Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 3 Study to Evaluate the Efficacy and Safety of OV101 in Pediatric Individuals With Angelman Syndrome (NEPTUNE)

Published: 10-12-2019
Last updated: 10-04-2024

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

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

Summary

ID

NL-OMON49584

Source
ToetsingOnline

Brief title
NEPTUNE

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: Ovid Therapeutics Inc.,Sponsor

Intervention

Keyword: Angelman Syndrom, GABA, OV101-19-001

Outcome measures

Primary outcome

Efficacy assessments will include the CGI I-AS; the CGI S-AS; the VABS 3; the CSHQ; the Peds QL (Cerebral Palsy, Multidimensional Fatigue, and Family Impact modules); actigraphy; and sleep diary.

Secondary outcome

Pharmacokinetic Assessments and Analysis:

On Day 1, all subjects will take their first dose of study drug at the study site during the daytime, and blood will be sampled for determination of plasma OV101 concentrations at 3 time points following the initial dose: 45 minutes ± 15 minutes; 90 minutes ± 15 minutes and 4 hours ± 30 minutes. Study site staff will record the time of dosing and the time of blood sampling. Topical application of a cooling agent or local anesthetic is permitted if necessary. Approximately 2 mL of blood will be collected per PK sample for a total of 6 mL during Day 1. Blood samples will be processed to plasma within 2 hours. Plasma samples will be frozen, stored and shipped according to instructions to be provided to the study site. The PK samples will be analyzed for OV101 concentrations by a Sponsor-contracted bioanalytical facility using a validated

bioanalytical assay. Plasma concentrations of OV101 for each of the above 3 time points following the initial dose will be determined from a minimum of 3 evaluable sentry subjects receiving OV101 within each age band (9 to 12 and 4 to 8 years of age). Plasma concentrations within each time window will be evaluated by the IDMC to confirm that individual OV101 concentration-time data align with respective data obtained previously from adolescents.

At the EOS, OV101 concentration and time data obtained from sparse sampling in this study will subsequently be subjected to population PK modeling and resulting exposure estimates will be evaluated using validated physiologically-based PK (PBPK) modeling to confirm predicted exposure estimates for the pediatric study population 2 to 12 years old at various weight bands. The population PK OV101 plasma exposure parameters will be further evaluated using a PBPK model specific for OV101 that was developed using a commercially available PBPK software platform applied to extant PK data from adult and adolescent subjects. The PBPK modeling details will be reported separately. In addition to Cmax and AUC exposure estimates, elimination half-life and tmax values may also be estimated.

Safety Assessments:

Safety assessments will include frequency, severity, and causality of AEs (including serious AEs [SAEs] and AEs leading to study discontinuation), and other safety assessments including assessment of suicidality (ABC-I), collection of seizure diaries, clinical laboratory assessments, vital sign measurements, and physical examinations. A total of up to 7 mL of blood is

expected to be taken for laboratory measurements at each of screening, baseline, Week 6, and Week 12 visits. Total blood collected will not exceed 19 mL in a 30-day period. This is in accordance with the US Department of Health and Human Services, Office for Human Research Protections recommendations of 3 ml/kg, up to 50 ml total within 8 weeks (Table 2 in Howie 2011).

Study 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 Angelman syndrome (AS) and Fragile X syndrome. Gaboxadol was initially developed for the treatment of insomnia by H. Lundbeck A/S and Merck, but its development was discontinued in 2007. Extensive nonclinical and clinical data were generated during the initial stages of development, including data from exposure to gaboxadol in more than 4,300 adult subjects with insomnia and approximately 500 adult subjects in non insomnia related studies.

Angelman syndrome is a severe, complex, and rare neurogenetic disorder with a prevalence estimated at 1 in every 10,000 to 24,000 live births (16;20;12). The condition is associated with impaired expression of the ubiquitin protein ligase E3A gene (UBE3A). While UBE3A is expressed from both gene copies in the cells of other tissues, in neurons the paternal allele is preferentially silenced through the epigenetic process known as imprinting. Therefore, any alteration in the maternal copy of UBE3A results in AS. Clinical findings range in severity and include developmental delay/intellectual disability, movement and/or balance disorder, and tremulous movement of limbs. Unique behavioral characteristics include the combination of a happy, smiling demeanor with easily provoked laughter and excitability (exhibited by hand-flapping and stereotypic movements). Individuals with AS frequently have motor dysfunction related to gait and balance, severe disruptions in sleep, little to no speech, short attention span, anxiety, and seizures with characteristic abnormal electroencephalogram patterns.

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 as an orthosteric agonist to the *4- and *-containing subunit of extrasynaptic GABA receptors. Research has shown that absence (or dysfunction) of Ube3a results in an aberrant increase in the uptake of GABA, which is the main inhibitory neurotransmitter in the brain. The extrasynaptic GABA receptors mediate tonic inhibition and sleep maintenance. In a mouse model of AS, OV101 was shown to restore tonic inhibition in Ube3a-deficient cerebellar neurons and correct motor abnormalities in Ube3a-deficient mice. These results suggest that OV101 may alleviate the motor dysfunction observed in individuals with AS. Importantly, OV101*s ability to potentiate tonic inhibition is unlike any other GABAergic agent, including benzodiazepines, zolpidem, zaleplon, zopiclone, barbiturates, neurosteroids, and drugs that act on GABA metabolism or uptake. Unlike many of these drugs that are allosteric modulators and therefore require endogenous GABA to function, OV101 is a GABA agonist and can function when GABA is deficient or absent. In addition to the data on presynaptic dysfunction leading to reduced tonic inhibition, there are additional studies which speak to the potential of OV101 in AS, including modulation of sleep and cognition domains that are impaired in subjects with AS.

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

Study objective

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

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

The secondary efficacy objectives of this study are:
* To evaluate the efficacy of OV101 versus placebo:
on latency of sleep onset (LSO), sleep efficiency, and daytime sleep assessed by actigraphy.
on Communications, Socialization, Daily Living Skills, Motor Skills, and Maladaptive Behavior domains assessed by the Vineland Adaptive Behavior Scale, 3rd Edition (VABS 3).
on the Clinical Global Impressions-Severity-Angelman syndrome (CGI-S-AS) Symptoms Overall score.

* To evaluate the relationships of CGI-S-AS Symptoms Overall and CGI-S-AS domains at baseline with CGI-I-AS at Week 12.

The tertiary efficacy objectives of this study are to evaluate the efficacy of OV101 versus placebo:
* on total sleep time and total activity assessed by actigraphy
* based on sleep diary data (caregiver reported)
* based on the Children*s Sleep Habits Questionnaire (CSHQ)
* based on the Pediatric Quality of Life Inventory* (Peds QL*) (Cerebral Palsy, Multidimensional Fatigue, and Family Impact modules).

Pharmacokinetic Objectives:
The pharmacokinetic (PK) objectives of this study are to estimate systemic plasma exposure to OV101 (maximum plasma concentration [Cmax] and area under the concentration-time curve [AUC]) following a single oral dose using sparse sampling and a population PK approach as well as to evaluate estimated PK parameters in the context of a validated physiologically-based PK (PBPK) model for the pediatric study population 2 to 12 years old.

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

Study design

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

Random assignment of subjects for efficacy assessment (to either OV101 or placebo treatment in a 1:1 ratio) will be stratified by age at baseline across all study sites, with a maximum of 12 subjects per study site (unless authorized by Sponsor). The randomization strata will be 9 to 12 years old

(inclusive) and 4 to 8 years old (inclusive), with at least 24 subjects per stratum. Up to 5 subjects 2 to 3 years old (inclusive) will be enrolled for safety and PBPK assessments only and will be assigned to treatment with OV101. Within each age group, dosing will be assigned based on body weight at screening.

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

On Day 1, subjects will take their first dose of study drug at the study site during the daytime, and blood will be sampled 45 minutes ± 15 minutes, 90 minutes ± 15 minutes and 4 hours ± 30 minutes after dosing for determination of OV101 concentrations (sparse sampling for population PK modeling). Subjects will take all subsequent doses approximately 30 minutes before anticipated bedtime, starting with the evening of Day 2.

Each subject*s dose of study drug (OV101 or placebo) will be adjusted from the starting dose to the maintenance dose according to the titration schedule, as tolerated by the subject. On Days 1 through 5, each subject will receive the starting dose. On Day 6, each subject will up-titrate to the maintenance dose. Phone calls to assess tolerability will occur on Day 6 and Day 11. The maintenance dose will be set based on the subject*s weight at screening and will be continued to the EOT.

Downward dose adjustments may be permitted to mitigate tolerability concerns with OV101. These adjustments will be at the investigator*s discretion and should be discussed with the medical monitor or his/her delegate. Unscheduled study site visits are optional at any time to confirm tolerability.

Subject assignment to treatment will be stratified and staged by age and gated by an Independent Data Monitoring Committee (IDMC). Subjects 9 to 12 years old at baseline will begin treatment first. Initial enrollment of randomized subjects will be used to collect at least 3 evaluable OV101 PK samples in each efficacy age group and these subjects will be termed *sentry subjects.* No age cohort may begin treatment without IDMC review of tolerability and PK in sentry subjects in the previous older cohort. The tolerability assessment of the sentry subjects at Day 11, 5 days after initiation of the maintenance dose, will be forwarded to the IDMC for review as blinded data. If the IDMC considers the tolerability and PK acceptable, subjects 4 to 8 years old at baseline may begin treatment (initiation of treatment in the 9 to 12 age group continues

during the review). Similarly, following IDMC review and approval of the tolerability in the sentry subjects 4 to 8 years old, subjects 2 to 3 years old may begin treatment (initiation of treatment in the 4 to 8 age group continues during the review).

The LARs/caregivers will complete sleep diaries on behalf of subjects over the periods where the subject is scheduled to wear the actigraph. An actigraph will be issued to each subject at the screening visit, so that actigraphy data can be collected for 7 consecutive days before travel for the baseline visit. Subjects will be given 3 attempts within the 28-day screening window to wear the actigraph for at least 7 consecutive days, and subjects will be excluded after 3 unsuccessful attempts to wear the actigraph for 7 consecutive days. Actigraphy data collected during the first 7-consecutive day period that includes 2 weekend days during screening will be used as the baseline actigraphy assessment. These 7 consecutive days should include 2 consecutive weekend days and should not include any travel days. The actigraph it is to be worn for a maximum of 14 days preceding travel for the scheduled study site visits at Week 6 and Week 12 visits to collect at least 7 consecutive days of data including 2 consecutive weekend days. If the subject requires an additional attempt to keep the actigraph on for 7 consecutive days (including 2 consecutive weekend days) after the Week 6 visit, the subject will be given an actigraph to be worn for 7 days after Week 6.

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

Safety information will be collected during phone calls on Day 6 and Day 11 and during the EOS visit, as well as during every study site visit. Each subject*s LAR/caregiver will be instructed to contact the study center if the subject experiences any adverse events (AEs), is unable to take the study drug as prescribed, or is unable to tolerate wearing the actigraph.

At the investigator*s discretion throughout the study, subjects may be evaluated at unscheduled clinic visits for reasons related to subject safety. At unscheduled visits, subjects will be queried about AEs and changes in concomitant medications and evaluated for suicidality. Safety laboratory assessments may be conducted. Periodic interim review of safety data will be performed by the IDMC and as part of routine pharmacovigilance activities.

Intervention

Study drug dosage will be assigned based on body weight at the screening visit. Study drug will be titrated from the starting dose to the maintenance dose according to Table 1.
If at randomization on Day 1 a subject is assigned to placebo, the number of capsules per dose will correspond to the number of OV101 capsules for a subject

of the same weight.
Dosing will be initiated at the starting dose for the first 5 days. On Day 6, tolerability will be assessed by the investigator. If there are no tolerability concerns (eg, excessive somnolence, dizziness, vomiting, negative behavior changes) and no AE related to the study drug has been observed since Day 1 by the LAR/caregiver or the investigator, then the dose of OV101 will be increased to the maintenance dose for the duration of the study. The maintenance dose identified at screening will remain consistent throughout the study. If tolerability concerns are observed on Day 6, the subject will discontinue study drug.
The subject*s maintenance dose for the duration of the study will be set based on the subject*s weight at the screening visit, and the subject should continue taking the maintenance dose after the Day 6 assessment until the EOS.
Tolerability will again be assessed during the Day 11 phone call while the subject is taking the maintenance dose. The investigator may initiate down-titration on Day 11 by 1 capsule (Table 2) based on investigator assessments of tolerability and AEs, or medical necessity. If down-titration is initiated, then the investigator should reassess tolerability with the modified dose regimen within 3 days of the dosing change. No further changes in dose regimen should be made after Day 15.
If tolerability is not acceptable at any other time during the 12 weeks of treatment, the investigator should discuss the situation with the medical monitor or his/her delegate. Any intolerability must be documented as an AE.
The daily dose may not be lower for any subject than the reduced maintenance dose indicated in Table 2. If a subject cannot tolerate the reduced maintenance dose, that subject must discontinue treatment. Any dose adjustments or changes in dosing must be documented in the electronic case report form and supporting rationale must be documented in the medical record or other appropriate source document.

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

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

Contacts

Public
Ovid Therapeutics Inc.

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

1460 Broadway -
- NY 10036 New York
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. Is male or female and 2 to 12 years old (inclusive) at the time of informed consent.
2. Has a diagnosis of AS with molecular confirmation
3. Has a CGI-S-AS score of 3 or more.
4. Meets the following age-appropriate body weight criterion:
a) Subjects 2 to 3 years old must have a minimum body weight of 9 kg.
b) Subjects 4 years and older must be between 17 kg and 64 kg (inclusive).
5. Has a legally acceptable representative (LAR)/caregiver capable of providing written informed consent and able to attend all scheduled study visits, oversee the administration of study drug, and provide feedback regarding the subject*s symptoms and performance as described in the protocol.
6. Provides assent to the protocol. Subjects providing assent must do so at the same visit as LAR/caregiver written informed consent is provided.
7. Can swallow study drug capsules with water or ingest the contents of study drug capsules after sprinkling the contents of each capsule onto up to 1 teaspoon of low fat semiliquid food.
8. If a subject is currently receiving a regimen of concomitant medications such as antiepileptic medication, gabapentin, clonidine, trazodone, melatonin, or a special diet regimen, that subject*s regimen is stable for at least 4 weeks before Day 1 (first day of study drug administration) and will be maintained throughout the duration of the study (in the judgment of the investigator).
9. If a subject is a sibling in a family with multiple children diagnosed with AS, then only one of the siblings may enroll in study. The eldest eligible subject should be enrolled (investigator discretion may be used to enroll a younger sibling instead).
10. Has LAR(s)/caregiver(s) who agree not to post any of the subject*s personal medical data or information related to the study on any website, message board(s), online support group(s), or social media site (eg, Facebook, Instagram, Twitter, etc.) until notified that the study is completed.
11. Female subjects who are of child-bearing potential (defined as having experienced their first menarche) must agree to use either a highly effective or acceptable form of birth control during the study and for 30 days following the last dose of the study.

Exclusion criteria

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

2. Has poorly controlled seizures defined as any of the following:
a. Weekly seizures of any frequency with a duration more than 3 minutes.
b. Weekly seizures occurring more than 3 times per week, each with a duration of less than 3 minutes.
c. Investigator assessment.
3. Has any of the following laboratory abnormalities: total bilirubin >1.5 × upper limit of normal (ULN), unless known Gilbert*s syndrome; alanine aminotransferase or aspartate aminotransferase >2.5 × ULN; serum creatinine >1.2 × ULN; absolute neutrophil count <1.5 × 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.
4. Use of benzodiazepines, zolpidem, zaleplon, zopiclone, eszopiclone, barbiturates, or ramelteon for sleep, or minocycline or levodopa within the 4 weeks prior to Day 1 or during the study. Benzodiazepines administered as needed for situational anxiety related to occasional procedures or events are permitted, and benzodiazepines are also permitted for seizure control.
5. Cannot tolerate wearing the actigraph for at least 7 consecutive days (including 2 consecutive weekend days) during the 28-day screening period of the study, after 3 attempts.
6. Is at risk of harming self and/or others (based on investigator assessment).
7. Has enrolled in any clinical study or used any investigational agent or device, or has participated in any investigational procedure, within the 30 days before screening or does so concurrently with this study.
8. Is allergic to OV101 or any excipients of study drug.
9. The subject or LAR/caregiver is unable to comply with study requirements (based on investigator assessment).
10. Is a family member of the investigator and/or study site staff.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-07-2020
Enrollment:	12
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	10-12-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-02-2020
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-04-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-05-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-08-2020

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-10-2020
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	EUCTR2019-002907-17-NL
ClinicalTrials.gov	NCT04106557
CCMO	NL71050.078.19

Study results