Phase 3, Open-Label, Single-Arm, Single-Dose Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type 1 with One or Two SMN2 Copies Delivering AVXS-101 by Intravenous Infusion

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Primary* Determine efficacy by demonstrating achievement of developmental milestone of sitting without support up to 18 months of age as defined by WHO Motor Developmental Milestones[22].Secondary* Determine efficacy based on survival at 14 months...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Congenital and peripartum neurological conditions
Study type	Interventional

Summary

ID

NL-OMON48542

Source
ToetsingOnline

Brief title
AVXS-101

Condition

- Congenital and peripartum neurological conditions

Synonym
Spinal muscular atrophy type 1 / Reduction of nerve cells in the spinal cord resulting in muscle paralysis

Research involving
Human

Sponsors and support

Primary sponsor: AveXis
Source(s) of monetary or material Support: Industry

Intervention

Keyword: Children younger than 6 months, Gene replacement therapy, Spinal muscular atrophy type 1

Outcome measures

Primary outcome

Proportion of symptomatic SMA Type 1 patients who are homozygous negative for SMN1 exon 7 and have two copies of SMN2 without the SMN2 genetic modifier that achieve the ability to sit without support for at least 10 seconds up to and including the 18 month trial visit. Sitting without supportIt is defined by the World Health Organization Multicentre Growth Reference Trial (WHO MGRS), confirmed by video recording, as a patient who sits up straight with head erect for at least 10 seconds; child does not use arms or hands to balance body or support position.

Secondary outcome

Survival at 14 months of age amongst symptomatic SMA Type 1 patients who are homozygous negative for SMN1 exon 7 and have two copies of SMN2 without the SMN2 genetic modifier. Survival is defined by the avoidance of the combined endpoint of either (a) death or (b) permanent ventilation, which is defined by tracheostomy or by the requirement of * 16 hours of respiratory assistance per day (via non invasive ventilatory support) for * 14 consecutive days in the

absence of an acute reversible illness, excluding perioperative ventilation.

Permanent ventilation, so defined, is considered a surrogate for death.

Study description

Background summary

Spinal muscular atrophy is a neurogenetic disorder caused by a loss or mutation in the survival motor neuron 1 gene (SMN1) on chromosome 5q13, which leads to reduced SMN protein levels and a selective dysfunction of motor neurons.
It is an autosomal recessive, early childhood disease with an incidence of approximately 1:10,000 live births. Spinal muscular atrophy is the leading cause of infant mortality due to genetic diseases.
Disease severity and clinical prognosis depends on the number of copies of survival motor neuron 2 gene (SMN2). In its most common and severe form (Type 1), hypotonia and progressive weakness are recognized in the first few months of life, leading to diagnosis before 6 months of age and early death due to respiratory failure before 2 years of age.

The findings from various neurophysiological and animal studies have shown an early loss of motor neurons in the embryonic and early post-natal periods. From a clinical perspective, these findings emphasize the importance of first targeting the SMA Type 1 group for gene transfer of SMN2 in hopes of rescuing neurons at this critical stage.
Trial AVXS-101-CL-302 is a pivotal Phase 3 clinical gene therapy trial investigating the efficacy and safety of a single intravenous (IV) infusion of AVXS-101 in up to 30 patients with Type 1 spinal muscular atrophy (SMA) with one or two copies of SMN2.

The survival motor neuron (SMN) gene will be transferred using self-complementary adeno-associated virus (scAAV) Type 9 under control of the chicken-*-actin hybrid promoter.

Pre-clinical studies have demonstrated survival of the SMN*7 mouse model for SMA from a median of 15.5 days to over one year, following IV delivery to the peripheral vein. Additionally, preliminary results from an ongoing Phase 1 clinical trial (AVXS-101-CL-101) of AVXS-101 in SMA Type 1 patients demonstrates broad improvements in survival, motor function, pulmonary function, and nutritional function.

The goal in continuing the development plan for AVXS-101 is to modify the SMA Type 1 phenotype, which will hopefully lead to a milder disease course and

prolonged survival as seen in SMA Type 2 and Type 3 patients.

Study objective

Primary
* Determine efficacy by demonstrating achievement of developmental milestone of sitting without support up to 18 months of age as defined by WHO Motor Developmental Milestones[22].

Secondary
* Determine efficacy based on survival at 14 months of age. Survival is defined by the avoidance of combined endpoint of either (a) death or (b) permanent ventilation which is defined by tracheostomy or by the requirement of * 16 hours of respiratory assistance per day (via non invasive ventilatory support) for * 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation. Permanent ventilation, so defined, is considered a surrogate for death.

Exploratory
Determine efficacy by demonstrating achievement of other developmental milestones.

Safety
* Evaluate the safety of AVXS 101 in patients with SMA Type 1.
* Determine the safety of AVXS 101 based on the development of unacceptable toxicity defined as the occurrence of any Common Terminology Criteria for Adverse Events [25] (CTCAE) Grade 3 or higher, unanticipated, treatment-related toxicity.

Study design

Phase 3, open-label, single-arm, single-dose, trial of AVXS 101 (gene replacement therapy) in patients with spinal muscular atrophy (SMA) Type 1 who meet enrollment criteria and are genetically defined by a biallelic pathogenic mutation of the survival motor neuron 1 gene (SMN1) with one or two copies of survival motor neuron 2 gene (SMN2). Up to 30 patients < 6 months (< 180 days) of age at the time of gene replacement therapy (Day 1) will be enrolled.

The trial includes a screening period, a gene replacement therapy period, and a follow-up period. During the screening period (Days *30 to *2), patients whose parent(s)/legal guardian(s) provide informed consent will complete screening procedures to determine eligibility for trial enrollment. Patients who meet the entry criteria will enter the in patient gene replacement therapy period (Day *1 to Day 3). On Day *1, patients will be admitted to the hospital for pre treatment baseline procedures.
On Day 1, patients will receive a one time intravenous (IV) infusion of AVXS

101, and will undergo in patient safety monitoring over the next 48 hours. Patients may be discharged 48 hours after the infusion, based on Investigator judgment. During the outpatient follow-up period (Days 4 to End of Trial at 18 months of age), patients will return at regularly scheduled intervals for efficacy and safety assessments until the End of Trial when the patient reaches 18 months of age. After the End of Trial visit, eligible patients will be asked to rollover into the long-term follow up trial, AVXS-101-LT-002. All post-treatment visits will be relative to the date on which gene replacement therapy is administered, except for the 14 and 18 months of age visits, which will be relative to the patient*s date of birth.

In an attempt to dampen the host immune response to the adeno-associated virus (AAV) derived therapy, all patients will receive prophylactic prednisolone at approximately 1 mg/kg/day beginning 24 hours prior to AVXS 101 infusion until at least 30 days post infusion. Overall management of prophylactic prednisolone is at the discretion of the Investigator. After 30 days of treatment, the dose of prednisolone can be tapered for patients whose alanine aminotransferase (ALT) values and aspartate aminotransferase (AST) values are *2 X ULN, and T-cell response are < 100 SFC/106 PBMCs in accordance with the following treatment guideline: 1 mg/kg/day until at least 30 days post-infusion, 0.5 mg/kg/day at Weeks 5 and 6, 0.25 mg/kg/day at Weeks 7 and 8, and discontinued at Week 9. If the AST or ALT values are *2 X ULN, or if T-cell response is * 100 SFC/106 PBMCs after 30 days of treatment, the dose of prednisolone will be maintained until the AST and ALT values decrease below threshold. If T cell response continues past Day 60, Investigator discretion should be used considering risk benefit for maintaining prednisolone. Variance from these recommendations will be at the discretion of the Investigator based on potential safety issues for each patient.

Efficacy will be assessed by achievement of the key developmental milestone of sitting without support for at least 10 seconds based on World Health Organization [WHO] Child Growth Standards [22] at any point up to and including the 18 months of age trial visit, and survival at 14 months of age.

Safety will be assessed through monitoring adverse events (AEs), concomitant medication usage, physical examinations, vital sign assessments, cardiac assessments, and laboratory evaluations. A Data Safety Monitoring Board (DSMB) / Data Monitoring Committee (DMC) will review safety data on a quarterly basis, and will also convene within 48 hours should any patient experience an unanticipated CTCAE Grade 3, or higher AE/toxicity that is possibly, probably, or definitely related to gene replacement therapy, and is associated with clinical symptoms and/or requires medical treatment. This includes any patient death, important clinical laboratory finding, or any complication attributed to administration of gene replacement therapy. In such instances, the DSMB/DMC will review the safety information and provide its recommendation. Based upon the DSMB/DMC*s review, the DSMB/DMC can recommend continuing enrollment,

halting enrollment, or early termination of the trial for safety reasons.

Intervention

AVXS 101 will be administered as a one time IV infusion over 30-approximately 60 minutes, dependent upon volume.
Active ingredient: Survival Motor Neuron Gene by Self*Complementary Adeno Associated Virus Serotype 9 (AAV9).

Study burden and risks

Given the devastating clinical course of Type 1 SMA, the irreversible and progressive nature of motor neuron loss as the disease progresses, and the urgent and substantial unmet medical need in this serious disorder, the available data strongly support a positive benefit/risk relationship and strongly support continued study of AVXS-101 in patients with symptomatic and presymptomatic SMA.
Because of the limited number of patients treated with AVXS-101 to date, the potential risks associated with AVXS-101 are not fully known at this time. Patients could develop an immune response to the AAV9 viral vector, which could interfere with or prevent future use of gene transfer interventions using this vector. Elevated liver function tests have been observed in the ongoing AVXS-101-CL-101 trial, which is believed to reflect a T-cell immune response to the AAV9 vector. None of the liver enzyme abnormalities observed in the trial were accompanied by clinical sequelae, and all have resolved following treatment with prednisolone. Although no other treatment-related AEs have been reported to date, other potential risks of treatment may exist that are not currently known given the limited clinical experience to date, and the benefit/risk profile will continue to become better characterized with continued study.
Non clinical data in nonhuman primates and mouse models of SMA provide additional support for a positive benefit/risk relationship, and support continued clinical investigation of AVXS-101 in patients with SMA. Efficacy studies in the SMN*7 mouse model of SMA have demonstrated significant apparent benefits in several disease-associated phenotypes, including motor functioning, body weight, and survival. Local vascular necrosis of the ear pinna was observed in some treated SMN*7 mice. Because similar findings have been reported in other studies of SMN*7 mice and have been observed in several other SMA mouse models, it is believed this finding is unlikely to be related to treatment. In preclinical toxicology studies conducted in wild-type mice and cynomolgus macaques, no toxicologically significant treatment related effects were seen on body weight or on hematology, clinical chemistry and histopathology evaluations.
Taken together, results from the clinical and nonclinical studies to date support continued clinical investigation of the efficacy and safety of AVXS-101 in patients with SMA Type 1, and additionally support further investigation of

intravenous and intrathecal administration of AVXS-101 in a broader population of patients with SMA.

While there is only one dose of AVXS-101 given during the study, participation in the study requires significant time commitment from the child*s family. In addition to the screening visit, an in-patient hospital stay is required, weekly clinic visits for the first month after gene replacement, and then monthly visits until the child reaches 18 months of age. Due to protocol required assessments, including videotaping of motor function milestones, post treatment visits could last up to 8 hours.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

1. Patients with SMA Type 1 as determined by the diagnosis of SMA based on gene mutation

analysis with bi-allelic SMN1 mutations (deletion or point mutations) and one or two copies of SMN2 [inclusive of the known SMN2 gene modifier mutation (c.859G>C)]
2. Patients must be < 6 months (< 180 days) of age at the time of AVXS 101 infusion.
3. Patients must have a swallowing evaluation test performed prior to administration of gene replacement therapy.

Exclusion criteria

1. Use of invasive ventilatory support (tracheotomy with positive pressure) or pulse oximetry < 95% saturation at screening
a. Pulse oximetry saturation must not decrease * four (4) percentage points between screening and dosing with confirmatory oximetry reading
b. Patients may be put on non-invasive ventilatory support for less than < 12 hours per day at the discretion of their physician or trial staff.;2. Use or requirement of non-invasive ventilatory support for *12 or more hours daily in the two 2 weeks prior to dosing.;3 Patient with signs of aspiration based on a swallowing test or whose weight-for-age is below the 3rd percentile based on World Health Organization (WHO) Child Growth Standards and is unwilling to use an alternative method to oral feeding.;4. Participation in recent SMA treatment clinical trial (with the exception of observational cohort studies or non-interventional studies) or receipt of an investigational or commercial compound, product or therapy administered with the intent to treat SMA (eg, nusinersen, valproic acid,) at any time prior to screening for this trial. Oral *-agonists must be discontinued at least 30 days before gene therapy dosing. Inhaled albuterol specifically prescribed for the purposes of respiratory (bronchodilator) management is acceptable.;5. Patient < 35 weeks gestational age at time of birth

Study design

Design

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

Recruitment

NL
Recruitment status: Will not start

Enrollment:	5
Type:	Anticipated

Ethics review

Approved WMO Date:	01-05-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-03-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-04-2019
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	EUCTR2017-000266-29-NL

Register	ID
ClinicalTrials.gov	NCT03461289
CCMO	NL62156.000.18