



Clinical trial results:

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

Summary

EudraCT number	2021-003474-31
Trial protocol	DK GR
Global end of trial date	29 April 2025

Results information

Result version number	v2 (current)
This version publication date	28 January 2026
First version publication date	12 November 2025
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	COAV101B12301
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05089656
WHO universal trial number (UTN)	-
Other trial identifiers	EudraCT: 2021-003474-31

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-002168-PIP01-06
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 April 2025
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	29 April 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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?

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 February 2022
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	China: 27
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	India: 23
Country: Number of subjects enrolled	Malaysia: 6
Country: Number of subjects enrolled	Mexico: 14
Country: Number of subjects enrolled	Saudi Arabia: 1
Country: Number of subjects enrolled	Singapore: 5
Country: Number of subjects enrolled	South Africa: 10
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	Thailand: 9
Country: Number of subjects enrolled	United States: 2

Country: Number of subjects enrolled	Viet Nam: 22
Worldwide total number of subjects	126
EEA total number of subjects	3

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	117
Adolescents (12-17 years)	9
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

121 total participants were treated with a single dose of OAV101B (either in Period 1 (even if they did not complete Period 1) or Period 2).

Period 1

Period 1 title	Period 1 - First Intervention (52 weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	OAV101 first, then sham control

Arm description:

OAV101 administered as a single, one-time intrathecal dose of 1.2×10^{14} vector genomes (vg) in Period 1, then a skin prick in the lumbar region without any medication in Period 2

Arm type	Experimental
Investigational medicinal product name	OAV101B
Investigational medicinal product code	OAV101B
Other name	onasemnogene abeparvovec
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

OAV101B administered one time at a dose of 1.2×10^{14} vg intrathecally in Period 1. (For eligible participants, a sham control needle prick was administered in Period 2)

Arm title	Sham control first, then OAV101
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Arm description:

A skin prick in the lumbar region without any medication in Period 1, then OAV101 administered as a single, one-time intrathecal dose of 1.2×10^{14} vector genomes (vg) in Period 2

Arm type	A skin prick without any medication.
Investigational medicinal product name	OAV101B
Investigational medicinal product code	OAV101B
Other name	onasemnogene abeparvovec
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

For eligible participants OAV101B administered one time at a dose of 1.2×10^{14} vg intrathecally in Period 2. (Sham control needle prick was administered in Period 1)

Number of subjects in period 1	OAV101 first, then sham control	Sham control first, then OAV101
Started	75	51
Completed period 1	73	50
Completed	67	46
Not completed	8	5
Physician decision	1	-
Protocol-specified withdrawal criterion met	6	4
Adverse event, non-fatal	-	1
Guardian decision	1	-

Period 2

Period 2 title	Period 2 - 2nd Intervention (12 weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	OAV101 first, then sham control

Arm description:

OAV101 administered as a single, one-time intrathecal dose of 1.2×10^{14} vector genomes (vg) in Period 1, then a skin prick in the lumbar region without any medication in Period 2

Arm type	Experimental
Investigational medicinal product name	OAV101B
Investigational medicinal product code	OAV101B
Other name	onasemnogene abeparvovec
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

OAV101B administered one time at a dose of 1.2×10^{14} vg intrathecally in Period 1. (For eligible participants, a sham control needle prick was administered in Period 2)

Arm title	Sham control first, then OAV101
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Arm description:

A skin prick in the lumbar region without any medication in Period 1, then OAV101 administered as a single, one-time intrathecal dose of 1.2×10^{14} vector genomes (vg) in Period 2

Arm type	A skin prick without any medication.
Investigational medicinal product name	OAV101B
Investigational medicinal product code	OAV101B
Other name	onasemnogene abeparvovec
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

For eligible participants OAV101B administered one time at a dose of 1.2×10^{14} vg intrathecally in Period 2. (Sham control needle prick was administered in Period 1)

Number of subjects in period 2	OAV101 first, then sham control	Sham control first, then OAV101
Started	67	46
Completed	67	46

Baseline characteristics

Reporting groups

Reporting group title	OAV101 first, then sham control
Reporting group description: OAV101 administered as a single, one-time intrathecal dose of 1.2×10^{14} vector genomes (vg) in Period 1, then a skin prick in the lumbar region without any medication in Period 2	
Reporting group title	Sham control first, then OAV101
Reporting group description: A skin prick in the lumbar region without any medication in Period 1, then OAV101 administered as a single, one-time intrathecal dose of 1.2×10^{14} vector genomes (vg) in Period 2	

Reporting group values	OAV101 first, then sham control	Sham control first, then OAV101	Total
Number of subjects	75	51	126
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	69	48	117
Adolescents (12-17 years)	6	3	9
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	5.71	5.68	
standard deviation	± 3.575	± 3.045	-
Sex: Female, Male Units: Participants			
Female	41	23	64
Male	34	28	62
Race (NIH/OMB) Units: Subjects			
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

Subject analysis sets

Subject analysis set title	Overall OAV101 in Periods 1 and 2
Subject analysis set type	Full analysis

Subject analysis set description:

OAV101 administered as a single, one-time intrathecal dose of 1.2×10^{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

Subject analysis set title	Overall OAV101 in Periods 1 and 2
Subject analysis set type	Full analysis

Subject analysis set description:

OAV101 administered as a single, one-time intrathecal dose of 1.2×10^{14} vector genomes (vg).

-For 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

Subject analysis set title	Overall OAV101 in Periods 1 and 2
Subject analysis set type	Full analysis

Subject analysis set description:

OAV101 administered as a single, one-time intrathecal dose of 1.2×10^{14} vector 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

Subject analysis set title	OAV101 Period 1
Subject analysis set type	Full analysis

Subject analysis set description:

OAV101 administered as a single, one-time intrathecal dose of 1.2×10^{14} vector genomes (vg) in Period 1

Subject analysis set title	Sham control Period 1
Subject analysis set type	Full analysis

Subject analysis set description:

A skin prick in the lumbar region without any medication in Period 1

Reporting group values	Overall OAV101 in Periods 1 and 2	Overall OAV101 in Periods 1 and 2	Overall OAV101 in Periods 1 and 2
Number of subjects	121	121	121
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: years			
arithmetic mean		1	17
standard deviation	±	±	±
Sex: Female, Male Units: Participants			
Female			

Male			
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Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Unknown or Not Reported			

Reporting group values	OAV101 Period 1	Sham control Period 1	
Number of subjects	75	51	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: years arithmetic mean standard deviation	±	±	
Sex: Female, Male Units: Participants			
Female Male			
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Unknown or Not Reported			

End points

End points reporting groups

Reporting group title	OAV101 first, then sham control
Reporting group description: OAV101 administered as a single, one-time intrathecal dose of 1.2×10^{14} vector genomes (vg) in Period 1, then a skin prick in the lumbar region without any medication in Period 2	
Reporting group title	Sham control first, then OAV101
Reporting group description: A skin prick in the lumbar region without any medication in Period 1, then OAV101 administered as a single, one-time intrathecal dose of 1.2×10^{14} vector genomes (vg) in Period 2	
Reporting group title	OAV101 first, then sham control
Reporting group description: OAV101 administered as a single, one-time intrathecal dose of 1.2×10^{14} vector genomes (vg) in Period 1, then a skin prick in the lumbar region without any medication in Period 2	
Reporting group title	Sham control first, then OAV101
Reporting group description: A skin prick in the lumbar region without any medication in Period 1, then OAV101 administered as a single, one-time intrathecal dose of 1.2×10^{14} vector genomes (vg) in Period 2	
Subject analysis set title	Overall OAV101 in Periods 1 and 2
Subject analysis set type	Full analysis
Subject analysis set description: OAV101 administered as a single, one-time intrathecal dose of 1.2×10^{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	
Subject analysis set title	Overall OAV101 in Periods 1 and 2
Subject analysis set type	Full analysis
Subject analysis set description: OAV101 administered as a single, one-time intrathecal dose of 1.2×10^{14} vector genomes (vg). -For 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	
Subject analysis set title	Overall OAV101 in Periods 1 and 2
Subject analysis set type	Full analysis
Subject analysis set description: OAV101 administered as a single, one-time intrathecal dose of 1.2×10^{14} vector 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	
Subject analysis set title	OAV101 Period 1
Subject analysis set type	Full analysis
Subject analysis set description: OAV101 administered as a single, one-time intrathecal dose of 1.2×10^{14} vector genomes (vg) in Period 1	
Subject analysis set title	Sham control Period 1
Subject analysis set type	Full analysis
Subject analysis set description: A skin prick in the lumbar region without any medication in Period 1	

Primary: 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

End point title	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
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End point 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.

End point type	Primary
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End point timeframe:

Baseline, Week 52 (or Week 48)

End point values	OAV101 first, then sham control	Sham control first, then OAV101		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	50		
Units: Scores on a scale				
least squares mean (standard error)	2.39 (± 0.439)	0.51 (± 0.532)		

Statistical analyses

Statistical analysis title	OAV101 v Sham control
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Statistical analysis description:

Change from baseline at End of Follow-up Period 1

Comparison groups	OAV101 first, then sham control v Sham control first, then OAV101
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0074
Method	Mixed models analysis
Parameter estimate	LS-Means difference
Point estimate	1.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	3.25
Variability estimate	Standard error of the mean
Dispersion value	0.69

Secondary: 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

End point title	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
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End point 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.

End point type	Secondary
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End point timeframe:

Baseline, Week 52 (or Week 48)

End point values	OAV101 first, then sham control	Sham control first, then OAV101		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	29		
Units: Scores on a scale				
least squares mean (standard error)	3.00 (± 0.569)	1.56 (± 0.683)		

Statistical analyses

Statistical analysis title	OAV101 v Sham control
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Statistical analysis description:

Change from baseline at End of Follow-up Period 1

Comparison groups	OAV101 first, then sham control v Sham control first, then OAV101
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Number of subjects included in analysis	70
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Analysis specification	Pre-specified
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Analysis type	
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P-value	= 0.1097
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Method	Mixed models analysis
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Parameter estimate	LS-Means - difference
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Point estimate	1.44
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	-0.33
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upper limit	3.22
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Variability estimate	Standard error of the mean
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Dispersion value	0.889
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Secondary: 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

End point title	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
End point 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.	
End point type	Secondary
End point timeframe: Baseline, Week 52 (or Week 48)	

End point values	OAV101 first, then sham control	Sham control first, then OAV101		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	50		
Units: Scores on a scale				
least squares mean (standard error)	2.44 (± 0.381)	0.92 (± 0.462)		

Statistical analyses

Statistical analysis title	OAV101 v Sham control
Statistical analysis description: Change from baseline at End of Follow-up Period 1	
Comparison groups	OAV101 first, then sham control v Sham control first, then OAV101
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0122
Method	Mixed models analysis
Parameter estimate	LS-Means difference
Point estimate	1.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	2.71
Variability estimate	Standard error of the mean
Dispersion value	0.599

Secondary: 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

End point title	Change from baseline in the RULM total score at the end of
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End point 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.

End point type	Secondary
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End point timeframe:

Baseline, Week 52 (or Week 48)

End point values	OAV101 first, then sham control	Sham control first, then OAV101		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	29		
Units: Scores on a scale				
least squares mean (standard error)	3.27 (\pm 0.535)	1.82 (\pm 0.642)		

Statistical analyses

Statistical analysis title	OAV101 v Sham control
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Statistical analysis description:

Change from baseline at End of Follow-up Period 1

Comparison groups	OAV101 first, then sham control v Sham control first, then OAV101
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0873
Method	Mixed models analysis
Parameter estimate	LS-Means difference
Point estimate	1.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	3.12
Variability estimate	Standard error of the mean
Dispersion value	0.836

Secondary: % 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

End point title	% of participants who achieved at least a 3-point improvement from baseline in HFMSE total score at the end of Follow-up
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End point 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.

End point type	Secondary
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End point timeframe:

Baseline, Week 52 (or Week 48) (end of Period 1)
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End point values	OAV101 first, then sham control	Sham control first, then OAV101		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	50		
Units: % of participants				
number (confidence interval 95%)	39.2 (28.07 to 50.31)	26.0 (13.84 to 38.16)		

Statistical analyses

Statistical analysis title	OAV101 v Sham control
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Statistical analysis description:

End of Followup Period 1 (Week 52)

Comparison groups	OAV101 first, then sham control v Sham control first, then OAV101
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Number of subjects included in analysis	124
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Analysis specification	Pre-specified
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Analysis type	
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P-value	= 0.0879
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Method	Regression, Logistic
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Parameter estimate	Odds ratio (OR)
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Point estimate	2.03
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Confidence interval	
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level	95 %
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sides	2-sided
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lower limit	0.9
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upper limit	4.57
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Secondary: % 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

End point title	% 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
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End point 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.

End point type	Secondary
End point timeframe:	
Baseline, Week 52 (or Week 48)(end of Period 1)	

End point values	OAV101 first, then sham control	Sham control first, then OAV101		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	29		
Units: % of participants				
number (confidence interval 95%)	48.8 (33.48 to 64.08)	37.9 (20.27 to 55.59)		

Statistical analyses

Statistical analysis title	OAV101 v Sham control
Statistical analysis description:	
End of Followup Period 1 (Week 52)	
Comparison groups	OAV101 first, then sham control v Sham control first, then OAV101
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6448
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	3.56

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

End point title	Number of participants with treatment emergent Adverse Events and Serious Adverse Events
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End point 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

End point type	Secondary
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End point timeframe:

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

End point values	Overall OAV101 in Periods 1 and 2	OAV101 Period 1	Sham control Period 1	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	121	75	51	
Units: Participants				
Any treatment-emergent adverse event (TEAE)	104	74	46	
Any TEAE related to study treatment	36	27	5	
Any serious treatment-emergent adverse event	34	21	17	
Any serious TEAE related to study treatment	12	8	1	
Any severe treatment-emergent adverse event	12	8	9	
Any TEAE leading to study disc.	0	0	1	
Any TEAE leading to death	0	0	0	
Any TEAE of special interest	21	12	7	

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of participants with adverse events of special interest (AESI)
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End point 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.

End point type	Secondary
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End point timeframe:

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

End point values	Overall OAV101 in Periods 1 and 2	OAV101 Period 1	Sham control Period 1	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	121	75	51	
Units: Participants				
Hepatotoxicity	10	7	5	
Transient thrombocytopenia	9	4	2	
Cardiac adverse events	0	0	0	
Signs and symptoms of dorsal root ganglia toxicity	3	2	1	
Thrombotic microangiopathy	0	0	0	
New malignancies	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number (and percentage) of patients with intracardiac thrombi

End point title	Number (and percentage) of patients with intracardiac thrombi
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End point 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.

End point type	Secondary
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End point timeframe:

Baseline up to 64 weeks

End point values	Overall OAV101 in Periods 1 and 2	OAV101 Period 1	Sham control Period 1	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	121	75	51	
Units: Participants	1	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number(and percentage) of patients with low cardiac function

End point title	Number(and percentage) of patients with low cardiac function
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End point description:

Low cardiac function is defined as left ventricular ejection fraction <56% or left ventricular fractional shortening <28% 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.

End point type	Secondary
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End point timeframe:

Baseline up to 64 weeks

End point values	Overall OAV101 in Periods 1 and 2	OAV101 Period 1	Sham control Period 1	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	121	75	51	
Units: Participants	17	8	9	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting 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.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	28.0
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Reporting groups

Reporting group title	Period 1: OAV101B
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Reporting group description:

Period 1: OAV101B

Reporting group title	Overall: OAV101B@Period 1 + Period 2
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Reporting group description:

Overall: OAV101B@Period 1 + Period 2

Reporting group title	Period 1: Sham
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Reporting group description:

Period 1: Sham

Serious adverse events	Period 1: OAV101B	Overall: OAV101B@Period 1 + Period 2	Period 1: Sham
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 75 (28.00%)	34 / 121 (28.10%)	17 / 51 (33.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 75 (1.33%)	1 / 121 (0.83%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 75 (1.33%)	1 / 121 (0.83%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			

subjects affected / exposed	1 / 75 (1.33%)	1 / 121 (0.83%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 75 (1.33%)	1 / 121 (0.83%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			
subjects affected / exposed	1 / 75 (1.33%)	1 / 121 (0.83%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 75 (1.33%)	3 / 121 (2.48%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 2	3 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	0 / 75 (0.00%)	1 / 121 (0.83%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 75 (1.33%)	1 / 121 (0.83%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 75 (1.33%)	1 / 121 (0.83%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 75 (0.00%)	0 / 121 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vomiting			
subjects affected / exposed	3 / 75 (4.00%)	5 / 121 (4.13%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 3	2 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	1 / 75 (1.33%)	1 / 121 (0.83%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 75 (1.33%)	2 / 121 (1.65%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiectasis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 121 (0.83%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 75 (1.33%)	1 / 121 (0.83%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wheezing			
subjects affected / exposed	0 / 75 (0.00%)	0 / 121 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 75 (0.00%)	1 / 121 (0.83%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal discomfort			

subjects affected / exposed	1 / 75 (1.33%)	1 / 121 (0.83%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 121 (0.83%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronavirus pneumonia			
subjects affected / exposed	1 / 75 (1.33%)	1 / 121 (0.83%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis viral			
subjects affected / exposed	0 / 75 (0.00%)	1 / 121 (0.83%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	0 / 75 (0.00%)	1 / 121 (0.83%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 75 (0.00%)	0 / 121 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	9 / 75 (12.00%)	16 / 121 (13.22%)	7 / 51 (13.73%)
occurrences causally related to treatment / all	0 / 12	0 / 19	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mycoplasma infection			
subjects affected / exposed	0 / 75 (0.00%)	1 / 121 (0.83%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metapneumovirus infection			

subjects affected / exposed	1 / 75 (1.33%)	1 / 121 (0.83%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	2 / 75 (2.67%)	2 / 121 (1.65%)	4 / 51 (7.84%)
occurrences causally related to treatment / all	2 / 8	2 / 9	1 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	2 / 75 (2.67%)	2 / 121 (1.65%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of bronchiectasis			
subjects affected / exposed	0 / 75 (0.00%)	0 / 121 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 75 (0.00%)	0 / 121 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 75 (0.00%)	1 / 121 (0.83%)	2 / 51 (3.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 75 (0.00%)	0 / 121 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	1 / 75 (1.33%)	1 / 121 (0.83%)	2 / 51 (3.92%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			

subjects affected / exposed	1 / 75 (1.33%)	1 / 121 (0.83%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 75 (1.33%)	1 / 121 (0.83%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 75 (1.33%)	1 / 121 (0.83%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	1 / 75 (1.33%)	1 / 121 (0.83%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 75 (1.33%)	1 / 121 (0.83%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 75 (1.33%)	1 / 121 (0.83%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 75 (0.00%)	1 / 121 (0.83%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 75 (0.00%)	0 / 121 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Period 1: OAV101B	Overall: OAV101B@Period 1 + Period 2	Period 1: Sham
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 75 (84.00%)	85 / 121 (70.25%)	43 / 51 (84.31%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 75 (5.33%)	5 / 121 (4.13%)	1 / 51 (1.96%)
occurrences (all)	6	9	1
Headache			
subjects affected / exposed	7 / 75 (9.33%)	10 / 121 (8.26%)	2 / 51 (3.92%)
occurrences (all)	10	14	2
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	19 / 75 (25.33%)	23 / 121 (19.01%)	12 / 51 (23.53%)
occurrences (all)	25	32	17
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 75 (1.33%)	2 / 121 (1.65%)	8 / 51 (15.69%)
occurrences (all)	2	3	10
Constipation			
subjects affected / exposed	11 / 75 (14.67%)	15 / 121 (12.40%)	11 / 51 (21.57%)
occurrences (all)	12	18	14
Nausea			
subjects affected / exposed	4 / 75 (5.33%)	6 / 121 (4.96%)	3 / 51 (5.88%)
occurrences (all)	5	7	3
Vomiting			
subjects affected / exposed	13 / 75 (17.33%)	18 / 121 (14.88%)	6 / 51 (11.76%)
occurrences (all)	17	25	8
Respiratory, thoracic and mediastinal disorders			
Respiratory tract inflammation			
subjects affected / exposed	2 / 75 (2.67%)	2 / 121 (1.65%)	3 / 51 (5.88%)
occurrences (all)	2	2	3
Oropharyngeal pain			

subjects affected / exposed occurrences (all)	5 / 75 (6.67%) 6	8 / 121 (6.61%) 12	0 / 51 (0.00%) 0
Cough subjects affected / exposed occurrences (all)	11 / 75 (14.67%) 20	15 / 121 (12.40%) 27	11 / 51 (21.57%) 13
Skin and subcutaneous tissue disorders			
Rash subjects affected / exposed occurrences (all)	2 / 75 (2.67%) 2	5 / 121 (4.13%) 5	3 / 51 (5.88%) 3
Urticaria subjects affected / exposed occurrences (all)	2 / 75 (2.67%) 2	3 / 121 (2.48%) 3	4 / 51 (7.84%) 4
Musculoskeletal and connective tissue disorders			
Osteoporosis subjects affected / exposed occurrences (all)	0 / 75 (0.00%) 0	0 / 121 (0.00%) 0	3 / 51 (5.88%) 3
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 4	7 / 121 (5.79%) 8	3 / 51 (5.88%) 3
Influenza subjects affected / exposed occurrences (all)	4 / 75 (5.33%) 4	5 / 121 (4.13%) 5	5 / 51 (9.80%) 5
Lower respiratory tract infection subjects affected / exposed occurrences (all)	6 / 75 (8.00%) 12	7 / 121 (5.79%) 15	4 / 51 (7.84%) 11
Pharyngitis subjects affected / exposed occurrences (all)	3 / 75 (4.00%) 3	5 / 121 (4.13%) 5	4 / 51 (7.84%) 5
Nasopharyngitis subjects affected / exposed occurrences (all)	8 / 75 (10.67%) 11	11 / 121 (9.09%) 16	5 / 51 (9.80%) 7
Pneumonia subjects affected / exposed occurrences (all)	0 / 75 (0.00%) 0	1 / 121 (0.83%) 1	3 / 51 (5.88%) 3
Upper respiratory tract infection			

subjects affected / exposed	26 / 75 (34.67%)	34 / 121 (28.10%)	15 / 51 (29.41%)
occurrences (all)	43	57	22
Respiratory tract infection			
subjects affected / exposed	3 / 75 (4.00%)	5 / 121 (4.13%)	3 / 51 (5.88%)
occurrences (all)	3	6	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 March 2022	The data analysis and statistical methods section were revised to include the following two secondary endpoints: • 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. The schedule of sensory nerve action potential (SNAP) assessments were modified.
08 August 2022	The Central Treatment Site (hybrid model) was removed, adaptations were made to inclusion/exclusion criteria, updates were made on OAV101 risks, and the visit schedule for troponin I collection was modified.
02 June 2023	Several exclusion criteria were revised to be anchored to the Day 1 visit (day of OAV101 administration or the sham procedure) and a theoretical risk of tumorigenicity due to vector DNA integration has been added to the OAV101 risks section.
17 May 2024	Updated to enhance consultation between the Principal Investigator and Sponsors for retesting of abnormal laboratory parameters and to ensure compliance with expedited reporting of potential Hy's Law cases based on health authority guidance.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported