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

Published: 18-03-2020
Last updated: 17-01-2025

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

Ethical review	Approved WMO
Status	Completed
Health condition type	Congenital and peripartum neurological conditions
Study type	Interventional

Summary

ID

NL-OMON49727

Source
ToetsingOnline

Brief title
ELARA

Condition

- Congenital and peripartum neurological conditions

Synonym
Angelman Syndroom

Research involving
Human

Sponsors and support

Primary sponsor: Ovid Therapeutics Inc.

Source(s) of monetary or material Support: Sponsor

Intervention

Keyword: Angelman Syndrome, OV101

Outcome measures

Primary outcome

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

Descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum) will be presented for continuous variables and frequency and percentage will be presented for categorical and ordinal variables. If there are missing values, the number missing will be presented, but without a percentage. All data collected will be included in by-subject data listings.

Two sided 95% CIs will be provided where appropriate. Graphical displays will be utilized to investigate trends over time overall and by relevant subgroups as needed.

Secondary outcome

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

All safety analyses will be performed on the safety analysis set.

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

Treatment-related AEs will be identified as those that are at least possibly related to study drug based on the investigator*s assessment. The number and percentage of subjects with treatment-related AEs, SAEs, TEAEs leading to study discontinuation, and TEAEs leading to death will also be summarized by SOC and PT. For each SOC and each PT, a subject will be counted only once for subject-incidence tabulations. For summaries by severity or relationship, for a given subject, the highest severity and relationship for a specific PT will be considered.

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

Shift tables for laboratory parameters will be presented.

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

Abnormal findings in physical examinations will be listed

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

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

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

Study description

Background summary

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

and approximately 500 adult subjects in non-insomnia-related studies.
Angelman syndrome is a severe, complex, and rare neurogenetic disorder with the prevalence of approximately 1 in every 10,000 to 24,000 live births. The condition is associated with impaired expression of the ubiquitin protein ligase E3A gene (UBE3A). While ubiquitin protein ligase E3A (UBE3A) is expressed bi-allelically in the cells of other tissues, in neurons the paternal allele is preferentially silenced through the epigenetic process known as imprinting. Therefore, any alteration in the maternal copy of UBE3A results in AS. Clinical findings range in severity and include developmental delay/intellectual disability, movement and/or balance disorder, and tremulous movement of limbs. Unique behavioral characteristics include the combination of a happy, smiling demeanor with easily provoked laughter and excitability (exhibited by hand-flapping and stereotypic movements). Individuals with AS frequently have motor dysfunction related to gait and balance, severe disruptions in sleep, little to no speech, short attention span, anxiety, and seizures with characteristic abnormal electroencephalogram patterns.
Current treatments are aimed at managing symptoms and include antiepileptic medications for seizure control and medications for sleep and behavioral problems (eg, anxiety). Other therapies include speech therapy, physical therapy, occupational therapy, and educational resources. Notably, current treatments do not target the underlying brain deficits.
OV101 is the first highly selective, extrasynaptic gamma-aminobutyric acid (GABA) receptor agonist that binds orthosterically to the δ-subunit of extrasynaptic GABA receptors. The mechanism of action of OV101 is unique among GABAergic agents, including benzodiazepines, zolpidem and other zolpidem-like drugs, neurosteroids, and drugs that act on GABA metabolism or uptake. Research has shown that absence (or dysfunction) of UBE3A results in an aberrant increase in the uptake of GABA, which is the main inhibitory neurotransmitter in the brain. OV101 is the first highly selective GABA receptor agonist that acts on α4δ-containing GABA A-receptors. These receptors mediate tonic inhibition and sleep maintenance. In a mouse model of AS, OV101 was shown to restore tonic inhibition in UBE3A deficient cerebellar neurons and correct motor abnormalities in UBE3A deficient mice. These results suggest that OV101 may alleviate the motor dysfunction observed in individuals with AS.
Importantly, OV101*s ability to potentiate tonic inhibition is unlike any other GABAergic agent, including benzodiazepines, zolpidem, zaleplon, zopiclone, barbiturates, neurosteroids, and drugs that act on GABA metabolism or uptake.
In addition to the data on presynaptic dysfunction leading to reduced tonic inhibition, there are additional studies which speak to the potential of OV101 in AS, including modulation of sleep and cognition domains that are impaired in subjects with AS.
Phase 2 and Phase 3 studies in adult subjects with primary insomnia demonstrated that OV101 is effective in restoring classical sleep parameters (sleep induction and sleep maintenance) and slow wave sleep, resulting in an improvement in the quality and restorative effects of sleep.

Study objective

The primary objective of this study is to evaluate the long-term safety and tolerability of OV101 in individuals with AS assessed by the incidence and severity of AEs and SAEs in subjects who are at least 2 years old.
The secondary objectives of this study are the following:
• To evaluate the long-term efficacy of OV101 treatment assessed by changes in behavior and sleep in subjects with AS who are at least 4 years old
• To evaluate the long-term safety and tolerability of OV101 treatment assessed by changes in suicidality assessments, vital sign measurements, laboratory assessments, physical examinations, and seizure frequency in subjects with AS who are at least 2 years old
The exploratory objectives of this study are to evaluate changes in motor and adaptive function and quality of life with OV101 in subjects with AS who are at least 4 years old and to explore the relationships among study endpoints (eg, behavior and sleep), where appropriate.

Study design

This will be an open-label, long-term safety study for evaluation of treatment with OV101 in up to 200 subjects with AS who either have completed previous Ovid studies (OV101-15-001, OV101-16-001, or OV101-19-001) or are siblings (with AS) of subjects with AS who have completed previous Ovid studies of OV101.

As this study will enroll subjects who may have completed previous studies for different periods of time before entering this study (as well as subjects with AS who have not been themselves enrolled in an Ovid study), subjects may be required to complete screening and baseline visits before receiving OV101 under this protocol.

The study will comprise a screening period of up to 30 days; a baseline visit on Day 1 for baseline assessments; a first dose of study drug to be taken in the evening of Day 1 (at bedtime); and clinic visits for safety and efficacy assessments over a 3-year treatment period. After the baseline visit, the clinic visits will occur at Weeks 12, 36, 64, 96, 128, and 160 (EOT). Phone visits will occur at Weeks 24, 48, 80, 112, and 144. A follow-up phone safety visit at the EOS will occur approximately 14 days after the last dose of study drug (EOT) to assess safety and tolerability associated with discontinuation of treatment. A subject will be considered to have completed the study after completing the EOS phone visit.

The following subjects will be required to complete screening and baseline visits (and assessments) to determine eligibility before receiving OV101 under this protocol:
• Subjects who completed OV101-15-001 or OV101-16-001

• Subjects who are siblings of subjects who have completed OV101-15-001, OV101-16-001, or OV101-19-001
• Subjects who completed treatment in OV101-19-001 more than 2 weeks before completing the baseline visit under this protocol (OV101-18-002)
For subjects required to complete the screening and baseline visits, the planned duration of study participation is approximately 166 weeks from the start of screening to the EOS visit, including 160 weeks of treatment with OV101.

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

Subjects who meet all eligibility criteria will be enrolled on Day 1 (baseline visit) and start the study drug that evening at bedtime (not in the clinic).
Each subject*s LAR/caregiver will receive a package of study drug at the baseline visit, sufficient to last until the Week 12 visit.
Each subject*s dose of OV101 will be titrated to a maintenance dose, as tolerated by the subject. The maximum tolerated dose (up to 15 mg at bedtime) will be maintained to the EOT. Subjects 2 to 12 years old (inclusive) weighing more than 64 kg and subjects at least 13 years old will have a targeted maximum dose of 15 mg. Subjects 2 to 12 years old (inclusive) weighing 64 kg or less will have a target maximum dose determined by their weight.

Phone calls to manage titration will occur on Days 6, 11, and 15 for all subjects. Subjects 2 to 12 years old (inclusive) weighing 64 kg or less will have their body weight measured at every clinic visit after the initial titration to allow for adjustment of the maximum dose to a greater weight. Phone calls to manage dose titration, if needed due to weight gain, will occur 5 days later to assess tolerability.

At the Week 12, 36, 64, 96, and 128 visits, each subject*s LAR/caregiver will receive a package of study drug sufficient to last until the next scheduled clinic visit at the maximum possible dose. Unused study drug will be collected at Week 12, 36, 64, 96, 128, and 160 clinic visits.
The LAR/caregivers will complete sleep diaries on behalf of subjects over the 7-day periods immediately preceding Baseline and the Week 12, 36, 64, 96, 128, and 160 clinic visits.
The LAR/caregivers will complete seizure diaries each day during the 160 weeks of treatment.

Safety information will be collected during phone calls and during clinic visits. If a subject experiences any AEs or is unable to take the study drug as prescribed, the caregiver/LAR is instructed to contact the study center. Dose

adjustments are permitted for subjects who are unable to tolerate the specified dosing regimen.
At the investigator*s discretion throughout the study, subjects may be evaluated at unscheduled clinic visits for reasons related to subject safety.
At unscheduled visits, subjects will be queried about AEs, changes in concomitant medications, and suicidality, and safety laboratory assessments may be conducted. Periodic interim review of safety data will be performed as part of routine pharmacovigilance activities and to support regulatory submission.

Intervention

OV101 will be supplied as capsules containing 5-mg, 2-mg, or 0.5-mg of study drug.
Each subject will be titrated to his/her maximum tolerated daily dose, up to a maximum daily dose of 15 mg (see Study Design, above).
Subjects will take all doses orally (assisted by an LAR/caregiver, if necessary), in the evening at bedtime. Capsules may be opened, with the contents sprinkled onto up to 1 teaspoon of low-fat semiliquid food (eg, applesauce, yogurt, pudding) for ingestion, but this approach must be followed consistently throughout the study.

Study burden and risks

OV101 has been studied in adult and adolescent subjects with AS. In this study, 58 patients were treated with OV101 either once daily (15 mg at bedtime) or twice daily (10 mg in the morning, 15 mg at bedtime) and 29 patients were treated with placebo. The side effects seen commonly (occurring in 10 or more out of 100 of the participants) in all subjects receiving OV101 were the following:
• GI (gastrointestinal)- vomiting, nausea (feeling the need to vomit), diarrhea, decreased appetite
• Behaviour - somnolence (sleepiness), irritability, aggression
• Neurologic - seizure*
• Other - pyrexia (fever)*, nasopharyngitis (runny nose, sore throat), upper respiratory tract infection (cold), rash*
*Pyrexia (fever), seizure, and rash occurred more frequently in those receiving OV101 than placebo.

There were no deaths linked to these side effects.

OV101 has been previously tested in over 3,396 subjects at dosage of 5 to 20 mg in 3 other studies for participants who have insomnia (problem with sleeping). The side effects seen commonly (occurring in 2 out of 100 of the participants) with 15 mg dose are:
• Dizziness
• Somnolence (Sleepiness)

• Nausea
• Vomiting
• Headache

Blood draw
Obtaining blood may sometimes cause pain/discomfort at the site where the blood is drawn, including bruising, bleeding, occasional light-headedness, and, rarely, infection or fainting. Approximately 37mL of blood will be collected during the entire study.

Questionnaires about your child*s well-being and behaviour
Some questions in the questionnaires may cause the LAR to distress or make the LAR feel uncomfortable.

Contacts

Public
Ovid Therapeutics Inc.

1460 Broadway -
New York 10036
US
Scientific
Ovid Therapeutics Inc.

1460 Broadway -
New York 10036
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)

Children (2-11 years)

Inclusion criteria

1. Ovid study enrollment criteria:
• Has completed the OV101-19-001 study up to the end of treatment (EOT), or
• Is a sibling of a subject with AS who has completed OV101-19-001.
2. Has a previous diagnosis of AS with molecular confirmation.
3. Is at least 2 years old and has a body weight of at least 9 kg.
4. Has a legally acceptable representative (LAR)/caregiver capable of providing informed consent and able to attend all scheduled study visits, oversee the administration of study drug, and provide feedback regarding the subject*s symptoms and performance as described in the protocol.
5. Provides assent to the protocol (to the extent possible and in accordance with local institutional review board and regulatory requirements) and has an LAR/caregiver who will provide written informed consent. Subjects providing assent must do so at the same visit as LAR/caregiver written informed consent is provided.
6. Can swallow study drug capsules with water or ingest the contents of study drug capsules after sprinkling the capsule contents onto up to 1 teaspoon of low-fat semiliquid food.
7. If a subject is currently receiving a regimen of concomitant medications such as antiepileptic medication, gabapentin, clonidine, trazodone, melatonin, and/or a special dietary regimen, that subject*s regimen is stable for at least 4 weeks before Day 1 (first day of study drug administration) and will be maintained throughout the duration of the study (in the judgment of the investigator).
8. Has LAR/caregiver(s) who agree not to post any of the subject*s personal medical data or information related to the study on any website, message board, online support group, or social media site (eg, Facebook, Instagram, Twitter) until notified that the study is completed.
9. Female subjects who are of childbearing potential (defined as having experienced their first menarche) must agree to use either a highly effective or acceptable form of birth control during the study and for 30 days following the last dose of the study drug.

Exclusion criteria

1. Discontinued from the OV101-19-001 study due to safety reasons causally related to OV101.
2. Has a circumstance, condition, concomitant disease (eg, gastrointestinal, renal, hepatic, endocrine, respiratory, or cardiovascular system disease), or any clinically significant finding that could interfere with the conduct of the study or that would pose an unacceptable risk to the subject in this study.
3. Has poorly controlled seizures defined as any of the following:

• Weekly seizures of any frequency with a duration of more than 3 minutes each
• Weekly seizures occurring more than 3 times per week, each with a duration of less than 3 minutes
• Investigator assessment
4. Has any of the following laboratory abnormalities: total bilirubin >1.5 × upper limit of normal (ULN), unless known Gilbert*s syndrome; alanine aminotransferase or aspartate aminotransferase >2.5 × ULN; serum creatinine >1.2 × ULN; absolute neutrophil count <1.5 × 109/L; platelets <80 × 109/L; hemoglobin <80 g/L; or thyroid stimulating hormone >1.25 × ULN or <0.8 × lower limit of normal. Retesting of clinical laboratory parameters may be allowed after consultation with the medical monitor or designee.
5. Use of benzodiazepines, zolpidem, zaleplon, zopiclone, eszopiclone, barbiturates, or ramelteon for sleep, or minocycline or levodopa within the 4 weeks prior to Day 1 or during the study. Benzodiazepines administered as needed or regularly scheduled for indications other than insomnia and benzodiazepines for seizure control are permitted.
6. Is at risk of harming self and/or others (based on investigator assessment).
7. With the exception of an Ovid study of OV101, has enrolled in any clinical or used any investigational agent or device, or has participated in any investigational procedure, within the 30 days before screening or does so concurrently with this study.
8. Is allergic to OV101 or any excipients of study drug.
9. The subject or LAR/caregiver is unable to comply with study requirements (based on investigator assessment).

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	12-10-2020
Enrollment:	4

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	OV101
Generic name:	Gaboxadol monohydrate

Ethics review

Approved WMO Date:	18-03-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-08-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-09-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2019-004478-24-NL
ClinicalTrials.gov	NCT03882918
CCMO	NL72465.078.20

Study results

Date completed: 04-06-2021

Results posted: 27-09-2021

First publication
13-09-2021