Clinical trial results:
Phase IIIb, open-label, single-arm, multi-center study to evaluate the safety, tolerability and efficacy of OAV101 administered intrathecally (1.2 x 10^14 vector genomes) to participants 2 to <18 years of age with spinal muscular atrophy (SMA) who have discontinued treatment with nusinersen (Spinraza®) or risdiplam (Evrysdi®)

Summary

EudraCT number	2021-006709-31
Trial protocol	ES FR DE BE NL IT
Global end of trial date	29 November 2024

Results information

Result version number	v1 (current)
This version publication date	31 May 2025
First version publication date	31 May 2025

Trial information

Trial identification

Sponsor protocol code	COAV101B12302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05386680
WHO universal trial number (UTN)	-

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)	EMEA-002168-PIP01-17
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 November 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 November 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to characterize the safety and tolerability of OAV101B (administered by lumbar intrathecal injection) over a 52-week period in participants with SMA aged 2 to <18 years who had discontinued treatment with nusinersen or risdiplam.

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	12 January 2023
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	Australia: 1
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Japan: 4
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	27
EEA total number of subjects	18

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)	25
Adolescents (12-17 years)	2
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:

The study aimed to enroll approximately 28 participants across each of 2 age brackets (2 to <6 years, and 6 to <18 years).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	OAV101 1.2x10^14 vg - All participants

Arm description:

Intrathecal administration of OAV101 at a dose of 1.2 x 10^14 vector genomes, one time dose

Arm type	Experimental
Investigational medicinal product name	onasemnogene abeparvovec-xioi
Investigational medicinal product code	OAV101
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

administered at a dose 1.2 x 10^14 vector genomes as a one-time injection

Number of subjects in period 1	OAV101 1.2x10^14 vg - All participants
Started	27
Completed	25
Not completed	2
Guardian decision	2

Baseline characteristics

Reporting groups	
Reporting group title	OAV101 1.2x10^14 vg - All participants
Reporting group description:	
Intrathecal administration of OAV101 at a dose of 1.2 x 10^14 vector genomes, one time dose	

Reporting group values	OAV101 1.2x10^14 vg - All participants	Total	
Number of subjects	27	27	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	25	25	
Adolescents (12-17 years)	2	2	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	7.40		
standard deviation	± 3.348	-	
Sex: Female, Male Units: Participants			
Female	12	12	
Male	15	15	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	6	6	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	13	13	
More than one race	1	1	
Unknown or Not Reported	7	7	

End points

End points reporting groups

Reporting group title	OAV101 1.2x10^14 vg - All participants

Reporting group description:

Intrathecal administration of OAV101 at a dose of 1.2 x 10^14 vector genomes, one time dose

Primary: Overview of treatment-emergent adverse events by age subgroup

End point title	Overview of treatment-emergent adverse events by age subgroup[1]

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. 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.

disc. = discontinuation

End point type	Primary

End point timeframe:

Adverse events were reported from single dose of study treatment plus 52 weeks, up to a maximum time period of 52 weeks.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: not applicable for single arm study

End point values	OAV101 1.2x10^14 vg - All			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: Participants				
Any treatment-emergent adverse event (TEAE)	27			
Any TEAE related to study treatment	13			
Any serious TEAE	4			
Any serious TEAE related to study treatment	0			
Any severe TEAE	1			
Any TEAE leading to study disc.	0			
Any TEAE leading to death	0			
Any TEAE of special interest	13			

Statistical analyses

No statistical analyses for this end point

Primary: Treatment-emergent adverse events related to treatment by system organ

class, preferred term, age subgroup (>= 10%)

End point title	Treatment-emergent adverse events related to treatment by system organ class, preferred term, age subgroup (>= 10%)[2]

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. 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.

adm. = administration

End point type	Primary

End point timeframe:

Adverse events were reported from single dose of study treatment plus 52 weeks, up to a maximum time period of 52 weeks.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: not applicable for single arm study

End point values	OAV101 1.2x10^14 vg - All			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: Participants				
Number of participants with at least one event	13			
Gastrointestinal disorders	7			
-Vomiting	6			
General disorders and adm. site conditions	5			
-Pyrexia	3			
Nervous system disorders	6			
-Headache	4			

Statistical analyses

No statistical analyses for this end point

Primary: Adverse events of special interest by system organ class, preferred term, age subgroup

End point title	Adverse events of special interest by system organ class, preferred term, age subgroup[3]

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. 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.

An adverse event of special interest (AESI) is primarily defined by using standard Medical Dictionary for Regulatory Activities (MedDRA) queries, and identified as follows: Hepatotoxicity, Transient thrombocytopenia, Thrombotic microangiopathy, Cardiac adverse events, signs and symptoms that may

be suggestive dorsal root ganglia toxicity, and new malignancies.

End point type	Primary

End point timeframe:

Adverse events were reported from single dose of study treatment plus 52 weeks, up to a maximum time period of 52 weeks.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: not applicable for single arm study

End point values	OAV101 1.2x10^14 vg - All			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: Participants				
Hepatotoxicity	4			
-Hepatic enzyme increased	3			
-Hypertransaminasaemia	1			
Transient thrombocytopenia -	8			
-Epistaxis	3			
-Contusion	2			
-Bone contusion	1			
-Gastric haemorrhage	1			
-Lower gastrointestinal haemorrhage	1			
-Petechiae	1			
Signs of dorsal root ganglia toxicity -	2			
-Paraesthesia	1			
-Sensory disturbance	1			
Thrombotic microangiopathy -	0			
Cardiac adverse events	0			
New malignancies	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline at Week 52 visit in the HFMSE total score - Mean (SD)

End point title	Change from baseline at Week 52 visit in the HFMSE total score - Mean (SD)

End point description:

The Hammersmith Functional Motor Scale Expanded (HFMSE) is a SMA-specific 33-item assessment that is administered by qualified clinical evaluators. Each motor skill item is scored on a 3-point Likert scale from 0 (no response) to 2 (full response), with a total score range of 0 to 66. A higher score indicates a higher ability level.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	OAV101 1.2x10^14 vg - All			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: scores on a scale				
arithmetic mean (standard deviation)	0.17 (± 2.878)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline at Week 52 visit in the RULM total Score - Mean (SD)

End point title	Change from baseline at Week 52 visit in the RULM total Score - Mean (SD)

End point description:

The Revised Upper Limb Model (RULM) is a validated, SMA-specific assessment that measures motor performance in the upper limbs from childhood through adulthood in ambulatory and never ambulatory individuals with SMA. The revised version of the test 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). These item scores are summed to give a total score ranging from 0 to 37 points with lower scores reflecting poorer ability.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	OAV101 1.2x10^14 vg - All			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: scores on a scale				
arithmetic mean (standard deviation)	0.29 (± 2.849)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline at Week 52 visit in Assessment of Caregiver Experience in ACEND instrument score - Mean (SD)

End point title	Change from baseline at Week 52 visit in Assessment of Caregiver Experience in ACEND instrument score - Mean (SD)

End point description:

The Assessment of Caregiver Experience in Neuromuscular Disease (ACEND) instrument quantifies the caregiver impact experienced by parents/caregivers of children affected with severe neuromuscular diseases, including children with SMA. The total score is on a scale of 0 to 100 with a higher score indicating that caregivers experienced less intense caregiving impact.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	OAV101 1.2x10^14 vg - All			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: scores on a scale				
arithmetic mean (standard deviation)	1.43 (± 9.318)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline at Week 52 visit in the HFMSE total score - LS Means

End point title	Change from baseline at Week 52 visit in the HFMSE total score - LS Means

End point description:

The Hammersmith Functional Motor Scale Expanded (HFMSE) is a SMA-specific 33-item assessment that is administered by qualified clinical evaluators. Each motor skill item is scored on a 3-point Likert scale from 0 (no response) to 2 (full response), with a total score range of 0 to 66. A higher score indicates a higher ability level.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	OAV101 1.2x10^14 vg - All			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: scores on a scale				
least squares mean (confidence interval 95%)	1.05 (-0.21 to 2.32)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline at Week 52 visit in the RULM total Score - LS Means

End point title	Change from baseline at Week 52 visit in the RULM total Score - LS Means

End point description:

The Revised Upper Limb Model (RULM) is a validated, SMA-specific assessment that measures motor performance in the upper limbs from childhood through adulthood in ambulatory and never ambulatory individuals with SMA. The revised version of the test 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). These item scores are summed to give a total score ranging from 0 to 37 points with lower scores reflecting poorer ability.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	OAV101 1.2x10^14 vg - All			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: scores on a scale				
least squares mean (confidence interval 95%)	0.59 (-0.56 to 1.73)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline at Week 52 visit in Assessment of Caregiver Experience in ACEND instrument score - LS Means

End point title	Change from baseline at Week 52 visit in Assessment of Caregiver Experience in ACEND instrument score - LS Means

End point description:

The Assessment of Caregiver Experience in Neuromuscular Disease (ACEND) instrument quantifies the caregiver impact experienced by parents/caregivers of children affected with severe neuromuscular diseases, including children with SMA. The total score is on a scale of 0 to 100 with a higher score indicating that caregivers experienced less intense caregiving impact.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	OAV101 1.2x10^14 vg - All			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: scores on a scale				
least squares mean (confidence interval 95%)	1.06 (-2.90 to 5.02)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from single dose of study treatment plus 52 weeks, up to a maximum time period of 52 weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.1

Reporting groups

Reporting group title	Overall

Reporting group description:

Overall

Serious adverse events	Overall		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 27 (14.81%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Influenza virus test positive			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Cyclic vomiting syndrome			

subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory distress			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Lung disorder			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nasal congestion			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis viral			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
COVID-19			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Pneumonia			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 27 (100.00%)		
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	3		
Weight increased			
subjects affected / exposed	5 / 27 (18.52%)		
occurrences (all)	5		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 27 (11.11%)		
occurrences (all)	6		
Contusion			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 27 (29.63%)		
occurrences (all)	18		
Tremor			
subjects affected / exposed	4 / 27 (14.81%)		
occurrences (all)	5		
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		
General disorders and administration site conditions			

Fatigue subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 5		
Pyrexia subjects affected / exposed occurrences (all)	13 / 27 (48.15%) 26		
Swelling face subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 3		
Constipation subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Abdominal pain upper subjects affected / exposed occurrences (all)	6 / 27 (22.22%) 7		
Abdominal pain subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 6		
Dysphagia subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 4		
Nausea subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 4		
Toothache subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Vomiting subjects affected / exposed occurrences (all)	13 / 27 (48.15%) 21		
Respiratory, thoracic and mediastinal disorders			

Rhinorrhoea subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 3		
Oropharyngeal pain subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3		
Nasal congestion subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3		
Epistaxis subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 5		
Cough subjects affected / exposed occurrences (all)	5 / 27 (18.52%) 8		
Productive cough subjects affected / exposed occurrences (all)	5 / 27 (18.52%) 5		
Psychiatric disorders Affect lability subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3		
Initial insomnia subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Irritability subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	3 / 27 (11.11%) 3		
Muscular weakness subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2		
Back pain			

subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Scoliosis subjects affected / exposed occurrences (all)	4 / 27 (14.81%) 6 5 / 27 (18.52%) 8 2 / 27 (7.41%) 2		
Infections and infestations COVID-19 subjects affected / exposed occurrences (all) Ear infection subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all)	 4 / 27 (14.81%) 5 4 / 27 (14.81%) 4 3 / 27 (11.11%) 6 15 / 27 (55.56%) 25 3 / 27 (11.11%) 3		
Metabolism and nutrition disorders Increased appetite subjects affected / exposed occurrences (all) Decreased appetite subjects affected / exposed occurrences (all)	 5 / 27 (18.52%) 5 2 / 27 (7.41%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 May 2023	The purpose of this amendment was to expand the age group for inclusion in the study from 2 to 12 years of age, to 2 to <18 years of age to cover the full pediatric age range and for consistency with the study population age range of Novartis Phase III study (COAV101B2301) in treatment naïve participants aged 2 to <18 years. In addition, the risk language has been revised to include the theoretical risk of tumorigenicity due to the very low potential incorporation of AAV vector DNA into chromosomal DNA that has been noted based on published literature for AAV-based therapies; also, the liver safety monitoring for elevated levels has been updated to apply more stringent monitoring to ensure a timely follow-up and to align with FDA guidance for drug induced liver toxicity.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported