Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even after the subject has been withdrawn from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported to Ovid Therapeutics Inc. on a pregnancy outcomes report form.

16.1.4 Medical Emergency

In a medical emergency requiring immediate attention, study center staff will apply appropriate medical intervention, according to standards of care. The investigator should contact the study Medical Director.

16.1.5 Safety Responsibilities

16.1.5.1 Investigator

The investigator responsibilities include:

- Monitor and record all AEs and SAEs, regardless of severity or relationship to study treatment

- Determine the seriousness, relationship, and severity of each event
- Determine the onset and resolution dates of each event
- Complete an SAE form for each SAE and fax it to [redacted] Safety within 24 hours of the study center becoming aware of the event
- Pursue SAE follow-up information actively and persistently
- Ensure all AE and SAE reports are supported by documentation in the subject's medical records
- Pursue AE follow-up information, if possible, until the event has resolved or become stable
- Report SAEs to local ethics committees as required by local law

16.1.5.2 Ovid Therapeutics Inc.

Ovid Therapeutics Inc. responsibilities include:

- Before study center activation and subject enrollment, ensure the study center staff reviewed the definitions of AE and SAE and the instructions for monitoring, recording, and reporting them
- Notify all appropriate regulatory authorities, ethics committees, and investigators of SAEs as required by local laws within required timeframes

17. STATISTICAL EVALUATION

17.1 Sample Size and Power

Sample size calculations for this study are based on the objective of estimating AE rates within each active treatment group. The sample size of 25 subjects per group provides sufficient precision for estimation of incidence of common AEs. For example, a 2-sided 95% confidence interval (CI) for a true incidence of 25% will estimate that incidence with a 17% precision (half-width of the 95% CI).

While the expected enrollment is 25 subjects per treatment group, if enrollment expectations are not realized, the sample size may be as low as 20 subjects per group. A sample size of 20 subjects per group provides sufficient precision for estimation of incidence of common AEs. For example, a 2-sided 95% CI for the true incidence of 25% will estimate that incidence with 19% precision.

[redacted]

17.2 Statistical Methods

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a separate Statistical Analysis Plan (SAP), which will be maintained by [redacted] This document may modify the plans outlined in the protocol; however, any major modifications of the endpoint definition and/or its analysis will also be reflected in a protocol amendment. Adverse events and efficacy variables may be further described by additional subgroups, such as age group, and details of this analysis will be provided in the SAP. Additional unplanned analyses may be required after all planned analyses have been completed. Any unplanned analyses will be clearly identified in the SAP.

17.2.1 General Considerations

All statistical analyses will be performed using Version 9.4 of Statistical Analysis Software (SAS®).

Data summaries will use descriptive statistics (number of subjects [n], mean, standard deviation [SD], Q1, median, Q3, minimum, and maximum) for continuous variables, and frequency and percentage for categorical and ordinal variables. If there are missing

values, the number missing will be presented, but without a percentage. All data collected will be included in by-subject data listings.

Unless otherwise specified, all tests will be 2-tailed using a 0.05 level of significance. All CIs will be 2-sided 95% CIs.

17.2.2 Statistical Analysis Sets

The following 4 analysis sets will be included:

Safety Analysis Set

The Safety Analysis Set (SS) will consist of all subjects who receive at least one dose of study drug. Subjects will be analyzed according to the treatment they actually receive. The SS will be the primary analysis set for safety analyses.

Intent-to-Treat Set

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

Full Analysis Set

The Full Analysis Set (FAS) will consist of all randomized subjects who receive at least 1 dose of study drug, and have at least 1 efficacy evaluation after receiving study drug. Subjects will be analyzed according to their randomized group. The FAS will be the primary analysis set for efficacy analyses.

Per Protocol Set

The Per Protocol Set is a subset of the FAS that includes all subjects who complete the Week 12 visit, and have no significant protocol violations that are deemed to impact efficacy. These violations include but are not limited to violations of inclusion/exclusion criteria, less than 80% study drug compliance, and usage of prohibited concomitant medications. Further details will be provided in the SAP. Subjects will be analyzed according to their randomized group.

17.2.3 Baseline, Efficacy, and Safety Variables

All baseline efficacy and safety variables will be presented using descriptive statistics by treatment group. The 2-sided 95% CIs will be provided where meaningful.

More details of subgroup analysis will be provided in the SAP.

17.2.3.1 Baseline Variables

Baseline variables include:

- Demographic characteristics: age, age group (adolescents aged 13 to 17 versus adults aged 18 to 49 years), gender, race, and ethnicity
- Enrollment by Study center/geographic region
- Presence of baseline comorbidities
- Baseline psychometric measures/scales

- Prior and concomitant medications
- Medical and surgical history

17.2.3.2 Safety Variables

The following safety variables will be evaluated:

- SAEs, and TEAEs throughout the study, TEAEs leading to study discontinuation, treatment-related TEAEs, and TEAEs of special interest
- Clinical safety laboratory values at Weeks 6 and 12
- Suicidality (using the ABC–C Irritability subscale) at Weeks 6 and 12
- Vital signs at Weeks 6 and 12
- EEG and seizure diary assessments from baseline to end-of-study
- Physical Exam at weeks 6 and 12

17.2.3.3 Efficacy Variables

[redacted]

[redacted]

17.2.4 Methods of Statistical Analyses

The SS and FAS will be used for safety and efficacy data analysis, respectively. Subjects in the FAS will be analyzed according to their randomized treatment arm.

17.2.4.1 Safety Analysis

All AEs will be coded using MedDRA Dictionary Version 19.1 and will be classified by MedDRA system organ class (SOC) and preferred term (PT).

The number and percentage of subjects who experience at least one TEAE and the number and percentage of subjects who experience at least one TEAE within each specific SOC and PT will be presented by treatment group. The 95% CIs will be displayed for the frequency of TEAEs. Treatment-related AEs will be considered those at least possibly related to investigational product based on the investigator's assessment. The number and percentage of subjects reporting serious AEs, treatment-related AEs, and AEs leading to treatment discontinuation will also be summarized for each treatment group by MedDRA SOC and PT.

Descriptive statistics for laboratory values and vital signs at each time point will be summarized by treatment group. Clinically significant laboratory values may be tabulated by treatment group.

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

Tables and graphical displays (such as scatter plots of baseline versus worst post-baseline values) of key safety parameters may be generated to better understand the study drug safety profile.

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

17.2.4.2 [redacted]

[redacted]

[redacted]

17.2.4.3

[redacted]

18. DIRECT ACCESS TO SOURCE DATA/NOTES

The investigator/institution shall provide direct access to source data/documents for study-related monitoring, audits, IRB review and regulatory inspection.

19. QUALITY CONTROL AND QUALITY ASSURANCE

19.1 Conduct of the Study

Ovid Therapeutics Inc. or [redacted] shall implement and maintain quality control and quality assurance procedures with written standard operating procedures (SOPs) to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, GCP and applicable regulatory requirements.

This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 1996) and all revisions thereof, and in accordance with Food and Drug Administration (FDA) regulations (Code of Federal Regulations, Sections 312.50 and 312.56) and with ICH Guidelines on GCP (CPMP 135/95).

The investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IRB, except when necessary to eliminate immediate hazards to the subject or when the change(s) involve(s) only logistical or administrative aspects of the study. Deviations must be reported to [redacted] and the IRB per local guidelines.

19.2 Study Monitoring

The investigator shall permit the Study Center Monitor to review study data as frequently as deemed necessary to ensure that data are being recorded in an adequate manner and that protocol adherence is satisfactory.

The investigator shall access medical records for the Study Center Monitor so that entries in the eCRFs may be verified. The investigator, as part of his/her responsibilities, is expected to co-operate with [redacted] in ensuring that the study adheres to GCP requirements.

The investigator may not recruit subjects into the study until such time that a site visit, or with the agreement of Ovid Therapeutics Inc., attendance at the investigator meeting, has been made by an Ovid Therapeutics Inc. or [redacted] monitor to conduct a detailed review of the protocol and eCRF.

20. ETHICS

20.1 Institutional Review Board

Prior to the start of the study, the investigator is responsible for ensuring that the protocol and ICF have been reviewed and approved by a relevant IRB. The IRB shall be appropriately constituted and perform its functions in accordance with FDA, ICH/GCP, and local requirements as applicable.

The IRB shall approve all protocol amendments (except for logistical or administrative changes), written ICFs and documents updates, subject recruitment procedures (e.g. advertisements), written information to be provided to the subjects, Investigator's Brochure, available safety information, information about payment and compensation available to subjects, the investigators curriculum vitae and/or other evidence of qualifications and any other documents requested by the IRB and Regulatory Authority (Competent Authority) as applicable.

When required, the IRB and Regulatory Authority must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

20.2 Written Informed Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent from the parent/caregiver (or legally authorized representative) and assent, as appropriate, from the potential subject must be provided separately for each subject and their legally authorized caregiver in accordance with local practice and regulations. [redacted] Should a subject gain the ability to sufficiently comprehend the situation and consent during the course of the study, written informed consent or verbal assent will be documented as required or recommended by the institution's IRB.

The background of the proposed study, the procedures, the benefits and risks of the study, and that the study participation is voluntary for the subject must be explained to the subject (or the subject's legally authorized representative). The subject's caregiver must be given sufficient time to consider whether to participate in the study.

The form of consent to be obtained will depend on the condition of the subject as determined by the Principal Investigator. The ICF, as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50.

A copy of the signed and dated ICF (and assent as applicable) must be given to the subject's caregiver or legally authorized representative. The signed and dated ICF will be retained with the study records. Local regulations must be followed with respect to the final disposition of the original (wet signature) and copies of the signed and dated ICFs.

The ICF for subject participation must also be available as part of the subject's medical record for review by the site's dedicated study monitor or any authorized auditor of Ovid Therapeutics Inc. or regulatory authorities.

All ICFs must be approved by the appropriate IRB and by Ovid Therapeutics Inc. The ICF must not be altered without the prior agreement of the relevant IRB and Ovid Therapeutics Inc.

21. DATA PROTECTION

Prior to any testing under this protocol, including screening test and assessments, subjects must also provide all authorizations required by local law (e.g. Protected Heath Authorization in North America).

The subject will not be identified by name in the eCRF or in any study reports, and these reports will be used for research purposes only. Ovid Therapeutics Inc., its partners and designees, IRBs, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical information confidential.

22. CONFLICT OF INTEREST

The investigators should address potential conflicts of interest (e.g. financial interest in Ovid or partnering companies) with the caregivers before the caregiver makes a decision to participate in the study.

23. CLINICAL TRIAL STEERING COMMITTEE

A Clinical Trial Steering Committee will oversee all aspects of study design and execution and provide oversight and overall direction for the study. The committee members will contribute to the study design, protocol, protocol amendments, and ensure ethical conduct of study. The committee members will champion the study for investigators and study centers and ensure the well-being, rights, and safety of study participants, and will be responsible for communication of study results.

24. CHANGES TO FINAL STUDY PROTOCOL

All protocol amendments must be submitted to the IRB and regulatory authorities as required by local law. Protocol modifications that affect subject safety, the scope of the study, or the scientific quality of study must be approved by the IRB before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation. However, Ovid Therapeutics Inc. may at any time amend the protocol to eliminate an apparent immediate hazard to a subject. In this case, appropriate regulatory authorities will be notified subsequent to the modification. In the event of a protocol modification, the ICF may require similar modifications.

25. DATA HANDLING AND RECORD KEEPING

25.1 Electronic Case Report Forms/Source Data Handling

The investigator shall be provided with standardized eCRFs and shall ensure that all data from subject visits are promptly entered into the eCRFs in accordance with the specific instructions given. The investigator must sign each eCRF to verify the integrity of the data recorded.

A list of the normal ranges for all laboratory tests to be undertaken forms part of the documentation to be collated prior to study start. If a central laboratory has been selected to conduct any or all tests, it is essential that all samples be analyzed at that laboratory.

The investigator must maintain source documents, such as laboratory reports, EEGs, consultation reports, and complete medical history and physical examination reports.

Data to be recorded directly on the eCRFs (i.e. no prior written or electronic record of data) and considered to be source data must be identified in the protocol.

25.2 Retention of Essential Documents

The minimum retention time for study records will meet the strictest standard applicable to that study center, as dictated by institutional requirements or local laws or regulations. Prior to proceeding with destruction of records, the investigator must notify Ovid Therapeutics Inc. in writing and receive written authorization from them to destroy study records. The investigator must also notify Ovid Therapeutics Inc. of any changes in archival arrangements, including but not limited to, archival at an offsite facility or transfer of ownership if the investigator leaves the study center.

The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents should be retained until at least 5 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 until at least 5 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 Ovid Therapeutics Inc. It is the responsibility of Ovid Therapeutics Inc. to inform the investigator/institution as to when these documents no longer need to be retained.

26. FINANCING AND INSURANCE

Ovid Therapeutics Inc. shall carry an insurance policy to cover compensation of subjects' health injuries arising from the study. Subjects who incur a study-related injury may be treated (and other necessary measures taken) at the study center and/or another medical institution. If it is necessary to compensate for the treatment, Ovid Therapeutics Inc. will cover the cost and shall not impose on the subject the burden of proving the causal relation between the study and the injury.

If any of the following is confirmed, Ovid Therapeutics Inc. may refuse or restrict the payment of the compensation:

- A serious GCP or protocol deviation by the investigator or sub-investigator (except deviation medically necessary to avoid an immediate hazard to study subjects)
- Intentional act or negligence on the part of the investigator or sub-investigator or malpractice thereby
- Injury caused by unlawful act or delinquency of a third party
- Injury caused by intentional act or negligence of the subject

If compensation becomes necessary for a study-related injury, the study center will promptly notify Ovid Therapeutics Inc. and will co-operate with Ovid Therapeutics Inc. and its insurer (or their legal representatives) in their handling thereof.

27. REGISTRATION OF STUDY AND DISCLOSURE OF RESULTS

Ovid Therapeutics Inc. will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations. Ovid Therapeutics Inc. shall retain the ownership of all data. When the study is complete Ovid Therapeutics Inc. shall arrange the analysis and tabulation of data. A clinical study report shall then be prepared, which may be used for publication, presentation at scientific meetings or submission to regulatory authorities. All proposed publications based on this study must be subject to Ovid Therapeutics Inc.' approval requirements.

28. SIGNATURE OF INVESTIGATOR

I agree to conduct the study outlined above in accordance with the terms and conditions of the protocol, ICH guidelines for GCP and with applicable regulatory requirements. All information pertaining to the study shall be treated in a confidential manner.

Investigator Signature	Date (day/month/year)

Print Name

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