Sponsor

Novartis Gene Therapies, Inc.

Generic Drug Name

AVXS-101

Trial Indication(s)

Spinal Muscular Atrophy (SMA) Type 1

Protocol Number

AVXS-101-CL-306 (COAV101A12304)

Protocol Title

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

Clinical Trial Phase

Phase III

Phase of Drug Development

Phase III

Study Start/End Dates

31 May 2019 to 29 Jun 2021

Study Design/Methodology

This was a Phase 3, open-label, single-arm, single-dose study of AVXS-101 (gene replacement therapy) in participants with SMA Type 1 with one or 2 copies of the survival of motor neuron (*SMN*) *2* gene.

The study includes 3 study periods: screening, gene replacement therapy, and follow-up. During the screening period (Days -30 to –2), participants whose parent(s)/legal guardian(s) provided informed consent underwent screening procedures to determine eligibility for study enrollment. Participants who met the entry criteria entered the in-patient gene replacement therapy period (Day –1 to Day 3). On Day -1, participants were admitted to the hospital for pre-treatment baseline procedures. On Day 1, participants received a one-time intravenous (IV) infusion of 1.1 $x10^{14}$vg/kg AVXS-101 and underwent in-patient safety monitoring over the next 48 hours. Participants could be discharged 48 hours after gene replacement therapy, based on Investigator judgment. Participants also received daily doses of prophylactic oral prednisolone starting at a dose of 1-2 mg/kg/day from 1 day prior to AVXS-101 infusion until at least 30 days post-infusion at which point the prednisolone dose could be tapered downwards. At Week 9, prednisolone could be discontinued. During the outpatient follow-up period (Days 4 to End of Study at 18 months of age), participants returned at regularly scheduled intervals for efficacy and safety assessments until the participant reached 18 months of age.

Centers

One center in Taiwan.

Objectives:

Primary Objective(s)

To determine efficacy by demonstrating achievement of developmental milestone of ‘sitting without support’ for at least 10 seconds up to 18 months of age as assessed by the World Health Organization (WHO)-Multicentre Growth Reference Study (MGRS).

Secondary Objective(s)

To 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.

Test Product (s), Dose(s), and Mode(s) of Administration

AVXS-101 was administered as a one-time IV infusion at a dose of 1.1 x 10^{14}vg/kg.

Statistical Methods

The study was originally designed to enrol at least six patients and have sufficient power, when combined with an identically designed study AVXS-101-CL-302, to establish efficacy with regard to the primary and secondary endpoints. However, after 2 patients had enrolled in the study, enrolment was terminated for reasons unrelated to safety or efficacy. Due to the change in data analysis and narrowed scope of AVXS-101-CL-306, no combined analysis or stand-alone analysis was conducted. Primary and secondary efficacy endpoints were presented as a dichotomous outcome for each patient. The final analysis was primarily composed by individual data listings and participant profiles after the final database lock. No inferential statistical approaches were performed.

Efficacy Analysis

Efficacy analyses were conducted using the intention-to-treat (ITT) population. The ITT population consisted of symptomatic participants with biallelic SMN2 deletions and 2 copies of SMN2 without the genetic modifier (c.859G>C). The final analysis was primarily composed by individual data listings and participant profiles after the final database lock. No inferential statistical approaches were performed.

Safety Analysis

Safety was assessed through the incidence and severity of adverse events (AEs), vital sign assessments, cardiac assessments, laboratory evaluations (chemistry, hematology, immunology, urinalysis), physical examinations, and use of

concomitant medications. Adverse events were coded in accordance with the Medical Dictionary of Regulatory Activities (MedDRA) coding dictionary. Safety assessments were presented in data listings or participant profiles for the Safety population. The safety population consisted of all participants who received an IV infusion of AVXS-101. In addition, summary tables were prepared for treatment-emergent AEs (TEAEs) and serious AEs (SAEs) together with an overview of adverse events.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

- Participants with SMA Type 1 as determined by diagnosis of SMA based on gene mutation analysis with biallelic *SMN1* mutations (deletion or point mutations) and 1 or 2 copies of *SMN2* [inclusive of the known *SMN2* gene modifier mutation (c.859G>C)].
- Participants must have been < 6 months (< 180 days) of age at the time of AVXS-101 infusion.
- Participants must have had a swallowing evaluation test performed prior to administration of gene replacement therapy.

Exclusion criteria:

- Previous, planned or expected scoliosis repair surgery/procedure prior to 18 months of age
- Use of invasive ventilatory support (tracheotomy with positive pressure) or pulse oximetry < 95% saturation at screening
    - Pulse oximetry saturation must not decrease ≥ 4 percentage points between screening and dosing with confirmatory oximetry reading
    - Participants may have been put on non-invasive ventilatory support for less than 12 hours per day at the discretion of their physician or trial staff
- Use or requirement of non-invasive ventilatory support for 12 or more hours daily in the 2 weeks prior to dosing
- Participant with signs of aspiration based on a swallowing test or whose weight-for-age fell below the 3rd percentile based on WHO Child Growth Standards and unwilling to use an alternative method to oral feeding

- Anti-AAV9 antibody titer > 1:50 as determined by enzyme-linked immunosorbent assay (ELISA) binding immunoassay. If a potential participant demonstrated anti-adeno-associated virus 9 (AAV9) antibody titer > 1:50, he or she may have retested within 30 days of the screening period and been eligible to participate if the anti-AAV9 antibody titer upon retesting was ≤ 1:50

- Clinically significant abnormal laboratory values (gamma-glutamyl transferase, alanine aminotransferase, aspartate aminotransferase, total bilirubin > 2× the upper limit of normal, creatinine ≥ 1.0 mg/dL, hemoglobin < 8 or > 18 g/dL; white blood cell > 20,000 per cmm) prior to gene replacement therapy. Participants with an elevated bilirubin level that was unequivocally the result of neonatal jaundice should not have been excluded

- Participants < 35 weeks gestational age at time of birth.

Participant Flow Table (All Participants)

Disposition of Participants	All Participants n
Participants screened	5
Screen failures	3
Eligibility criteria not met	3
Participants in the All Enrolled population	2
Participants in the ITT population	2
Participants in the Safety population	2
Participants who completed the study	2
Participants discontinued from the study	0

Baseline Characteristics (Safety Population)

Characteristic Category/Statistic	All Participants (N = 2)
Age at Baseline (days), n (%)	
0 - 27 days	1 (50.0)
28 days - 23 months	1 (50.0)
Sex, n (%)	
Male	1 (50.0)
Female	1 (50.0)
Ethnicity, n (%)	
Hispanic or Latino	0
Not Hispanic or Latino	2 (100.0)
Race, n (%)	
Asian	2 (100.0)
Black or African American	0
White	0
Other	0

Primary Outcome Result(s)

Number of participants demonstrating independent sitting for at least 10 seconds at any point up to 18 months of age (ITT Population)

Time Frame: From baseline up to 18 months of age visit

	All Participants (N = 2)
Timing of milestone demonstration, n (%)	
Achieved independent sitting for at least 10 seconds inside of normal developmental window (age ≤ 279 days), n (%)	0
Achieved independent sitting for at least 10 seconds outside of normal development window, n (%)	1 (50.0)
Did not achieve independent sitting for at least 10 seconds, n (%)	1 (50.0)

Secondary Outcome Result(s)

Event-free Survival at ≥ 14 months of age (ITT Population)

Time Frame: From baseline up to 14 months of age

	All Participants (N = 2)
n (%)	2 (100.0)

Safety Results

Serious Adverse Events and Deaths (Safety Population)

Time Frame: From Day 1 up to 18 Months of Age Visit (total duration of approximately 12-18 months depending on age at dosing)

	All Participants (N = 2)
No. (%) of subjects studied	2
No. (%) of subjects with AE(s)	2 (100)
Number (%) of subjects with serious or other significant events	n (%)
Death	0
SAE(s)	1 (50)
Discontinued due to SAE(s)	0

Serious Adverse Events by System Organ Class and preferred term (Safety Population)

Time Frame: From Day 1 up to 18 Months of Age Visit (total duration of approximately 12-18 months depending on age at dosing)

System Organ Class **Preferred term**	**All Participants (N = 2)** **n (%)**
Gastrointestinal disorders	1 (50)
Dysphagia	1 (50)

Non-Serious Adverse Events by System Organ Class and Preferred Term n (%)

Time Frame: From Day 1 up to 18 Months of Age Visit (total duration of approximately 12-18 months depending on age at dosing)

Treatment-emergent adverse events by System Organ Class and preferred term (Safety Population)

System Organ Class Preferred term	All Participants (N = 2) n (%)
Congenital, familial and genetic disorders	1 (50)
Cleft palate	1 (50)

Gastrointestinal disorders	2 (100)
Dysphagia	1 (50)
Gastrointestinal hypomobility	1 (50)
Gastroesophageal reflux disease	1 (50)
Hiatus hernia	1 (50)
Upper gastrointestinal haemorrhage	1 (50)
General disorders and administration site conditions	1 (50)
Pyrexia	1 (50)
Infections and infestations	2 (100)
Gingivitis	1 (50)
Pharyngitis	1 (50)
Upper respiratory tract infection	1 (50)
Urinary tract infection	1 (50)
Investigations	1 (50)
Glucose urine present	1 (50)
Metabolism and nutrition disorders	2 (100)
Failure to thrive	2 (100)
Renal and urinary disorders	1 (50)
Glycosuria	1 (50)
Respiratory, thoracic and mediastinal disorder	1 (50)
Respiratory distress	1 (50)
Rhonchi	1 (50)
Tachypnea	1 (50)
Skin and subcutaneous tissue disorder	1 (50)
Dermatitis diaper	1 (50)
Eczema	1 (50)
Rath	1 (50)

Overview of Treatment-emergent Adverse Events (Safety Population)

Time Frame: From Day 1 up to 18 Months of Age Visit (total duration of approximately 12-18 months depending on age at dosing)

Adverse event category	All Participants (N = 2) n (%) [number of events]
Any TEAE	2 (100.0) [30]
TEAEs related to study treatment	0
TEAEs of Grade 3 severity or higher	1 (50.0) [1]
Serious TEAEs	1 (50.0) [1]
Serious TEAEs related to study treatment	0
TEAEs leading to study discontinuation	0
TEAEs leading to death	0
Adverse events of Special Interest	1 (50.0) [1]
Hepatoxicity	0
Thrombocytopenia	1 (50.0) [1]
Cardiac adverse events	0
Sensory abnormalities suggestive of ganglionopathy	0
Thrombotic microangiopathy	0

Conclusion:

Two participants were enrolled in this study. The efficacy and safety findings from this study are consistent with results of other AVXS-101 clinical studies within the AVXS-101 clinical program. No new safety signals were identified in the study.

Date of Clinical Study Report

22 October 2021.