A Global Study of a Single, One-Time Dose of AVXS-101 Delivered to Infants with Genetically Diagnosed and Pre-Symptomatic Spinal Muscular Atrophy with Multiple Copies of SMN2

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Safety:* Evaluate the safety of AVXS-101 through incidence of adverse events (AEs) and/or serious adverse events (SAEs)* Evaluate the safety of AVXS-101 based on the change from baseline in clinical laboratory parametersEfficacy objectives will be...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Neuromuscular disorders
Study type	Interventional

Summary

ID

NL-OMON46178

Source
ToetsingOnline

Brief title
SPR1NT

Condition

- Neuromuscular disorders

Synonym
SMA, Spinal Muscular Atrophy

Research involving

Human

Sponsors and support

Primary sponsor: NA
Source(s) of monetary or material Support: AveXis;Inc.

Intervention

Keyword: AVXS-101, Infants, SMA

Outcome measures

Primary outcome

Criteria for Evaluation:

Safety:

Primary:

*Incidence of adverse events (AEs) and/or serious adverse events (SAEs)

*Change from baseline in clinical laboratory parameters

Efficacy objectives will be assessed independently for each cohort.

Efficacy for patients with bi-allelic SMN1 deletions and 2 copies of SMN2:

Primary:

*Proportion of patients achieving the development milestone of functional

independent sitting at any visit up to 18 months of age

Efficacy for patients with bi-allelic SMN1 deletions and 3 copies of SMN2:

Primary:

*Proportion of patients achieving the ability to stand without support for at

least three seconds at any visit up to 24 months of age

Secondary outcome

Patients with 2 copies of SMN2:

* Proportion of patients that have survived and have not required permanent ventilation in the absence of acute illness or perioperatively assessed at 14 months of age

* Proportion of patients that have achieved the ability to maintain weight at or above the third percentile without need for nonoral/mechanical feeding support at any visit up to 18 months of age

Patients with 3 copies of SMN2:

* Proportion of patients demonstrating the ability to walk alone definedas the ability to take at least five steps independently displaying coordination and balance at any visit up to 24 months of age

Study description

Background summary

see page 20, 5.1 background of the study

Study objective

Safety:
* Evaluate the safety of AVXS-101 through incidence of adverse events (AEs) and/or serious adverse events (SAEs)
* Evaluate the safety of AVXS-101 based on the change from baseline in clinical laboratory parameters
Efficacy objectives will be assessed independently for each cohort.
Efficacy for patients with bi-allelic SMN1 deletions and 2 copies of SMN2:
Primary:
* Assess the efficacy of AVXS-101 by demonstrating functional independent sitting for at least 30 seconds up to 18 months of age
Secondary:
* Determine the efficacy of AVXS-101 based on survival, defined as avoidance of

death or the requirement of permanent ventilation in the absence of acute illness or perioperatively as assessed at 14 months of age
* Assess efficacy of AVXS-101 by demonstrating the ability to maintain weight at or above the third percentile without need for non-oral/mechanical feeding support at any visit up to 18 months of age
Exploratory:
* Assess the efficacy of AVXS-101 by demonstrating achievement of motor milestones as assessed by World Health Organization-Multicentre Growth Reference Study (WHO-MGRS) [30] criteria at any visit up to 18 months of age:
o Sitting without support
o Hands and knees crawling
o Standing with assistance
o Walking with assistance
o Standing alone
o Walking alone
* Assess the efficacy of AVXS-101 based on the time to respiratory intervention
* Assess the efficacy of AVXS-101 based on the requirement for respiratory intervention at 18 months of age
* Assess the efficacy of AVXS-101 based on survival, defined as avoidance of death or the requirement of permanent ventilation in the absence of acute illness or perioperatively as assessed at 18 months of age
* Assess efficacy of AVXS-101 based on the proportion of patients alive and without tracheostomy at 18 months of age
* Assess the efficacy of AVXS-101 by the proportion of patients achieving an improvement over baseline of *15 points on Bayley V.3 Gross and Fine Motor Subsets (raw score) at any visit up to 18 months of age
* Assess the efficacy of AVXS-101 by demonstrating the ability to achieve a scaled score on Bayley V.3 Gross and Fine Motor Subtests within 1.5 standard deviations of a chronological development reference standard at any visit up to 18 months of age
* Assess efficacy of AVXS-101 by demonstrating achievement of Children*s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) motor function scale score *40 at any visit up to 18 months of age
* Assess efficacy of AVXS-101 by demonstrating achievement of CHOP INTEND score >50 at any visit up to 18 months of age
* Assess efficacy of AVXS-101 by demonstrating achievement of CHOP INTEND score *58 at any visit up to 18 months of age
* Maintenance of achieved milestones at visits up to 18 months of age in the absence of acute illness or perioperatively
Efficacy for patients with bi-allelic SMN1 deletions and 3 copies of SMN2:
Primary:
* Assess the efficacy of AVXS-101 based on the proportion of patients achieving the ability to stand without support for at least 3 seconds up to 24 months of age
Secondary:
* Assess the efficacy of AVXS-101 by demonstrating the ability to walk alone defined as the ability to take at least five steps independently displaying

coordination and balance at any visit up to 24 months of age
Exploratory:
* Assess the efficacy of AVXS-101 by demonstrating achievement of motor milestones as assessed by WHO-MGRS [30] criteria at any visit up to 24 months of age:
o Standing with assistance
o Walking with assistance
* Assess the efficacy of AVXS-101 based on the time to respiratory intervention
* Assess the efficacy of AVXS-101 based on the proportion of patients requiring respiratory intervention at 24 months of age
* Assess the efficacy of AVXS-101 based on survival, defined as avoidance of death or the requirement of permanent ventilation in the absence of acute illness or perioperatively as assessed at 24 months of age
* Assess the efficacy of AVXS-101 by the proportion of patients achieving an improvement over baseline of *15 points on Bayley V.3 Gross and Fine Motor Subsets (raw score) at any visit up to 24 months of age
* Assess the efficacy of AVXS-101 by demonstrating the ability to achieve a scaled score on Bayley V.3 Gross and Fine Motor Subtests within 1.5 standard deviations of a chronological development reference standard as assessed at any visit up to 24 months of age
* Assess efficacy of AVXS-101 by demonstrating ability to maintain weight at or above the third percentile without need for non-oral/mechanical feeding support at any visit up to 24 months of age
* Maintenance of achieved milestones at visits up to 24 months of age in the absence of acute illness or perioperatively

Study design

Phase 3, open-label, single-arm study of a single, one-time dose of AVXS-101 (gene replacement therapy) in patients with spinal muscular atrophy (SMA) who meet enrollment criteria and are genetically defined by bi-allelic deletion of SMN1 with 2 or 3 copies of survival motor neuron 2 gene (SMN2). Patients with SMN1 point mutations or the SMN2 gene modifier mutation (c.859G>C) may enroll but will not be included in the efficacy analysis sets.
The study will enroll at least fifteen (15) patients with 2 copies of SMN2 that meet the Intent To Treat (ITT) criteria and at least twelve (12) patients with 3 copies of SMN2 that meet the ITT criteria. Patients in both cohorts must be *6 Weeks of age at the time of gene replacement therapy (Day 1).
The study 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 undergo screening procedures to determine eligibility for study enrollment. Patients who meet the entry criteria will enter the in-patient gene replacement therapy period (Day *1 to Day 2). On Day *1, patients will be admitted to the hospital for pre-treatment baseline procedures. On Day 1, patients will receive a single, one-time intravenous (IV) infusion of AVXS-101 and will undergo in-patient safety monitoring for a minimum of 24 hours post infusion. Patients may be

discharged 24 hours after the infusion, based on Investigator judgment. During the outpatient follow-up period (Days 3 to End of Study at 18 or 24 months of age, dependent upon respective SMN2 copy number), patients will return at regularly scheduled intervals for efficacy and safety assessments until the End of Study when the patient reaches 18 months of age (SMN2 = 2) or 24 months of age (SMN2 = 3). After the End of Study visit, eligible patients will be asked to rollover into a long-term follow up study.
Following dosing, follow-up visits will be conducted every Week for the first four Weeks and at Month 2 and Month 3 followed by every 3 months, based on patient age, at 6 months old, 9 months old, 12 months old, 15 months old, 18 months old and, if applicable, 21 months old and 24 months old. The EOS visit for patients with 2 and 3 copies of SMN2 will be the 18 and 24 months old visits, respectively. Any missed visit should be rescheduled as soon as possible, but within 7 days.
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. After 30 days of treatment, the dose of prednisolone can be tapered for patients whose alanine aminotransferase (ALT) values, aspartate aminotransferase (AST) values are below the threshold of 2 × Upper Limit Normal (ULN) 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.
Efficacy will be assessed by achievement of the key developmental milestone of functional independent sitting for at least 30 seconds (SMN2 = 2) at any visit up to 18 months of age; and ability to stand without support for at least 3 seconds (SMN2 = 3) at any visit up to 24 months of age. Additional developmental milestones will be assessed using the WHO-MGRS and Bayley Scales of Infant and Toddler Development© (Version 3). Safety will be assessed through monitoring AEs, concomitant medication usage, physical examinations, vital sign assessments, cardiac assessments, and laboratory evaluations. The primary efficacy analysis for each SMN2 copy number cohort will be completed separately at such time that enrollment in the respective cohort is complete and the last patient has completed the EOS visit at the respective age or has discontinued (SMN2 = 2, End of Study (EOS) = 18 months of age; SMN2 = 3, EOS = 24 months of age).

Intervention

Patients will receive a one time dose of AVXS 101 at 1.1 x 1014 vg/kg.
AVXS 101 will be administered as a one time IV infusion over approximately 30 minutes

Study burden and risks

There is only one prior clinical study completed in which AVXS-101 was given to

children. A full understanding of all risks is not known at this time. The child may have an immune response to the virus being used to deliver the missing SMN gene. Participation in this study may prevent the child from participating in a future gene therapy study using this virus to deliver the gene. If, however, gene therapy is found to be effective for the child*s disease, treatment might be possible with a different virus or by using a different way to deliver the gene.

The SMN gene vector will likely spread to other parts of the child*s body. The consequences of this are not known at this time.
It is possible that the SMN gene vector could interact with other viruses with which the child comes into contact with, like cold viruses. If this happens, the SMN gene vector might form a virus that makes thr child sick. We think this is unlikely to happen, but cannot be certain.

Some mice affected with SMA Type 1 that were treated with AVXS-101 experienced changes in liver function enzymes and also tiny deterioration and repair of tissues in the heart and liver; the heart and liver changes were visible only by a microscope.

During a study in mice, AVXS-101-related findings were present in the heart, liver and lungs at doses higher than what is being used in this study. Some mice had atrial thrombosis (a blood clot in one of the four chambers of the heart); this can be very serious causing stroke and stopping blood from reaching important organs. Adverse AVXS-101-related atrial thrombosis and associated heart muscle changes in mice were dose-related; thrombosis occurred at the highest dose tested in the mice and in some cases resulted in death. Cardiac complications have not been observed in human patients treated with AVXS-101 to date.

Abnormalities of liver enzymes in the blood have been observed in patients with SMA Type 1. We believe this is related to an immune response to the virus carrying the gene. Because of this, there is a possibility of prolonged liver enzyme elevation in the blood, which could be a sign of an inflamed liver. Liver enzymes and immune responses will be closely monitored in this study. The study doctor will perform additional tests and/or treatments, which are necessary to ensure the safety of participants.

Risks Related to Prednisolone Treatment
The possible side effects of prednisolone include acne, increased hair growth, thinning of the skin, glaucoma, roundness of the face, weight gain, changes in behavior, disturbance of sleep and increase of blood glucose level. If the child takes prednisolone for more than a few weeks, the child*s adrenal glands decrease production of cortisol, a natural hormone made by the body. A gradual reduction in prednisolone dose gives the child*s adrenal glands time to resume their normal function. Abruptly stopping prednisolone or tapering off too quickly may result in the following withdrawal symptoms: severe fatigue,

weakness, body aches and joint pain. The dosing regimen will be determined by the doctor and will be provided with a tapering schedule to help wean the child off this medication.

Risks Associated with *Vector Shedding*
Research has shown that some of the vector can be excreted from the body for up to a few weeks after infusion. This is called *vector shedding.* This shedding of vector can be found in the blood, urine, saliva and stool for up to a few weeks following infusion. We do not know if the shed vector can hurt someone who comes into contact with the child*s bodily fluids during this period, although we believe this is unlikely to occur because the vector virus used is non-infectious and cannot replicate (reproduce).

We will provide instructions to family members and caregivers to practice good hand hygiene for a minimum of one month after the injection. This requires washing hands with soap regularly and using appropriate protective gloves if coming into direct contact with the child*s bodily fluids and waste. The child will not be allowed to donate blood for 2 years following the vector AVXS-101 infusion.

Contacts

Public
NA

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Scientific
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

All patients
* Age *6 Weeks (*42 days) at time of dose
* Ability to tolerate thin liquids as demonstrated through a formal bedside swallowing test
* Compound muscle action potential (CMAP) *2 mV at Baseline; centralized review of CMAP data will be conducted
* Gestational age of 35 to 42 weeks
* Up-to-date on childhood vaccinations. Seasonal vaccinations that include palivizumab prophylaxis (also known as Synagis) to prevent respiratory syncytial virus (RSV) infections are also recommended in accordance with the guidance of local health authorities.
* Able and willing to follow the Consensus Statement for Standard of Care in Spinal Muscular Atrophy.
* Parent(s)/legal guardian(s) willing and able to complete the informed consent process and comply with study procedures and visit schedule
* Genetic diagnosis as described below, obtained from an acceptable newborn or pre-natal screening test method
Patients with 2 copies of SMN2 (n *15)
* Patients with pre-symptomatic SMA Type 1 as determined by the following features:
* 2 copies of SMN2
Patients with 3 copies of SMN2 (n *12)
* Patients with pre-symptomatic SMA Type 2 as determined by the following features:
* 3 copies of SMN2

Exclusion criteria

* Weight at screening visit <2 kg
* Hypoxemia (oxygen saturation <96% awake or asleep without any supplemental oxygen or respiratory support) at the screening visit or for altitudes >1000 m, oxygen saturation <92% awake or asleep without any supplemental oxygen or respiratory support at the screening visit
* Any clinical signs or symptoms at screening or immediately prior to dosing that are, in the opinion of the Investigator, strongly suggestive of SMA (e.g., tongue fasciculation, hypotonia, areflexia)
* Tracheostomy or current prophylactic use or requirement of non invasive ventilatory support at any time and for any duration prior to screening or during the screening period
* Patients with signs of aspiration/inability to tolerate non thickened liquids based on a formal swallowing test performed as part of screening or patients receiving any non-oral feeding

method
* Clinically significant abnormalities in hematology or clinical chemistry parameters as determined by the investigator or medical monitor
* Treatment with an investigational or commercial product, including nusinersen, given for the treatment of SMA. This includes any history of gene therapy, prior antisense oligonucleotide treatment, or cell transplantation.
* Patients whose weight-for-age is below the third percentile based on World Health Organization (WHO) Child Growth Standards [33]
* Biological mother with active viral infection as determined by screening laboratory samples (includes human immunodeficiency virus [HIV] or positive serology for hepatitis B or C)
* Biological mothers with clinical suspicion of Zika virus that meet Centers for Disease Control and Prevention (CDC) Zika virus epidemiological criteria including history of residence in or travel to a geographic region with active Zika transmission at the time of travel will be tested for Zika virus RNA; positive results warrant confirmed negative Zika virus ribonucleic acid (RNA) testing in the patient prior to enrollment
* Serious non respiratory tract illness requiring systemic treatment and/or hospitalization within 2 Weeks prior to screening
* Upper or lower respiratory infection requiring medical attention, medical intervention, or increase in supportive care of any manner within 4 Weeks prior to dosing
* Severe non pulmonary/respiratory tract infection (e.g., pyelonephritis, or meningitis) within 4 Weeks before administration of gene replacement therapy or concomitant illness that, in the opinion of the Investigator or Sponsor medical monitor, creates unnecessary risks for gene replacement therapy such as:
* Major renal or hepatic impairment
* Known seizure disorder
* Diabetes mellitus
* Idiopathic hypocalciuria
* Symptomatic cardiomyopathy
* Known allergy or hypersensitivity to prednisolone or other glucocorticosteroids or their excipients
* Previous, planned or expected major surgical procedure including scoliosis repair surgery/procedure during the study assessment period
* Concomitant use of any of the following: drugs for treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, immunosuppressive therapy within 4 Weeks prior to gene replacement therapy (e.g., corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, IV immunoglobulin, rituximab)
* Anti AAV9 antibody titer >1:50 as determined by Enzyme linked Immunosorbent Assay (ELISA) binding immunoassay
* Should a potential patient demonstrate Anti AAV9 antibody titer >1:50, he or she may receive retesting inside the 30-Day screening period and will be eligible to participate if the Anti AAV9 antibody titer upon retesting is *1:50, provided patient is still <6 Week of age at the time of dosing
* Biological mother involved with the care of the child refuses anti-AAV9 antibody testing prior to dosing
* Parent(s)/legal guardian(s) unable or unwilling to comply with study procedures or inability to travel for repeat visits

* Parent(s)/legal guardian(s) unwilling to keep study results/observations confidential or to refrain from posting confidential study results/observations on social media sites
* Parent(s)/legal guardian(s) refuses to sign consent form

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:	3
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	na
Generic name:	onasemnogene abeparvovec

Ethics review

Approved WMO

Date:	28-02-2019
Application type:	First submission
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	EUCTR2017-004087-35-NL
ClinicalTrials.gov	NCT03505099
CCMO	NL65636.000.18