Clinical trial results:
A Phase IV Open-label, single-arm, single-dose, multicenter study to evaluate the saFEty, toLerability and effIcacy of gene replacement therapy with intravenous OAV101 (AVXS-101) in pediatric participants from Latin America with spinal muscular atrophy (SMA) - OFELIA

Summary

EudraCT number	2023-000864-67
Trial protocol	Outside EU/EEA
Global end of trial date	08 August 2023

Results information

Result version number	v1 (current)
This version publication date	21 February 2024
First version publication date	21 February 2024

Trial information

Trial identification

Sponsor protocol code	COAV101A1IC01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05073133
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	08 August 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the safety and tolerability of OAV101 over an 18-months post-infusion period in participants with SMA weighing ≤ 17 kg.

The primary endpoint was to evaluate treatment emergent AEs and SAEs; to evaluate important identified and potential risks and to evaluate changes from baseline in vital signs, cardiac safety assessments, and clinical laboratory results. The secondary endpoint was to evaluate the efficacy of OAV101 at 6-, 12-, and 18-months post-infusion in participants with SMA weighing ≤ 17 kg, as measured by Development Motor Milestones according to the World Health Organization Multicentre Growth Reference Study (WHO-MGRS).

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	04 November 2021
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: 10
Country: Number of subjects enrolled	Argentina: 6
Worldwide total number of subjects	16
EEA total number of subjects	0

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)	16

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

16 participants were enrolled into the study, at five sites from Brazil (three sites) and Argentina (two sites). Six participants were from Argentina and 10 from Brazil.

Pre-assignment

Screening details:

On Day -1, participants were admitted to the hospital for pre-treatment baseline procedures including prednisolone treatment per study protocol.

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

Arm description:

A single IV infusion at 1.1e14 vg/kg over approximately 60 minutes

Arm type	Experimental
Investigational medicinal product name	Onasemnogene abeparvovec
Investigational medicinal product code	OAV101
Other name	AVXS-101; Zolgensma; Onasemnogene abeparvovec
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1.1e14 vg/kg

Number of subjects in period 1	OAV101
Started	16
Completed	14
Not completed	2
Adverse event, serious fatal	2

Baseline characteristics

Reporting groups	
Reporting group title	OAV101
Reporting group description:	
A single IV infusion at 1.1e14 vg/kg over approximately 60 minutes	

Reporting group values	OAV101	Total	
Number of subjects	16	16	
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)	16	16	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous Units: months			
arithmetic mean	15.79		
standard deviation	± 5.89	-	
Sex: Female, Male Units: Participants			
Female	11	11	
Male	5	5	

End points

End points reporting groups

Reporting group title	OAV101

Reporting group description:

A single IV infusion at 1.1e14 vg/kg over approximately 60 minutes

Primary: Number of Participants with treatment emergent AEs and SAEs

End point title	Number of Participants with treatment emergent AEs and

End point description:

An AE is any untoward medical occurrence (eg 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. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

Changes from baseline in vital signs, cardiac safety assessments, and clinical laboratory results are reported as Adverse Events if clinically significant and as applicable, per investigator assessment.

Disc. = discontinuation

End point type	Primary

End point timeframe:

Up to Month 18

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 AEs and also not applicable for single arm studies.

End point values	OAV101			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Participants				
Any treatment-emergent adverse events (AEs)	16			
Any treatment-emergent AEs related to OAV101	11			
Any serious treatment-emergent adverse events	11			
Serious treatment-emergent AEs related to OAV101	3			
Treatment-emergent AEs leading to study disc.	0			
Treatment-emergent AEs leading to death	2			
Treatment-emergent AEs of special interest	12			

Statistical analyses

No statistical analyses for this end point

Primary: Evaluation of important identified and important potential risks - treatment-emergent adverse events of special interest

End point title	Evaluation of important identified and important potential risks - treatment-emergent adverse events of special interest[2]

End point description:

An AE is any untoward medical occurrence (eg 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. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

Adverse events of special interest (AESI) are defined by the important identified risk and important potential risk: Hepatotoxicity, Thrombocytopenia, Cardiac adverse events, Sensory abnormalities suggestive of ganglionopathy, and Thrombotic microangiopathy. These were assessed by the investigator.

PT = preferred term

End point type	Primary

End point timeframe:

Up to Month 18

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 AEs and also not applicable for single arm studies.

End point values	OAV101			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Participants				
Risk name: Hepatotoxicity	11			
-PT: Aspartate aminotransferase increased	5			
-PT: Alanine aminotransferase increased	5			
-PT: Blood alkaline phosphatase increased	2			
-Preferred term: Bilirubin conjugated increased	2			
-PT: Gamma-glutamyltransferase increased	5			
-Preferred term: Hepatic enzyme increased	3			
-Preferred term: Hepatic failure	1			
-Preferred term: Transaminases increased	2			
Risk name: Thrombocytopenia	5			
-Preferred term: Platelet count decreased	4			
-Preferred term: Thrombocytopenia	1			
Risk name: Thrombotic microangiopathy	2			
-Preferred term: Thrombotic microangiopathy	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who achieve Development Motor Milestones according to the World Health Organization-Multicentre Growth Reference Study (WHO-MGRS)

End point title	Number of participants who achieve Development Motor Milestones according to the World Health Organization-Multicentre Growth Reference Study (WHO-MGRS)

End point description:

The World Health Organization-Multicentre Growth Reference Study (WHO-MGRS) was used to measure developmental motor milestones. This was assessed via the milestone checklist. The 6 developmental milestones are: sitting without support, hands-and-knees crawling, standing with assistance, walking with assistance, standing alone and walking alone. A yes response indicates that the patient reached a particular development milestone.

End point type	Secondary

End point timeframe:

Baseline (Screening), and at Weeks 26, 52 and 78

End point values	OAV101			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: Participants				
Screening - Sitting without support	6			
Screening - Hands-and-knees crawling	2			
Screening - Standing with assistance	1			
Screening - Walking with assistance	0			
Screening - Standing alone	0			
Screening - Walking alone	0			
Week 26 Sitting without support (n=14)	12			
Week 26 Hands-and-knees crawling (n=14)	2			
Week 26 Standing with assistance (n=14)	2			
Week 26 Walking with assistance (n=14)	2			
Week 26 Standing alone (n=14)	1			
Week 26 Walking alone (n=14)	0			
Week 52 Sitting without support (n=13)	10			
Week 52 Hands-and-knees crawling (n=13)	4			
Week 52 Standing with assistance (n=13)	7			
Week 52 Walking with assistance (n=13)	3			
Week 52 Standing alone (n=13)	6			
Week 52 Walking alone (n=13)	2			
Week 78 Sitting without support (n=12)	10			
Week 78 Hands-and-knees crawling (n=12)	3			
Week 78 Standing with assistance (n=12)	7			
Week 78 Walking with assistance (n=12)	2			
Week 78 Standing alone (n=12)	3			
Week 78 Walking alone (n=12)	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are reported from the single dose of study treatment plus 18 months post treatment, up to a maximum duration of 18 months.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	OAV101A1

Reporting group description:

A single IV infusion at 1.1e14 vg/kg over approximately 60 minutes

Serious adverse events	OAV101A1		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 16 (68.75%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	1		
Blood and lymphatic system disorders			
Thrombotic microangiopathy			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 1		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			

Hepatic failure				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Respiratory, thoracic and mediastinal disorders				
Pneumonia aspiration				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract congestion				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Renal failure				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Infections and infestations				
Bronchiolitis				
subjects affected / exposed	3 / 16 (18.75%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
COVID-19				
subjects affected / exposed	2 / 16 (12.50%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				

subjects affected / exposed	3 / 16 (18.75%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	OAV101A1		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 16 (100.00%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 16 (31.25%)		
occurrences (all)	5		
White blood cell count increased			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Transaminases increased			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	3		
Platelet count decreased			
subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	4		
Hepatic enzyme increased			
subjects affected / exposed	3 / 16 (18.75%)		
occurrences (all)	3		
Gamma-glutamyltransferase increased			
subjects affected / exposed	5 / 16 (31.25%)		
occurrences (all)	5		
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Bilirubin conjugated increased			

subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 16 (31.25%)		
occurrences (all)	9		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	7 / 16 (43.75%)		
occurrences (all)	14		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	7 / 16 (43.75%)		
occurrences (all)	8		
Stomatitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Salivary hypersecretion			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Diarrhoea			

subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Tonsillitis			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Laryngitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	4 / 16 (25.00%)		
occurrences (all)	4		
Catarrh			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Upper respiratory tract congestion			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	5		
Rhinorrhoea			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Subcutaneous emphysema			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Psychiatric disorders			
Irritability			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Infections and infestations			

Viral infection				
subjects affected / exposed	2 / 16 (12.50%)			
occurrences (all)	2			
Urinary tract infection				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	2			
Upper respiratory tract infection				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Rhinitis				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Pneumonia bacterial				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Pneumonia				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	3			
Influenza				
subjects affected / exposed	3 / 16 (18.75%)			
occurrences (all)	3			
Gastroenteritis				
subjects affected / exposed	2 / 16 (12.50%)			
occurrences (all)	2			
Coxsackie viral infection				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
Conjunctivitis				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			
COVID-19				
subjects affected / exposed	2 / 16 (12.50%)			
occurrences (all)	2			
Asymptomatic bacteriuria				
subjects affected / exposed	1 / 16 (6.25%)			
occurrences (all)	1			

Metabolism and nutrition disorders Hypoglycaemia subjects affected / exposed occurrences (all) Decreased appetite subjects affected / exposed occurrences (all)	 1 / 16 (6.25%) 1 1 / 16 (6.25%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 March 2022	Numbering correction in the Protocol summary section exclusion criteria; Removal of Canada as a participant country; Adjustment of project title considering the removal of Canada; Removal of Murray´s Secretions Severity Rating Scale; Removal of Yale Pharyngeal Severity Rating Scale; Removal of Anti-SMN antibodies in serum assessment as an exploratory objective; Protocol improvements to confirm that the participants may be discharged 12-48 hours after the infusion, based on Investigator judgment; Protocol improvements to confirm that the safety profile of OAV101 is described in the Investigator Brochure (IB) or package insert; Numbering adjustment performed for items 6.1.2 Additional Study Treatment and 6.1.3 Supply of study treatment; Adjustment in the item 8-1 Assessment Schedule – visit window.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported