Phase IIIb, open-label, single-arm, multi-center study to evaluate the safety, tolerability and efficacy of OAV101 administered intrathecally (1.2 x 1014 vector genomes) to participants 2 < 18 years of age with spinal muscular atrophy (SMA) who have discontinued treatment with nusinersen (Spinraza®) or risdiplam (Evrysdi®)

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The purpose of this study is to characterize the safety and tolerability of OAV101 IT in participants who have discontinued treatment with nusinersen (Spinraza®) or risdiplam (Evrysdi®). The data from this study will expand on the data generated...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Neuromuscular disorders
Study type	Interventional

Summary

ID

NL-OMON56088

Source
ToetsingOnline

Brief title
COAV101B12302 (STRENGTH)

Condition

- Neuromuscular disorders

Synonym
motor neuron disease, spinal muscular atrophy, Werdnig-Hoffmann disease

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma B.V

Intervention

Keyword: SMA, Spinal Muscular Atrophy, Zolgensma

Outcome measures

Primary outcome

To characterize the safety and tolerability of OAV101 IT over a 52-week period

in patients with SMA aged 2 to 18 years who have discontinued treatment with

nusinersen (Spinraza®) or risdiplam (Evrysdi®):

- Number and percentage of participants reporting AEs, related AEs, SAEs, and

AESIs

Secondary outcome

To assess the efficacy of OAV101 IT on motor function, and caregiver impact

over a 52-week period in patients with SMA aged 2 to 12 years who have

discontinued treatment with nusinersen (Spinraza®) or risdiplam (Evrysdi®):

* Change from baseline to Week 52 visit in the HFMSE total score

* Change from baseline to Week 52 visit in the RULM total Score

* Change from baseline to Week 52 visit in Assessment of Caregiver Experience

in ACEND instrument score

Study description

Background summary

Spinal muscular atrophy (SMA) is a neurogenetic disorder caused by a loss or mutation in the survival motor neuron 1 gene (SMN1) on chromosome 5q13, leading to decreased SMN protein levels and selective motor neuron dysfunction. SMA is an autosomal recessive early childhood disease with an incidence of approximately 1:10,000 live births. Before the available treatments, SMA was the leading cause of infant mortality due to genetic diseases. A small amount of SMN protein (about 10 - 15% of the total) is also produced by the SMN2 gene. The SMN2 gene is nearly identical to SMN1, but only partially functional. Disease severity and clinical prognosis generally correlate inversely with variable copy number of SMN2.
Currently, several treatments have been approved for the treatment of SMA with different mechanisms of action, such as splicing modulators (nusinersen (Spinraza®) and risdiplam (Evrysdi®)) that modulate the splicing of the SMN2 gene and thus functionally converting tge SNB2 gene into SMN1 gene to increase the level of SMN protein in the central nervous system (CNS), and gene therapy (Zolgensma IV) that replaces a mutated or deleted SMN1 with a functional copy. Unlike Zolgensma (OAV101), which is a single gene therapy, nusinersen (Spinraza®) and risdiplam (Evrysdi®) require lifelong treatment to maintain effectiveness. Therefore, targeting the major source of SMN protein and ensuring sustained and uninterrupted SMN protein levels, OAV101 may provide an important treatment option for patients who are unwilling or unable to commit to chronic, lifelong therapy. In addition, individuals with SMA may discontinue nusinersen (Spinraza®) or risdiplam (Evrysdi®) for other reasons (eg, sub-optimal efficacy, safety, compliance, burden). The mechanism of action of OAV101 is designed to address the root cause of (5q)SMA through the delivery of a functional copy of the SMN1 gene encoding the SMN protein into target cells. The goal is to increase the SMN proteins in motor neuron prior to development of irreversible injury and motor neuron loss, thereby modyfying the patient's SMA phenotype to a milder course with improved quality of life and prolonged survival. The data from this study will expand on the data generated from other studies of OAV101 IT in the treatment-naive SMA population. Specificallly, data from this study may provide evidence in support in management and monitoring of patients with SMA who discontinue nusinersen (Spinraza®) or risdiplam (Evrysdi®) to receive OAV101 IT. In addition to collecting safety and tolerability data, efficacy will be assessed to support the evaluation of OAV101 IT for the treatment of this SMA population.

Study objective

The purpose of this study is to characterize the safety and tolerability of OAV101 IT in participants who have discontinued treatment with nusinersen (Spinraza®) or risdiplam (Evrysdi®). The data from this study will expand on the data generated from other studies of OAV101 IT in the treatment naive SMA population. Specifically, data from this study may provide evidence in support of management and monitoring for patients with SMA who discontinue nusinersen (Spinraza®) or risdiplam (Evrysdi®) to receive OAV101 IT. In addition to the collection of safety and tolerability data, efficacy will be assessed to support evaluation of OAV101 IT for the treatment of this SMA population. Participants will receive a single dose of OAV101 (1.2 x 1014 vector genomes) by lumbar IT injection after the defined period off nusinersen (Spinraza®) or risdiplam (Evrysdi®); and safety, tolerability, and efficacy will be evaluated over a 52-week period. Approximately 28 participants aged 2 to 18 years will be enrolled. Age of participants enrolled will be stratified as 2 to 5 years (inclusive of all 5-year-olds) and 6 to 18 years, with at least 12 subjects in each stratum.

Study design

This is a 52-week, open-label, single arm, multi-center study design in pre-treated patients with SMA

Intervention

Name: OAV101 (formerly AVXS-101)
Unit Dose 1.2 x 1014 vector genomes
Route of administration Intrathecal (once)

The biological product is a non-replicating recombinant AAV9 containing the cDNA of the human SMN gene under the control of the CMV enhancer/CB promoter. The AAV inverted terminal repeats (ITR) has been modified to promote intramolecular annealing of the transgene, thus forming a double-stranded transgene ready for transcription. This modified ITR, termed a *self-complementary* (sc) ITR, has been shown to significantly increase the speed of which the transgene is transcribed, and the resulting protein is produced. The biological product, called OAV101, expresses the human SMN protein in transduced cells.

Study burden and risks

Risks: side-effects of the study medication and procedures (see E9)
Burden: amount of visits and examinations/procedures per visit (see E4)

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

* Written informed consent
* SMA diagnosis based on gene mutation analysis with bi-allelic SMN1 mutations and any copy of SMN2 gene
* Aged 2 < 18 years (screening visit must occur before the patient's 18th birthday) at time of Screening Visit 1
* Have had at least four loading doses of nusinersen (Spinraza®) or at least 3 months of treatment with risdiplam (Evrysdi®) at Screening
* Must be able to sit independently but must never have taken steps independently
* Diagnosed through newborn or neonatal screening or patients clinically diagnosed must have age of clinical symptom onset < 18 months

* Meets age-appropriate institutional criteria for use of anesthesia/sedation
* Female participants who are sexually active or have reached menarche must have a negative pregnancy test at Screening. Those females who are sexually active must also agree to use highly effective methods of contraception.

Exclusion criteria

* Excluding SMA, any medical condition considered clinically significant
* Positive for human immunodeficiency virus (HIV), hepatitis B or hepatitis
* Anti Adeno Associated Virus Serotype 9 (AAV9) antibody titer using an immunoassay is reported as elevated at Screening (reference to >1:50 or a validated result consistent with being elevated)
* Clinically significant abnormalities in test results during screening period and/or at Baseline
* Platelet count less than the lower limit of normal (LLN), or platelet transfusion within 1 month at Screening Visit 1
* Clinically significant abnormal coagulation panel results at Screening
* Hepatic dysfunction (i.e. alanine aminotransferase (ALT), total bilirubin (TBL), gamma-glutamyl transferase (GGT) or glutamate dehydrogenase (GLDH) > upper limit of normal (ULN) at Screening (with the exception of isolated AST elevation: in the absence of other liver laboratory abnormalities, isolated elevated AST is not considered exclusionary)
* Contraindications for lumbar puncture procedure
* At Baseline (Day-1), participants are excluded if they received:
* nusinersen (Spinraza®) within 4 months at Baseline
* risdiplam (Evrysdi®) within 15 days at Baseline
* Vaccinations 2 weeks prior to administration of OAV101
* Hospitalization for a pulmonary event, or for nutritional support within 2 months prior to Screening or inpatient major surgery planned.
* Presence of the following:
* An active infectious process requiring systemic antiviral or antimicrobial therapy up to 30 days prior to OAV101 administration, or
* An active but untreated viral or bacterial infectious process up to 30 days prior to administration of OAV101, or
* Any febrile illness up to 30 days prior to administration of OAV101
* Requiring invasive ventilation, awake noninvasive ventilation for > 6 hours during a 24-hour period, noninvasive ventilation for >12 hours during a 24-hour period or requiring tracheostomy, at Screening and up to OAV101 administration
* Concomitant use of any of the following medication categories within 90 days prior to administration of OAV101
* Ongoing systemic immunosuppressive therapy (e.g., corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, intravenous immunoglobulin, rituximab), plasmapheresis, immunomodulators (e.g., adalimumab)
* History of hypersensitivity to any of the study treatments or its excipients

or drugs of similar chemical classes

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	12-01-2023
Enrollment:	7
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Generic name:	Genetic modified organism
Product type:	Medicine
Brand name:	Zolgensma
Generic name:	Zolgensma
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	12-08-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	23-11-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-12-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-02-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-07-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-10-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-10-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-11-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-12-2023

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-01-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-02-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-02-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-03-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-07-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-08-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2021-0006709-3-NL
ClinicalTrials.gov	NCT05386680
CCMO	NL81692.000.22