Novartis - SPR1NT

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

Summary

This is a Phase 3 trial that studies a single dose of AVXS-101 (gene replacement therapy) in pre-symptomatic infants with SMA. The study involves one intravenous (IV) infusion followed by post-treatment monitoring of safety and efficacy. Depending on the number of SMN2 copies that the participant has, the study will involve 18 months (SMN2 = 2 copies) or 24 months (SMN2 = 3) of post-treatment monitoring. After this visit, eligible patients will be asked to rollover into a long-term follow-up study.

Study Number: NCT03505099

Description by Novartis Gene Therapies

Phase 3, open-label, single-arm study of a single, one-time dose of onasemnogene abeparvovec-xioi (gene replacement therapy) in patients with spinal muscular atrophy who meet enrollment criteria and are genetically defined by bi-allelic deletion of survival motor neuron 1 gene (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 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 onasemnogene abeparvovec-xioi, 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.

Primary Outcome Measures

- Percentage of participants achieving functional independent sitting for at least 30 seconds at any visit [Time Frame: 18 months]

  Participants with bi-allelic SMN1 deletions and 2 copies of SMN2

- Percentage of participants achieving the ability to stand without support for at least 3 seconds at any visit [Time Frame: 24 months]

  Participants with bi-allelic SMN1 deletions and 3 copies of SMN2

Secondary Outcome Measures

- Percentage of participants surviving without permanent ventilation in the absence of acute reversible illness and perioperatively [Time Frame: 14 months]

  Participants with bi-allelic SMN1 deletions and 2 copies of SMN2

- Percentage of participants achieving the ability to maintain weight at or above the 3rd percentile without non-oral/mechanical feeding support at any visit [Time Frame: 18 months]

  Participants with bi-allelic SMN1 deletions and 2 copies of SMN2

- Percentage of participants demonstrating the ability to walk alone at any visit [Time Frame: 24 months]

  Participants with bi-allelic SMN1 deletions and 3 copies of SMN2. Ability to walk alone is defined as the ability to take at least 5 steps independently displaying coordination and balance.

Can I take part?

Inclusion Criteria

- 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) ≥2mV at Baseline; centralized review of CMAP data will be conducted
- Gestational age of 35 to 42 weeks
- Patients with pre-symptomatic SMA Type 1 as determined by the following features:
  - 2 copies of SMN2 Patients with 2 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

AUSNMD

Trial Status
Trial complete

Locations
Sydney - Children's Hospital, Trial complete/terminated

Trial Sponsor
Novartis Gene Therapies

Age
Less than 6 weeks

SMASubtype
Type 1

SMN2 Copy Numbers Required
2 or more

Mode of delivery
IV

MRI
No

Phase
3

Length Of Participation
18-36 months

Recruitment Target
30

Therapeutic Category
Gene therapy

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
- Tracheostomy or current prophylactic use or requirement of noninvasive 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 nonthickened 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 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
- 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 RNA testing in the patient prior to enrollment.
- Serious nonrespiratory 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 nonpulmonary/respiratory tract infection 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
- AntiAAV9 antibody titer >1:50 as determined by Enzyme-linked Immunosorbent Assay (ELISA) binding immunoassay
    - Should a potential patient demonstrate AntiAAV9 antibody titer >1:50, he or she may receive retesting inside the 30-Day screening period and will be eligible to participate if the AntiAAV9 antibody titer upon retesting is ≤1:50, provided the <6 Week age requirement at the time of dosing is still met
- Biological mother involved with the care of the child refuses anti-AAV9 antibody testing prior to dosing

Other inclusion/exclusion criteria apply.

For contact details and to find out more, please refer to ausnmd.org.