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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

onasemnogene abeparvovec

Trial Indication

Type 2 spinal muscular atrophy (SMA)

Protocol Number

COAV101B12301

Protocol Title

A randomized, sham-controlled, double-blind study to evaluate the efficacy and safety of intrathecal OAV101 in Type 2 spinal muscular atrophy (SMA) patients who are ≥ 2 to < 18 years of age, treatment naive, sitting, and never ambulatory

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase III

Study Start/End Dates

Study Start Date: February 01, 2022 (Actual)
Primary Completion Date: November 12, 2024 (Actual)
Study Completion Date: April 29, 2025 (Actual)

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Reason for Termination (If applicable)

Study Design/Methodology

This was a Phase III multi-center, single dose (1.2 x 10^14 vector genomes), randomized, sham controlled, double-blind study that investigates the efficacy, safety and tolerability of OAV101B in treatment naive, sitting and never ambulatory Spinal muscular atrophy (SMA) patients 2 to <18 years of age.

Eligible participants received a single administration of OAV101B at the dose of 1.2 x 10^14 vector genomes intrathecally or the sham procedure on Day 1 (Treatment Period 1), and were followed for a period of 52 weeks for Period 1. In Period 2, participants who received the sham treatment in Period 1 were administered OAV101B, and participants who received OAV101B in Period 1 underwent the sham procedure. Participants were followed for 12 weeks in Period 2.

The study consisted of a Screening and Baseline Period followed by two Treatment and Follow-up Periods. Participants were admitted to the hospital on Day 1 (or Day -1 as per local standards of care). After receiving OAV101B or the sham procedure on Day 1, participants underwent in-patient safety monitoring through Day 2 and optionally for Day 3.

After Period 1, eligible participants could continue to Period 2 subsequently entering Period 2 in a rolling seamless fashion as participants completed Follow-up Period 1. In Treatment Period 2, eligible participants who received a sham procedure on Study Day 1 of Treatment Period 1 were hospitalized to receive OAV101B on Week 52 + 1 day and participants who received OAV101B on Study Day 1 of Treatment Period 1 were hospitalized to receive a sham procedure on the Week 52 + 1 Day. The total duration of the study including both Period 1 and Period 2 was 64 weeks. At the end of the study, all participants who received OAV101B were eligible to enroll in a long-term follow-up study to monitor long-term safety and efficacy.

Approximately 125 participants were planned to be randomized in a 3:2 ratio to receive OAV101B (N= ~75) or a sham procedure (N= ~50). The unequal randomization ratio allowed more participants to receive active treatment in Period 1. It was anticipated that approximately 65 randomized participants would be aged 2 to <5 years and approximately 60 randomized participants would be aged 5 to <18 years.

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Centers

42 centers in 13 countries: United States(6), Vietnam(2), South Africa(2), Thailand(2), China(9), Taiwan(2), Mexico(3), Denmark(2), India(8), Malaysia(2), Singapore(1), Saudi Arabia(1), Brazil(2)

Objectives:

The primary objective of this study was to compare the efficacy of OAV101B vs. sham procedure as measured by the change from baseline in Hammersmith Functional Motor Scale-Expanded (HFMSE) total score up to Week 52.

The primary question of interest was: What is the effect of OAV101B treatment versus the sham procedure on change from baseline in HFMSE total score after treatment in sitting but never ambulatory patients aged 2 to <18 years with Type 2 SMA, regardless of study discontinuation or receipt of prohibited concomitant medications not for the intent to treat SMA?

The secondary objectives were to compare the efficacy of OAV101B vs. sham control in two patient age groups: 2 to <5 years (HFMSE, Revised Upper Limb Module (RULM)); 2 to <18 years RULM and to evaluate the safety and tolerability of OAV101B vs. sham procedure in patients 2 to <18 years.

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

The investigational drug is OAV101B, administered one time at a dose of 1.2 x 10^14 vg intrathecally.

Statistical Methods

Novartis performed the analyses presented in this report. The analysis sets included the Intent to Treat Analysis Set (ITT) comprising all randomized participants.

The Full Analysis Set (FAS) and the Safety Analysis Set (SAF) both comprised all participants who received the study treatment or sham procedure during Treatment Period 1.

The primary efficacy endpoint was the change from baseline in HFMSE total score at the end of Follow-up Period 1 in the overall study population (2 to <18 years age group)

The secondary efficacy endpoints were:
• Change from baseline in HFMSE total score at the end of Follow-up Period 1 in the 2 to <5 years age group.
• Achievement of at least a 3-point improvement from baseline in HFMSE total score at the end of Follow-up Period 1 in the overall study population
• Achievement of at least a 3-point improvement from baseline in HFMSE total score at the end of Follow-up Period 1 in the 2 to <5 years age group
• Change from baseline in RULM at the end of Follow-up Period 1 in the 2 to <18 years age group
• Change from baseline in the RULM at the end of Follow-up Period 1 in the 2 to <5 years age group

The primary efficacy endpoint and continuous secondary endpoints of changes from baseline in HFMSE and RULM scores were analyzed using a linear mixed effects repeated measures model (MMRM) with the observed as the dependent variable using the FAS. The fixed effects in the MMRM model included treatment, strata, scheduled visit, treatment by visit interaction, and baseline HFMSE/baseline RULM as covariates. An unstructured covariance matrix was used. Least-squares means (LSMs) for each treatment arm, standard errors, and associated 95% confidence intervals (CIs), difference of LSMs compared to sham procedure arm, and the associated 95% CI for the difference, as well as the two-sided p-values were tabulated by visit and treatment. A hierarchical gate-keeping procedure and the Hochberg method was used to maintain the overall 2-sided study-wise type I error rate at 0.05 for the primary endpoint and secondary efficacy endpoints which are positively correlated. To assess the potential impact of excluding participants from the primary analysis who were randomized into the study but did not receive treatment, the primary and secondary efficacy analysis was repeated using the ITT.

All other endpoints were analyzed using descriptive statistics.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion criteria:

- Diagnostic confirmation during screening period of 5q SMA

- The patient must be treatment naive (historical or current use) for all SMN-targeting therapies (e.g., risdiplam (Evrysdi) and

nusinersen (Spinraza)).

- Onset of clinical signs and symptoms at ≥ 6 months of age

- A complete Hammersmith Functional Motor Scale - Expanded (HFMSE) assessment during the screening period for trial eligibility

- Able to sit independently at screening, but has never had the ability to walk independently.

Key Exclusion criteria:

· Anti-adeno-associated virus serotype 9 (AAV9) antibody titer reported as elevated (reference to > 1:50 or validated result consistent with being elevated) at screening as determined by sponsor designated lab.

· Infectious process (e.g., viral, bacterial) or febrile illness within 30 days prior to OAV101 treatment or sham procedure

· Hepatic dysfunction (i.e. alanine aminotransferase (ALT), total bilirubin, gamma-glutamyl transferase (GGT) or glutamate dehydrogenase (GLDH), > upper limit of normal (ULN).

· 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

· Complications at screening that would interfere with motor efficacy assessments including but not limited to, severe contractures or

Cobb angle > 40 in a sitting position

· Surgery for scoliosis or hip fixation in the 12 months prior to Screening or planned within the next 64 weeks

· Clinically significant sensory abnormalities in the neurological examination at Screening

Participant Flow Table

Period 1 - First Intervention (52 weeks)

	OAV101 first, then sham control	Sham control first, then OAV101	Total
Arm/Group Description	OAV101 administered as a single, one-time intrathecal dose of 1.2 x 10^14 vector genomes (vg) in Period 1, then a skin prick in the lumbar region without any medication in Period 2	A skin prick in the lumbar region without any medication in Period 1, then OAV101 administered as a single, one-time intrathecal dose of 1.2 x 10^14 vector genomes (vg) in Period 2	
Started	75	51	126
Patients completed follow-up period 1	73	50	123
Patients completed follow-up period 1 but did not enter treatment period 2	6	4	10
Patient who completed Week 48 but not Week 52	1	0	1
Primary reason for not entering treatment period 2	6	4	10
Completed	67	46	113
Not Completed	8	5	13

Physician Decision	1	0	1
Guardian decision	1	0	1
Adverse Event	0	1	1
Protocol-specified withdrawal criterion met	6	4	10

Period 2 - 2nd Intervention (12 weeks)

	OAV101 first, then sham control	Sham control first, then OAV101	Total
Arm/Group Description	OAV101 administered as a single, one-time intrathecal dose of 1.2 x 10^14 vector genomes (vg) in Period 1, then a skin prick in the lumbar region without any medication in Period 2	A skin prick in the lumbar region without any medication in Period 1, then OAV101 administered as a single, one-time intrathecal dose of 1.2 x 10^14 vector genomes (vg) in Period 2	
Started	67	46	113
Completed	67	46	113
Not Completed	0	0	0

Baseline Characteristics

	OAV101 first, then sham control	Sham control first, then OAV101	Total
Arm/Group Description	OAV101 administered as a single, one-time intrathecal dose of 1.2 x 10^14 vector genomes (vg) in Period 1, then a skin prick in the lumbar region without any medication in Period 2	A skin prick in the lumbar region without any medication in Period 1, then OAV101 administered as a single, one-time intrathecal dose of 1.2 x 10^14 vector genomes (vg) in Period 2	

Number of Participants [units: participants]	75	51	126
Baseline Analysis Population Description			
Age Continuous (units: years) Analysis Population Type: Participants Mean ± Standard Deviation			
	5.71±3.575	5.68±3.045	5.70±3.358
Sex: Female, Male (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
Female	41	23	64
Male	34	28	62
Race (NIH/OMB) (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
American Indian or Alaska Native	2	5	7
Asian	49	25	74
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	5	4	9
White	7	7	14
More than one race	0	0	0
Unknown or Not Reported	12	10	22

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Primary Outcome Result(s)

Change from baseline at the end of Period 1 in the Hammersmith Functional Motor Scale Expanded - total score - in the ≥ 2 to < 18 years age group

Description	The HFMSE is a validated SMA specific assessment devised for use in children with SMA to give objective information on motor ability and clinical progression. The HFMSE contains 33 items rated from 0 (unable to perform) to 2 (performs without modification/adaptation/compensation). Total scores range from 0-66. Higher scores indicate higher levels of motor ability.
Time Frame	Baseline, Week 52 (or Week 48)
Analysis Population Description	Full Analysis Set - all participants who were treated in treatment period 1 with a valid measurement (including 1 pt who dropped out between Week 48 and week 52; The data collected at Week 48 are included in this table.) (Participants who early terminated before Week 48 are not included).

	OAV101 first, then sham control	**Sham control first, then OAV101**
Arm/Group Description	OAV101 administered as a single, one-time intrathecal dose of 1.2 x 10^14 vector genomes (vg) in Period 1, then a skin prick in the lumbar region without any medication in Period 2	A skin prick in the lumbar region without any medication in Period 1, then OAV101 administered as a single, one-time intrathecal dose of 1.2 x 10^14 vector genomes (vg) in Period 2
Number of Participants Analyzed [units: participants]	74	50
Change from baseline at the end of Period 1 in the Hammersmith Functional Motor Scale Expanded - total score - in the ≥ 2 to < 18 years age group (units: Scores on a scale)	**Least Squares Mean ± Standard Error**	**Least Squares Mean ± Standard Error**
Change from baseline at End of Follow-up Period 1	2.39 ± 0.439	0.51 ± 0.532

Statistical Analysis

Groups	OAV101 first, then sham control, Sham control first, then OAV101	Change from baseline at End of Follow-up Period 1
Type of Statistical Test	Superiority	

P Value	0.0074
Method	Mixed Models Analysis
Other LS-Means difference	1.88
Standard Error of the mean	0.690
95 % Confidence Interval 2-Sided	0.51 to 3.25

Secondary Outcome Result(s)

Change from baseline in HFMSE total score at the end of Follow-up Period 1 in treated patients compared to sham controls in the ≥ 2 to < 5 years age group

Description	The HFMSE is a validated SMA specific assessment devised for use in children with SMA to give objective information on motor ability and clinical progression. The HFMSE contains 33 items rated from 0 (unable to perform) to 2 (performs without modification/adaptation/compensation). Total scores range from 0-66. Higher scores indicate higher levels of motor ability.
Time Frame	Baseline, Week 52 (or Week 48)
Analysis Population Description	Full Analysis Set - all participants who were treated in treatment period 1 with a valid measurement in the 2 to <5 years age group. (Participants who early terminated before Week 48 are not included.)

	OAV101 first, then sham control	**Sham control first, then OAV101**
Arm/Group Description	OAV101 administered as a single, one-time intrathecal dose of 1.2 x 10^14 vector genomes (vg) in Period 1, then a skin prick in the lumbar region without any medication in Period 2	A skin prick in the lumbar region without any medication in Period 1, then OAV101 administered as a single, one-time intrathecal dose of 1.2 x 10^14 vector genomes (vg) in Period 2
Number of Participants Analyzed [units: participants]	41	29

Change from baseline in HFMSE total score at the end of Follow-up Period 1 in treated patients compared to sham controls in the ≥ 2 to < 5 years age group (units: Scores on a scale)	**Least Squares Mean ± Standard Error**	**Least Squares Mean ± Standard Error**
Change from baseline at End of Follow-up Period 1	3.00 ± 0.569	1.56 ± 0.683

Statistical Analysis

Groups	OAV101 first, then sham control, Sham control first, then OAV101	Change from baseline at End of Follow-up Period 1
Type of Statistical Test	Superiority	
P Value	0.1097	
Method	Mixed Models Analysis	
Other LS-Means - difference	1.44	
Standard Error of the mean	0.889	
95 % Confidence Interval 2-Sided	-0.33 to 3.22	

Change from baseline in Revised Upper Limb Module (RULM) total score at the end of Follow-up Period 1 in treated patients compared to sham controls in the ≥ 2 to < 18 years age group

Description	The RULM is a validated SMA specific assessment of motor performance in the upper limbs from childhood through adulthood in ambulatory and non-ambulatory individuals with SMA. The scale consists of 19 scorable items: 18 items scored on 0 (unable) to 2 (full achievement) scale, and one item that is scored from 0 (unable) to 1 (able). Total scores range from 0-37 points. Higher scores reflect higher level of motor ability.
Time Frame	Baseline, Week 52 (or Week 48)
Analysis Population Description	Full Analysis Set - all participants who were treated in treatment period 1 with a valid measurement (including 1 pt who dropped out between Week 48 and week 52; The data collected at Week 48 are included in this table.) (Participants who early terminated before Week 48 are not included).

	OAV101 first, then sham control	Sham control first, then OAV101
Arm/Group Description	OAV101 administered as a single, one-time intrathecal dose of 1.2 x 10^14 vector genomes (vg) in Period 1, then a skin prick in the lumbar region without any medication in Period 2	A skin prick in the lumbar region without any medication in Period 1, then OAV101 administered as a single, one-time intrathecal dose of 1.2 x 10^14 vector genomes (vg) in Period 2
Number of Participants Analyzed [units: participants]	74	50
Change from baseline in Revised Upper Limb Module (RULM) total score at the end of Follow-up Period 1 in treated patients compared to sham controls in the ≥ 2 to < 18 years age group (units: Scores on a scale)	**Least Squares Mean ± Standard Error**	**Least Squares Mean ± Standard Error**
Change from baseline at End of Follow-up Period 1	2.44 ± 0.381	0.92 ± 0.462

Statistical Analysis

Groups	OAV101 first, then sham control, Sham control first, then OAV101	Change from baseline at End of Follow-up Period 1
Type of Statistical Test	Superiority	
P Value	0.0122	
Method	Mixed Models Analysis	
Other LS-Means difference	1.52	
Standard Error of the mean	0.599	
95 % Confidence Interval 2-Sided	0.34 to 2.71	

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Change from baseline in the RULM total score at the end of Follow-up Period 1 in treated patients compared to sham controls in the ≥ 2 to < 5 years age group

Description	The RULM is a validated SMA specific assessment of motor performance in the upper limbs from childhood through adulthood in ambulatory and non-ambulatory individuals with SMA. The scale consists of 19 scorable items: 18 items scored on a 0 (unable) to 2 (full achievement) scale, and one item that is scored from 0 (unable) to 1 (able). Total scores range from 0-37 points. Higher scores reflect higher level of motor ability.
Time Frame	Baseline, Week 52 (or Week 48)
Analysis Population Description	Full Analysis Set - all participants who were treated in treatment period 1 with a valid measurement in the 2 to <5 years age group. (Participants who early terminated before Week 48 are not included.)

	OAV101 first, then sham control	**Sham control first, then OAV101**
Arm/Group Description	OAV101 administered as a single, one-time intrathecal dose of 1.2 x 10^14 vector genomes (vg) in Period 1, then a skin prick in the lumbar region without any medication in Period 2	A skin prick in the lumbar region without any medication in Period 1, then OAV101 administered as a single, one-time intrathecal dose of 1.2 x 10^14 vector genomes (vg) in Period 2
Number of Participants Analyzed [units: participants]	41	29
Change from baseline in the RULM total score at the end of Follow-up Period 1 in treated patients compared to sham controls in the ≥ 2 to < 5 years age group (units: Scores on a scale)	**Least Squares Mean ± Standard Error**	**Least Squares Mean ± Standard Error**
Change from baseline at End of Follow-up Period 1	3.27 ± 0.535	1.82 ± 0.642

Statistical Analysis

Groups	OAV101 first, then sham control, Sham control first, then OAV101	Change from baseline at End of Follow-up Period 1
Type of Statistical Test	Superiority	
P Value	0.0873	

Method	Mixed Models Analysis
Other LS-Means difference	1.45
Standard Error of the mean	0.836
95 % Confidence Interval 2-Sided	-0.22 to 3.12

% of participants who achieved at least a 3-point improvement from baseline in HFMSE total score at the end of Follow-up Period 1 in the ≥ 2 to < 18 years age group

Description	The HFMSE is a validated SMA specific assessment devised for use in children with SMA to give objective information on motor ability and clinical progression. The HFMSE contains 33 items rated from 0 (unable to perform) to 2 (performs without modification/adaptation/compensation). Total scores range from 0-66. Higher scores indicate higher levels of motor ability.
Time Frame	Baseline, Week 52 (or Week 48) (end of Period 1)
Analysis Population Description	Full Analysis Set - all participants who were treated in treatment period 1 with a valid measurement (including 1 pt who dropped out between Week 48 and week 52; The data collected at Week 48 are included in this table.) (Participants who early terminated before Week 48 are not included).

	OAV101 first, then sham control	**Sham control first, then OAV101**
Arm/Group Description	OAV101 administered as a single, one-time intrathecal dose of 1.2 x 10^14 vector genomes (vg) in Period 1, then a skin prick in the lumbar region without any medication in Period 2	A skin prick in the lumbar region without any medication in Period 1, then OAV101 administered as a single, one-time intrathecal dose of 1.2 x 10^14 vector genomes (vg) in Period 2
Number of Participants Analyzed [units: participants]	74	50
% of participants who achieved at least a 3-point improvement from baseline in HFMSE total score at the end of Follow-up Period 1 in the ≥ 2 to < 18 years age group (units: % of participants)	**Number** **(95% Confidence Interval)**	**Number** **(95% Confidence Interval)**
End of Followup Period 1 (Week 52)	39.2 (28.07 to 50.31)	26.0 (13.84 to 38.16)

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Statistical Analysis

Groups	OAV101 first, then sham control, Sham control first, then OAV101	End of Followup Period 1 (Week 52)
Type of Statistical Test	Superiority	
P Value	0.0879	
Method	Regression, Logistic	
Odds Ratio (OR)	2.03	
95 % Confidence Interval 2-Sided	0.90 to 4.57	

% of participants who achieved at least a 3-point improvement from baseline in HFMSE total score at the end of Follow-up Period 1 for participants aged ≥ 2 to < 5 years

Description	The HFMSE is a validated SMA specific assessment devised for use in children with SMA to give objective information on motor ability and clinical progression. The HFMSE contains 33 items rated from 0 (unable to perform) to 2 (performs without modification/adaptation/compensation). Total scores range from 0-66. Higher scores indicate higher levels of motor ability.
Time Frame	Baseline, Week 52 (or Week 48)(end of Period 1)
Analysis Population Description	Full Analysis Set - all participants who were treated in treatment period 1 with a valid measurement in the 2 to <5 years age group. (Participants who early terminated before Week 48 are not included.)

	OAV101 first, then sham control	Sham control first, then OAV101
Arm/Group Description	OAV101 administered as a single, one-time intrathecal dose of 1.2 x 10^14 vector genomes (vg) in Period 1, then a skin prick in the lumbar region without any medication in Period 2	A skin prick in the lumbar region without any medication in Period 1, then OAV101 administered as a single, one-time intrathecal dose of 1.2 x 10^14 vector genomes (vg) in Period 2

Number of Participants Analyzed [units: participants]	41	29
% of participants who achieved at least a 3-point improvement from baseline in HFMSE total score at the end of Follow-up Period 1 for participants aged ≥ 2 to < 5 years (units: % of participants)	**Number (95% Confidence Interval)**	**Number (95% Confidence Interval)**
End of Followup Period 1 (Week 52)	48.8 (33.48 to 64.08)	37.9 (20.27 to 55.59)

Statistical Analysis

Groups	OAV101 first, then sham control, Sham control first, then OAV101	End of Followup Period 1 (Week 52)
Type of Statistical Test	Superiority	
P Value	0.6448	
Method	Regression, Logistic	
Odds Ratio (OR)	1.27	
95 % Confidence Interval 2-Sided	0.46 to 3.56	

Number of participants with treatment emergent Adverse Events and Serious Adverse Events

Description	An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. A Treatment Emergent Adverse Event (TEAE) is defined as an event that emerges during treatment, having been absent pretreatment, or worsens relative to the pretreatment state. The occurrence of AEs must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments. pt = participant pts = participants
Time Frame	Adverse events are reported from the start of treatment period 1 plus 64 weeks, up to a maximum time period of 64 weeks.
Analysis Population Description	Safety analysis set - all treated pts. AEs for Periods 1 and 2 are combined in the overall OAV101 arm because the same active treatment (and same single dose) was administered in either Period1 or 2. Because this is a gene therapy, which permanently impacts the genetics of

the study pt, pts randomized to OAV101 in Period 1 are still considered on treatment with OAV101 in Period 2 (after receiving sham control in Period 2). Therefore, AEs for the Sham arm can only be considered from Period 1.

	OAV101 Period 1	Sham control Period 1	Overall OAV101 in Periods 1 and 2
Arm/Group Description	OAV101 administered as a single, one-time intrathecal dose of 1.2 x 10^14 vector genomes (vg) in Period 1	A skin prick in the lumbar region without any medication in Period 1	OAV101 administered as a single, one-time intrathecal dose of 1.2 x 10^14 vector genomes (vg). -For participants randomized to OAV101B in Period 1: All AEs from Period 1 and 2 -For participants randomized to the sham control in Period 1 and who were administered OAV101 in Period 2: All AEs from Period 2
Number of Participants Analyzed [units: participants]	75	51	121
Number of participants with treatment emergent Adverse Events and Serious Adverse Events (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
Any treatment-emergent adverse event	74 (98.67%)	46 (90.2%)	104 (85.95%)
Any treatment-emergent adverse event related to study treatment	27 (36%)	5 (9.8%)	36 (29.75%)
Any serious treatment-emergent adverse event	21 (28%)	17 (33.33%)	34 (28.1%)
Any serious treatment-emergent adverse event related to study treatment	8 (10.67%)	1 (1.96%)	12 (9.92%)
Any severe treatment-emergent adverse event	8 (10.67%)	9 (17.65%)	12 (9.92%)
Any treatment-emergent adverse event leading to study discontinuation	0 (%)	1 (1.96%)	0 (%)

Any treatment-emergent adverse event leading to death	0 (%)	0 (%)	0 (%)
Any treatment-emergent adverse event of special interest	12 (16%)	7 (13.73%)	21 (17.36%)

Number of participants with adverse events of special interest (AESI)

Description	An AESI is primarily defined by using standard Medical Dictionary for Regulatory Activities (MedDRA) queries, and identified as follows: - Hepatotoxicity - Thrombocytopenia - Cardiac adverse events - Signs and symptoms that may be suggestive of dorsal root ganglia toxicity - Thrombotic microangiopathy - New malignancies Adverse events for Periods 1 and 2 are combined in the overall OAV101 arm because the same active treatment (and same single dose) was administered in either Period1 or Period 2. Because this is a gene therapy, which permanently impacts the genetics of the study participant, participants randomized to OAV101 in Period 1 are still considered on treatment with OAV101 in Period 2 (after receiving sham control in Period 2). Therefore, adverse events for the Sham arm can only be considered from Period 1.
Time Frame	Adverse events are reported from the start of treatment period 1 plus 64 weeks, up to a maximum time period of 64 weeks.
Analysis Population Description	Safety analysis set - all treated participants.

	OAV101 Period 1	Sham control Period 1	Overall OAV101 in Periods 1 and 2
Arm/Group Description	OAV101 administered as a single, one-time intrathecal dose of 1.2 x 10^14 vector genomes (vg) in Period 1	A skin prick in the lumbar region without any medication in Period 1	OAV101 administered as a single, one-time intrathecal dose of 1.2 x 10^14 vector genomes (vg). -For participants randomized to OAV101B in Period 1: All AEs from Period 1 and 2 -For participants randomized to the sham control in Period 1 and who were administered OAV101 in Period 2: All AEs from Period 2
Number of Participants Analyzed [units: participants]	75	51	121

Number of participants with adverse events of special interest (AESI) (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
Hepatotoxicity	7 (9.33%)	5 (9.8%)	10 (8.26%)
Transient thrombocytopenia	4 (5.33%)	2 (3.92%)	9 (7.44%)
Cardiac adverse events	0 (%)	0 (%)	0 (%)
Signs and symptoms that may be suggestive of dorsal root ganglia toxicity	2 (2.67%)	1 (1.96%)	3 (2.48%)
Thrombotic microangiopathy	0 (%)	0 (%)	0 (%)
New malignancies	0 (%)	0 (%)	0 (%)

Number (and percentage) of patients with intracardiac thrombi

Description	Intracardiac thrombi is defined as the presence of thrombus on post-baseline echocardiograms. Events for Periods 1 and 2 are combined in the overall OAV101 arm because the same active treatment (and same single dose) was administered in either Period1 or Period 2. Because this is a gene therapy, which permanently impacts the genetics of the study participant, participants randomized to OAV101 in Period 1 are still considered on treatment with OAV101 in Period 2 (after receiving sham control in Period 2). Therefore, events for the Sham arm can only be considered from Period 1.
Time Frame	Baseline up to 64 weeks
Analysis Population Description	Safety analysis set - all treated participants.

	OAV101 Period 1	**Sham control Period 1**	**Overall OAV101 in Periods 1 and 2**
Arm/Group Description	OAV101 administered as a single, one-time intrathecal	A skin prick in the lumbar region without any medication in Period 1	OAV101 administered as a single, one-time intrathecal dose of 1.2 x 10^14 vector genomes (vg). -For

	dose of 1.2 x 10^14 vector genomes (vg) in Period 1		participants randomized to OAV101B in Period 1: All intracardiac thrombi events from Period 1 and 2 -For participants randomized to the sham control in Period 1 and who were administered OAV101 in Period 2: All intracardiac thrombi events from Period 2
Number of Participants Analyzed [units: participants]	75	51	121
Number (and percentage) of patients with intracardiac thrombi (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
	0 (%)	1 (1.96%)	1 (.83%)

Number(and percentage) of patients with low cardiac function

Description	Low cardiac function is defined as left ventricular ejection fraction <56% or left ventricular fractional shortening <28% on post-baseline echocardigrams. Events for Periods 1 and 2 are combined in the overall OAV101 arm because the same active treatment (and same single dose) was administered in either Period1 or Period 2. Because this is a gene therapy, which permanently impacts the genetics of the study participant, participants randomized to OAV101 in Period 1 are still considered on treatment with OAV101 in Period 2 (after receiving sham control in Period 2). Therefore, events for the Sham arm can only be considered from Period 1.
Time Frame	Baseline up to 64 weeks
Analysis Population Description	Safety analysis set - all treated participants.

	OAV101 Period 1	**Sham control Period 1**	**Overall OAV101 in Periods 1 and 2**
Arm/Group Description	OAV101 administered as a single, one-time intrathecal	A skin prick in the lumbar region without any medication in Period 1	OAV101 administered as a single, one-time intrathecal dose of 1.2 x 10^14 vector

	dose of 1.2 x 10^14 vector genomes (vg) in Period 1		genomes (vg). -For participants randomized to OAV101B in Period 1: All low cardiac function events from Period 1 and 2 -For participants randomized to the sham control in Period 1 and who were administered OAV101 in Period 2: All low cardiac function events from Period 2
Number of Participants Analyzed [units: participants]	75	51	121
Number(and percentage) of patients with low cardiac function (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
	8 (10.67%)	9 (17.65%)	17 (14.05%)

Other Pre-Specified Outcome Result(s)

No data identified.

Post-Hoc Outcome Result(s)

No data identified.

Safety Results

Time Frame	Adverse events (AEs) are reported from the start of treatment period 1 plus 64 weeks, up to a maximum time period of 64 weeks.
Additional Description	AEs for Periods 1 and 2 are combined in the overall OAV101 arm because the same active treatment (and same single dose) was administered in either Period1 or Period 2. Because this is a gene therapy, which permanently impacts the genetics of the study

	participant, participants randomized to OAV101 in Period 1 are still considered on treatment with OAV101 in Period 2 (after receiving sham control in Period 2). Therefore, AEs for the Sham arm can only be considered from Period 1.
Source Vocabulary for Table Default	MedDRA (28.0)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	OAV101 Period 1 N = 75	**Sham control Period 1 N = 51**	**Overall OAV101 in Periods 1 and 2 N = 121**
Arm/Group Description	OAV101 administered as a single, one-time intrathecal dose of 1.2 x 10^14 vector genomes (vg) in Period 1	A skin prick in the lumbar region without any medication in Period 1	OAV101 administered as a single, one-time intrathecal dose of 1.2 x 10^14 vector genomes (vg). -For participants randomized to OAV101B in Period 1: All AEs from Period 1 and 2 -For participants randomized to the sham control in Period 1 and who were administered OAV101 in Period 2: All AEs from Period 2
Total Number Affected	0	0	0
Total Number At Risk	75	51	121

Serious Adverse Events

Time Frame	Adverse events (AEs) are reported from the start of treatment period 1 plus 64 weeks, up to a maximum time period of 64 weeks.

Additional Description	AEs for Periods 1 and 2 are combined in the overall OAV101 arm because the same active treatment (and same single dose) was administered in either Period1 or Period 2. Because this is a gene therapy, which permanently impacts the genetics of the study participant, participants randomized to OAV101 in Period 1 are still considered on treatment with OAV101 in Period 2 (after receiving sham control in Period 2). Therefore, AEs for the Sham arm can only be considered from Period 1.
Source Vocabulary for Table Default	MedDRA (28.0)
Collection Approach for Table Default	Systematic Assessment

	OAV101 Period 1 N = 75	**Sham control Period 1 N = 51**	**Overall OAV101 in Periods 1 and 2 N = 121**
Arm/Group Description	OAV101 administered as a single, one-time intrathecal dose of 1.2 x 10^14 vector genomes (vg) in Period 1	A skin prick in the lumbar region without any medication in Period 1	OAV101 administered as a single, one-time intrathecal dose of 1.2 x 10^14 vector genomes (vg). -For participants randomized to OAV101B in Period 1: All AEs from Period 1 and 2 -For participants randomized to the sham control in Period 1 and who were administered OAV101 in Period 2: All AEs from Period 2
Total # Affected by any Serious Adverse Event	21	17	34
Total # at Risk by any Serious Adverse Event	75	51	121
Cardiac disorders			
Arrhythmia	1 (1.33%)	0 (0.00%)	1 (0.83%)
Gastrointestinal disorders			
Abdominal pain	1 (1.33%)	0 (0.00%)	1 (0.83%)

Gastrointestinal disorder	0 (0.00%)	0 (0.00%)	1 (0.83%)
Nausea	1 (1.33%)	0 (0.00%)	1 (0.83%)
Stomatitis	0 (0.00%)	1 (1.96%)	0 (0.00%)
Vomiting	3 (4.00%)	0 (0.00%)	5 (4.13%)
General disorders and administration site conditions			
Pyrexia	1 (1.33%)	0 (0.00%)	3 (2.48%)
Hepatobiliary disorders			
Hepatitis	1 (1.33%)	0 (0.00%)	1 (0.83%)
Infections and infestations			
Bronchitis	0 (0.00%)	0 (0.00%)	1 (0.83%)
Bronchitis viral	0 (0.00%)	0 (0.00%)	1 (0.83%)
Coronavirus pneumonia	1 (1.33%)	0 (0.00%)	1 (0.83%)
COVID-19	0 (0.00%)	1 (1.96%)	1 (0.83%)
Hand-foot-and-mouth disease	0 (0.00%)	1 (1.96%)	0 (0.00%)
Infective exacerbation of bronchiectasis	0 (0.00%)	1 (1.96%)	0 (0.00%)
Influenza	2 (2.67%)	0 (0.00%)	2 (1.65%)
Lower respiratory tract infection	2 (2.67%)	4 (7.84%)	2 (1.65%)
Metapneumovirus infection	1 (1.33%)	0 (0.00%)	1 (0.83%)
Mycoplasma infection	0 (0.00%)	0 (0.00%)	1 (0.83%)
Pneumonia	9 (12.00%)	7 (13.73%)	16 (13.22%)
Pneumonia aspiration	0 (0.00%)	1 (1.96%)	0 (0.00%)
Pneumonia bacterial	0 (0.00%)	2 (3.92%)	1 (0.83%)
Pneumonia mycoplasmal	0 (0.00%)	1 (1.96%)	0 (0.00%)
Pneumonia viral	1 (1.33%)	2 (3.92%)	1 (0.83%)

Respiratory syncytial virus infection	1 (1.33%)	0 (0.00%)	1 (0.83%)
Respiratory tract infection	1 (1.33%)	1 (1.96%)	1 (0.83%)
Septic shock	1 (1.33%)	0 (0.00%)	1 (0.83%)
Urinary tract infection	1 (1.33%)	0 (0.00%)	1 (0.83%)
Viral infection	1 (1.33%)	0 (0.00%)	1 (0.83%)
Viral upper respiratory tract infection	1 (1.33%)	0 (0.00%)	1 (0.83%)
Metabolism and nutrition disorders			
Decreased appetite	0 (0.00%)	0 (0.00%)	1 (0.83%)
Dehydration	0 (0.00%)	1 (1.96%)	0 (0.00%)
Musculoskeletal and connective tissue disorders			
Back pain	0 (0.00%)	0 (0.00%)	1 (0.83%)
Musculoskeletal discomfort	1 (1.33%)	0 (0.00%)	1 (0.83%)
Nervous system disorders			
Dizziness	1 (1.33%)	0 (0.00%)	1 (0.83%)
Headache	1 (1.33%)	0 (0.00%)	1 (0.83%)
Hypoaesthesia	1 (1.33%)	0 (0.00%)	1 (0.83%)
Peripheral sensory neuropathy	1 (1.33%)	0 (0.00%)	1 (0.83%)
Respiratory, thoracic and mediastinal disorders			
Atelectasis	1 (1.33%)	1 (1.96%)	2 (1.65%)
Bronchiectasis	0 (0.00%)	0 (0.00%)	1 (0.83%)
Respiratory failure	1 (1.33%)	1 (1.96%)	1 (0.83%)
Wheezing	0 (0.00%)	1 (1.96%)	0 (0.00%)

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Other (Not Including Serious) Adverse Events

Time Frame	Adverse events (AEs) are reported from the start of treatment period 1 plus 64 weeks, up to a maximum time period of 64 weeks.
Additional Description	AEs for Periods 1 and 2 are combined in the overall OAV101 arm because the same active treatment (and same single dose) was administered in either Period1 or Period 2. Because this is a gene therapy, which permanently impacts the genetics of the study participant, participants randomized to OAV101 in Period 1 are still considered on treatment with OAV101 in Period 2 (after receiving sham control in Period 2). Therefore, AEs for the Sham arm can only be considered from Period 1.
Source Vocabulary for Table Default	MedDRA (28.0)
Collection Approach for Table Default	Systematic Assessment

Frequent Event Reporting Threshold 5%

	OAV101 Period 1 N = 75	**Sham control Period 1 N = 51**	**Overall OAV101 in Periods 1 and 2 N = 121**
Arm/Group Description	OAV101 administered as a single, one-time intrathecal dose of 1.2 x 10^14 vector genomes (vg) in Period 1	A skin prick in the lumbar region without any medication in Period 1	OAV101 administered as a single, one-time intrathecal dose of 1.2 x 10^14 vector genomes (vg). -For participants randomized to OAV101B in Period 1: All AEs from Period 1 and 2 -For participants randomized to the sham control in Period 1 and who were administered OAV101 in Period 2: All AEs from Period 2

Total # Affected by any Other Adverse Event	63	43	85
Total # at Risk by any Other Adverse Event	75	51	121
Gastrointestinal disorders			
Constipation	11 (14.67%)	11 (21.57%)	15 (12.40%)
Diarrhoea	1 (1.33%)	8 (15.69%)	2 (1.65%)
Nausea	4 (5.33%)	3 (5.88%)	6 (4.96%)
Vomiting	13 (17.33%)	6 (11.76%)	18 (14.88%)
General disorders and administration site conditions			
Pyrexia	19 (25.33%)	12 (23.53%)	23 (19.01%)
Infections and infestations			
Bronchitis	4 (5.33%)	3 (5.88%)	7 (5.79%)
Influenza	4 (5.33%)	5 (9.80%)	5 (4.13%)
Lower respiratory tract infection	6 (8.00%)	4 (7.84%)	7 (5.79%)
Nasopharyngitis	8 (10.67%)	5 (9.80%)	11 (9.09%)
Pharyngitis	3 (4.00%)	4 (7.84%)	5 (4.13%)
Pneumonia	0 (0.00%)	3 (5.88%)	1 (0.83%)
Respiratory tract infection	3 (4.00%)	3 (5.88%)	5 (4.13%)
Upper respiratory tract infection	26 (34.67%)	15 (29.41%)	34 (28.10%)
Musculoskeletal and connective tissue disorders			
Osteoporosis	0 (0.00%)	3 (5.88%)	0 (0.00%)
Nervous system disorders			
Dizziness	4 (5.33%)	1 (1.96%)	5 (4.13%)
Headache	7 (9.33%)	2 (3.92%)	10 (8.26%)

Respiratory, thoracic and mediastinal disorders			
Cough	11 (14.67%)	11 (21.57%)	15 (12.40%)
Oropharyngeal pain	5 (6.67%)	0 (0.00%)	8 (6.61%)
Respiratory tract inflammation	2 (2.67%)	3 (5.88%)	2 (1.65%)
Skin and subcutaneous tissue disorders			
Rash	2 (2.67%)	3 (5.88%)	5 (4.13%)
Urticaria	2 (2.67%)	4 (7.84%)	3 (2.48%)

Other Relevant Findings

Conclusion:

This study met the primary objective, showing a statistically significant and clinically meaningful difference between the OAV101B arm and Sham arm in change from baseline in Hammersmith Functional Motor Scale Expanded (HFMSE) total score to end of Follow-up Period 1 in the overall study population.

All secondary endpoints supported the primary endpoint and were consistently numerically in favor of OAV101B vs Sham despite not achieving statistical significance due to the prespecified multiple testing strategy.

The safety data is supportive of the proposed indication for the treatment of spinal muscular atrophy (SMA) in patients 2 years and older. The safety profile of OAV101B was consistent with previous observations in terms of type and severity of adverse events (AEs), serious adverse events (SAEs), or changes from baseline in vital signs, cardiac safety assessments, and clinical laboratory results, and remained consistent from Period 1 through the end of Period 2 of this study.

Based on the available data through the end of Period 2 of this study, there were no other new major safety findings observed and the safety profile continues to be favorable.

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Date of Clinical Trial Report

18-Sep-2025