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OAV101

Clinical Trial Protocol COAV101A12306 / NCT04851873

A Phase IIIb, 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 patients with spinal muscular atrophy (SMA)

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List of abbreviations

AAV	Adeno-Associated Virus
AAV2	Adeno-Associated Virus Serotype 2
AAV9	Adeno-Associated Virus Serotype 9
[redacted]	[redacted]
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BiPAP	Bi-Level Positive Airway Pressure
BLQ	Below the lower limit of quantitation
BMI	Body Mass Index
CB	Chicken-β-Actin-Hybrid
cDNA	Complementary Deoxyribonucleic Acid
CFR	Code of Federal Regulations
CMO&PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CNS	Central Nervous System
CNT	Can Not Test
CO	Country Organization
COA	Clinical Outcome Assessment
COVID	Coronavirus Disease
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DRG	Dorsal Root Ganglia
ECG	Electrocardiogram
ECHO	Echocardiogram
EDC	Electronic Data Capture
EOS	End of Study
EU	Europe
FAS	Full Analysis Set
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GLDH	Glutamate dehydrogenase
GLP	Good Laboratory Practice
HBsAg	Hepatitis B surface antigen
HEENT	Head, Eyes, Ears, Nose and Throat
HFMSE	Hammersmith Functional Motor Scale - Expanded
HIV	Human immunodeficiency virus

IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IT	Intrathecal
ITR	Inverted Terminal Repeats
IV	Intravenous
kg	Kilogram(s)
LFT	Liver function test
LV EF	Left Ventricular Ejection Fraction
LV FS	Left Ventricular Fractional Shortening
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
[redacted]	[redacted]
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PRO	Patient Reported Outcomes
PT	Prothrombin Time
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
RSV	Respiratory Syncytial Virus
RULM	Revised Upper Limb Module
SAE	Serious Adverse Event
SMA	Spinal muscular atrophy
SMN1	Survival of Motor Neuron 1
SMN2	Survival of Motor Neuron 2
SNAP	Sensory nerve action potential
SOP	Standard Operating Procedure(s)
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMA	Thrombotic Microangiopathy
ULN	upper limit of normal
US	United States
vg	Vector Genome
WHO	World Health Organization
WHO-MGRS	World Health Organization Multicentre Growth Reference Study

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy; concomitant medications)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives
Cohort	A specific group of participants fulfilling certain criteria and generally treated at the same time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the participant in a time unit
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
Estimand	A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the patient about the status of a participant's health condition without amendment or interpretation of the patient's report by a clinician or anyone else
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource

Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data

Amendment 01 (28-Feb-2022)

Amendment rationale

The main purpose of this amendment is to correct an error in the schedule of assessment in protocol Section 8. By error, virus serology has been added to visits Week 13, 26, 39 and 52 Week/EOS. Virus serology should be performed at screening to rule out specific viral infections before study start as mentioned in protocol Section 8.2.6. There is no reason, from a safety perspective, why this assessment would be repeatedly tested in a low-risk pediatric population such as children with SMA. As these assessments are performed through serum, blood draw volume should be limited, especially in pediatric patients so as to not create an anemia risk. Thus, virus serology assessments for the above-mentioned visits are removed. In addition to this, a local change, only applicable for Germany has been added. As requested by Paul-Ehrlich Institut, hematology assessments have been added to Week 4 and Week 10 in the schedule of assessments in protocol Section 8, to be consistent with platelet monitoring requirements in the SmPC. Furthermore, language regarding the collection of additional information from screening failures and for the use of remaining serum samples for the potential development of companion diagnostic assays has been added.

Changes to the Protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

- Protocol Summary:
- Key Exclusion Criteria, #13 Hepatic Dysfunction: Wording changed from '≥ ULN; CTCAE ≥ 1' to '> ULN ' for clarification.
- Key Exclusion Criteria, #16 Previous Treatment: Updated formatting for clarification.
- Data Analysis: Addition of 'WHO-MGRS & Bayley Scale of Infant and Toddler Development' to clarify the assessment included in Secondary Endpoints.
- Section 1.1, Background:
  - Removed reference to Foust et al study due to data discrepancies.

- Updated to replace 'likely' with 'potentially' in the ACO of EU renewal when describing acquired immune response to the viral capsid and/or transgene product, as there is no evidence that liver findings are caused by immune response.

[redacted]

- Section 3, Study Design:
  - Added language on remote visits and off-site study procedures offered to certain countries and site locations as determined by Novartis based on national and local regulations.
- Section 4.1, Rationale for study design:
  - Added 'planned immunizations' in exclusionary criteria. Wording changed for clarification purposes.

[redacted]

- Section 4.6, Risks and benefits
  - Potential risks associated with OAV101: Wording changed from 'Sensory abnormalities suggestive of ganglionopathy' to 'Dorsal root ganglia toxicity' -to align to risk description in the Investigator Brochure (version 9).
  - Updated the language of drug-drug interaction to clarify "There might be pharmacodynamic drug-drug interactions with other therapeutic agents for the treatment of SMA, [redacted]
- Section 5.2, Exclusion criteria
  - #13, Hepatic Dysfunction: Changed "≥ ULN" to "> ULN" to fix a mistake. Removed 'CTCAE grade 1 or greater' to hepatic dysfunction exclusion criteria for clarification.
- Section 6.2.2, Prohibited medication:
  - Removed 'intravenous immunoglobulins' from list of prohibited concomitant medication. Editorial error, this language is covered by the last bullet in same section (IVIG).
  - Removed "PD" from the drug interaction sentence to clarify there might be PD drug-drug interactions with other therapeutic agents for the treatment of SMA.
- Section 6.3.1, Participant numbering:
  - Added language to clarify that a new patient number will be assigned if a patient is re-screened as a result of screen failure.

- Section 7, Informed consent procedures:
  - [redacted] this study includes a mandatory DNA sample for SMA confirmation, [redacted]
  - Added language on off-site study procedures, including clarification that a separate consent would be required to allow for this, in order to align with standardized template language on COVID-19 mitigation procedures.
- Section 8, Visit schedule and assessments:
- Table 8-1, Assessment schedule:
  - Virus Serology: Removed assessments from Week 13, Week 26, Week 39, and Week 52/EOS visits, as these were originally added in error.
  - Hematology assessment at Day 2 has been added to align SoA with Section 8.4.1.1
  - Footnote 4 to specify that Day 2 assessment of hematology should be performed locally and that platelet counts should be monitored for the first week after infusion, has been added, to be consistent with the SmPC.
  - Hematology assessments at Week 4 and Week 10 have been added as per Paul-Ehrlich Institut request consistent with the summary of Product Characteristics (SmPC). This change is only applicable for Germany which is specified in Footnote 5.
  - Subsequent footnotes after Footnote 5 have been renumbered for consistency.
  - [redacted]
  - [redacted]
  - HFSME, RULM: Footnote 9 was added in line with Section 8.5.1.2 to both HFSME and RULM assessments, as this assessment is not applicable to all patients. Footnote 10 clarifies that physical assessments may occur over the span of more than one day within the visit window, but must not exceed 4 days.
  - [redacted]
- Section 8.1.1, Information to be collected on screening failures:
  - Collection of additional information on screening samples has been added for following eCRF pages if applicable and available: Diagnosis_SMA , Withdrawal of consent, Assessments, Rescreen, Anti-AAV9 Antibody Testing (Blood), 5q SMA Genetic Testing (SMN1 and SMN2), AE page is seriousness criteria is Death.
  - In addition, the request to enter available anti-AAV9 Antibody testing results and 5q SMA Genetic Testing (SMN1 and SMN2) into the Novartis database has been added.

- Added language to specify that participants who fail eligibility criteria for a temporary condition may be re-tested/re-assessed within the screening window up to two times, and re-screened once.
- Added clarification that participants who fail upper weight eligibility at Screening Visit 2 cannot be re-tested or re-screened.

[redacted]

- Section 8.4.1, Laboratory evaluations:
  - Added language clarifying that safety samples may be collected remotely (through local lab) during a Public Health emergency as declared by local or regional authorities in order to provide a potential pandemic mitigation strategy.
  - Added language clarifying that participants may visit local lab for lab assessments if they cannot visit primary institution in order to provide a potential pandemic mitigation strategy.
- Section 8.4.1.1, Hematology:
  - Language to specify that platelet counts should be monitored for the first week after infusion, has been added, consistent with the SmPC.
- Section 8.4.1.2, Coagulation panel:
  - Added Coagulation panel as a new section. Renumbered subsequent sections for consistency.
  - Added language clarifying that coagulation testing, including prothrombin time and INR and activated partial thromboplastin time, will be performed prior to OAV101 dosing. This was left out of original document by mistake.
- Section 8.4.2.1, 12-Lead Electrocardiogram:
  - Updated language regarding ECG readout availability, as study sites will only use one ECG model. Language is not applicable for site.
- Section 8.4.3, Vital signs:
  - Wording for screening weight changed from '≤14 days prior to Day 1' to 'at screening visit 2' as a correction.
- Section 8.4.4, Other safety evaluations:
  - Updated language to specify that SNAP data will be read locally but reviewed centrally by an external expert to ensure consistent implementation and quality control of the neurophysiology data. This language is aligned with the sensory nerve conduction studies manual.
  - Added guidance to consult the sensory nerve conduction studies manual for details on SNAP assessments and quality checks.
- Section 8.5.1.1, Hammersmith Functional Motor Scale-Expanded:
  - Additional assessment details added for clarification, including further support regarding reasoning behind assessment selection as well as details surrounding scoring for how a change over time will be reflected to support the secondary objectives.
- Section 8.5.1.2, Revised Upper Limb Module:

- Additional assessment details added for clarification, including further support regarding reasoning behind assessment selection as well as details surrounding scoring for how a change over time will be reflected to support the secondary objectives.
- It has been added that the site clinical evaluator must be trained for clarification

[redacted]

- DNA Samples (mandatory): Subheading has been clarified as "DNA samples for genetic confirmation of SMA (mandatory)" for consistency. Added clarification that current planned SMA testing may to detect SMN1 point mutation.

[redacted]

- Section 10.1.1, Adverse Events:
  - Wording changed from 'Sensory abnormalities suggestive of ganglionopathy' to 'Dorsal root ganglia toxicity' to align with Investigator Brochure (Edition 9).
- Section 10.1.3, SAE Reporting:
  - Updated SAE reporting language to provide more specific instructions on reporting SAEs to Novartis safety immediately and no later than within 24 hours of obtaining knowledge of events, or if more stringent, per local regulations for reporting timelines.
- Section 10.2.1, Liver Safety Monitoring:
  - Clarification in line with Section 16.1.2 has been added: "If elevated, repeated liver chemistry tests (i.e. ALT, AST, BIL, Fractionated BIL, INR, and GLDH) will be performed within 48-72 hours to confirm elevation. If results will not be available from the central laboratory, then repeated testing should be performed at a local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate eCRF page."
  - Clarification to consider based on Investigator judgement imaging, such as ultrasound/Fibroscan, and pathology assessments in case of a liver event has been added.

    - Clarification to consider based on Investigator judgement pediatric gastroenterology or hepatology consultation has been added
- Section 12.5.1, Efficacy and/or Pharmacodynamic endpoint(s):
    - Updated full title of 'WHO-MGRS & Bayley Scale of Infant and Toddler Development' for clarification.
- Section 15, References:
    - Added Flynn et al (2017), as exam and vital sign data can only be interpreted with a thorough understanding of normal values. Addition of this reference provides age-specific norms for pediatric blood pressure.
    - Removed Foust et al (2010), as this study is no longer relevant to the document. Additional text related to this study throughout the document was removed.
- Section 16.1.1, Potentially notable variables and vital signs:
    - Wording changed to 'Potentially clinically,' as definition of clinical relevance might be subjective.
    - Vital signs:
        - Added Flynn, et al reference, as exam and vital sign data can only be interpreted with a thorough understanding of normal values. Addition of this reference provides age-specific norms for pediatric blood pressure.
        - Deleted table containing normal range of lab values for vital signs and refer to align with AAP 2017 guidelines (Flynn et al 2017) for simplification.
- General grammatical, spelling, linking and referencing corrections and updates were made throughout the document.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation. The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Protocol summary

Protocol number	COAV101A12306
Full Title	A Phase IIIb, 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 patients with spinal muscular atrophy (SMA)
Brief title	Safety and efficacy of intravenous OAV101 (AVXS-101) in pediatric patients with spinal muscular atrophy (SMA)
Sponsor and Clinical Phase	Novartis and Phase IIIb
Investigation type	Participants will receive a single administration of OAV101 at 1.1e14 vg/kg
Study type	Interventional
Purpose and rationale	To evaluate the safety, tolerability and efficacy of intravenous administration of OAV101 (AVXS-101) in patients with SMA with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene weighing ≥ 8.5 kg and ≤ 21 kg, over a 12 month period.
Primary Objective(s)	To assess the safety and tolerability of intravenous (IV) OAV101 over a 12-month period in participants with SMA weighing ≥ 8.5 kg and ≤ 21 kg
Secondary Objectives	To determine the efficacy of IV OAV101 at 6 and 12 months post dose in participants with SMA weighing ≥ 8.5 kg and ≤ 21 kg as measured by change from baseline in: ● Achievement of development motor milestones according to the World Health Organization-Multicentre Growth Reference Study (WHO-MGRS) and Bayley Scales of Infant and Toddler Development-Third Edition (Bayley-III) criteria (See Table 2-1 for details) ● Hammersmith Functional Motor Scale - Expanded (HFMSE) ● Revised Upper Limb Module (RULM), as appropriate according to participant age.
Study design	This is an open-label, single arm, multi-center study to evaluate the safety, tolerability and efficacy of IV OAV101 in SMA participants. The study will enroll participants that weigh ≥ 8.5 kg and ≤ 21 kg. An even weight distribution across the desired range will be achieved by aiming to enroll approximately 6-10 participants across 3 weight brackets (≥ 8.5-13 kg, > 13-17 kg, > 17-21 kg). Participants will receive a single administration of IV OAV101 at the approved dose of 1.1e14 vg/kg. Participants who meet eligibility criteria at screening and baseline visits will receive a single-dose of IV OAV101 on Day 1 (Treatment period) and will be followed for a period of 12 months. The study will include a standard screening period that can last up to 45 days, during which eligibility will be assessed and baseline assessments will be performed prior to treatment. For the study duration, participants will complete visits as defined in the Schedule of Assessments. Prednisolone treatment will be given per study protocol. On Day –1, participants will be admitted to the hospital for pre-treatment baseline procedures. On Day 1, participants will receive a 1-time IV infusion of OAV101 and will undergo in-patient safety monitoring over the next 48 hours, after which the participant may be discharged, based on Investigator judgment. Safety monitoring will be performed as per study schedule and protocol requirement. Safety for the participants enrolled in the study will be evaluated by the clinical and safety team together with Data Monitoring Committee (DMC) as described in the charter. An interim analysis for safety and efficacy may be performed once the last participant completes 6-months of follow-up, and will include all available data up until that data cut-off. Final analysis will be planned after the 12 months visits (EOS). After study completion eligible participants will be invited to enroll into Long Term follow-up study to collect additional safety and efficacy data.
Study population	Participants with SMA with bi-allelic mutations in the SMN1 gene weighing ≥ 8.5 kg and ≤ 21 kg, at the time of Screening Visit 2.

Key inclusion criteria	1. Written informed consent/assent obtained prior to any assessment performed 2. Symptomatic SMA diagnosis based on gene mutation analysis with bi-allelic SMN1 mutations (deletion or point mutations) and any copy of survival of motor neuron 2 (SMN2) gene. 3. Weight ≥ 8.5 kg and ≤ 21 kg at the time of Screening Visit 2 4. Naive to treatment or have discontinued an approved drug/therapy 5. Up-to date on recommended childhood vaccinations and RSV prophylaxis with palivizumab (also known as Synagis), per local standard of care
Key exclusion criteria	Participants meeting any of the following criteria are not eligible for inclusion in this study. 1. Previous OAV101 use or previous use of any adeno-associated virus serotype 9 (AAV9) gene therapy 2. BMI < 3rd percentile based on WHO Child Growth Standard 3. Participant with history of aspiration pneumonia or signs of aspiration (e.g., coughing or sputtering of food) within 4 weeks prior to screening 4. Anti-AAV9 antibody titer > 1:50 as determined by ligand binding immunoassay at the time of screening 5. History of gene therapy, hematopoietic transplantation, or solid organ transplantation 6. Inability to take corticosteroids 7. Concomitant use of immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, or immunosuppressive therapy within 3 months prior to gene replacement therapy (e.g., cyclosporine, tacrolimus, methotrexate, rituximab cyclophosphamide, IV immunoglobulin) 8. Requiring invasive ventilation, tracheostomy or awake non-invasive ventilation (standard of care nocturnal BiPAP is not considered exclusionary) 9. Administration of vaccines 2 weeks prior to infusion of OAV101 10. Awake hypoxemia (O_2 saturation <95%) or awake oxygen saturation level decrease between screening and dosing that is clinically significant, as per investigator judgment 11. Clinically significant neurologic or neuromuscular conditions other than SMA as determined by the principal Investigator 12. Clinically significant abnormalities in laboratory test results at Screening as determined by the Investigator 13. Hepatic dysfunction (i.e. aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, gamma-glutamyl transferase (GGT) or glutamate dehydrogenas (GLDH), >ULN at Screening (with the exception of isolated AST elevation: in the absence of other liver laboratory abnormalities, isolated AST elevation is not considered exclusionary) 14. Excluding SMA, any medically unstable condition considered clinically significant by the Investigator, including cardiomyopathy, hepatic dysfunction, kidney disorder, endocrine disorder, GI disorders, metabolic disorders, severe respiratory compromise and significant brain abnormalities at either Screening or Baseline that, in the opinion of the investigator, would interfere with the overall interpretation of safety or efficacy of the study 15. Presence of a confirmed or suspected active infectious process from screening and up to dose administration 16. If previously treated with disease modifying therapy, participants are excluded if they received • less than 3 doses of nusinersen (Spinraza®) • nusinersen (Spinraza®) within 4 months prior to Screening • risdiplam (Evrysdi®) within 15 days prior to Screening (washout period of at least 5 half-lives before Screening)

	17. Use of other investigational drugs within 5 half-lives of enrollment/initiation of study treatment (select as appropriate) within 30 days (e.g., small molecules) / or until the expected pharmacodynamic effect has returned to baseline (e.g., biologics), whichever is longer; or longer if required by local regulations. 18. History of hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes. 19. Documented any parental consanguinity.
Study treatment	OAV101 will be administered as a single IV infusion at 1.1e14 vg/kg over approximately 60 minutes
Efficacy assessments	Developmental motor milestones will be assessed using relevant definition obtained from the following: ● WHO Multicentre Growth Reference Study (WHO-MGRS) and Bayley Scale of Infant and Toddler Development (Bayley-III) ● Hammersmith Functional Motor Scale - Expanded (HFMSE) ● Revised Upper Limb Module (RULM), as appropriate according to participant age
Key safety assessments	Safety and tolerability of OAV101 treatment includes evaluation of adverse events (AEs), laboratory data, vital signs, and cardiac safety monitoring.
Data analysis	The primary endpoints include: 1. Incidence and severity of treatment emergent AEs and severe adverse events (SAEs) 2. Incidence of important identified and important potential risks 3. Change from baseline in vital signs, clinical laboratory, and procedure (e.g. ECG, echocardiogram) results Incidence and severity for treatment emergent AEs and SAEs as well as important identified and important potential risks will be summarized by weight bracket and overall in the safety set. The number and proportion of participants reporting a treatment emergent AE or SAE, including investigator and Sponsor causalities will be reported. Summaries will also be provided by MedDRA System Organ Class and Preferred Term. Changes from baseline in vital signs, and clinical laboratory, and procedure (e.g. ECG, echocardiogram) results will be summarized descriptively by weight bracket and overall in the safety set. Mean, standard deviation, median, minimum, and maximum will be presented. For each applicable timepoint, only participants with a baseline and a measurement for that timepoint will be included in the summary. No hypothesis testing will be performed. For secondary endpoints, changes from baseline in HFMSE and RULM will be summarized descriptively; the number and proportion of patients achieving each WHO-MGRS & Bayley Scale of Infant and Toddler Development developmental motor milestones will be presented. Summaries will be presented by weight bracket as well as overall. An interim analysis may be performed once the last participant reaches the 6-month time point, and will include all available data up until that data cut-off. The size of approximately 24-30 participants is considered reasonable to provide descriptive safety information across 3 weight brackets ≥ 8.5 kg and ≤ 21 kg. A sample size of approximately 24-30 participants will provide 90% probability to observe at least one event if the underlying incidence of the event is 9%.
Key words	Spinal muscular atrophy, Zolgensma, OAV101, AVXS-101, gene therapy

1 Introduction

1.1 Background

Spinal muscular atrophy is an autosomal recessive, early childhood disease with an incidence of approximately 1:10,000 live births, of which approximately 45% to 60% of cases are SMA 1 (Ogino et al 2004, Sugarman et al 2012, Arnold et al 2015). Spinal muscular atrophy is conventionally classified into 4 phenotypes on the basis of age of onset and highest motor function achieved, with an additional phenotype (type 0) to describe the severe forms of antenatal onset (Kolb and Kissel 2011, Mercuri et al 2012) (Table 1-1). Prior to the availability of effective treatment, SMA was the leading cause of infant mortality due to genetic disease (Sugarman et al 2012, Awano et al 2014).

Table 1-1 Spinal Muscular Atrophy Classification

Type	Age at Symptom Onset		Maximum Motor Function	Life Expectancy	*SMN2* Copy No.
0	Fetal		Nil	Days – Weeks	1
1	< 6 months	1A: Birth – 2 weeks 1B: < 3 months 1C: > 3 months	Never sits	< 2 years	1, **2**, 3
2	6 – 18 months		Never walks	20 – 40 years	2, **3**, 4
3	1.5 – 10 years	3A: < 3 years 3B: > 3 years	Walks, regression	Normal	3, **4**, 5
4	> 35 years		Slow decline	Normal	4-8

bold = predominant *SMN2* copy number that defines the SMA type, the other copy numbers represent a small percentage of the designated SMA type.

Source: Adapted from Kolb and Kissel 2011 and Mercuri et al 2012

With the recent availability of *SMN*-targeting therapies, the SMA phenotype is shifting and current clinical practice increasingly relies on genotype and age-of-onset when considering prognosis and treatment (Mercuri et al 2012, Wirth et al 2020, Wirth 2021). Following the development of disease-modifying treatment for SMA, newer categories of nonsitter, sitter, and walker phenotypes are increasingly used to better inform disease management (Mercuri et al 2012, Finkel et al 2018, Wirth et al 2020, Wijngaarde et al 2020). For example, "Nonsitters", the majority of whom have SMA type 1, typically have 2 copies of *SMN2* gene (approximate range, 1-3 years) and are unable to sit independently. These patients also have bulbar and respiratory dysfunction requiring feeding and ventilatory support, respectively (Finkel et al 2018, Mercuri et al 2018, Wirth et al 2020). These patients would historically not have survived past the age of 2 years, but are now achieving developmental milestones such as sitting independently, standing and even walking.

The serious continuing unmet needs in SMA, all stemming from absence of the *SMN* protein most commonly due to biallelic deletion of the *SMN1* gene, is meaningfully addressed by OAV101 (AVXS-101) as the first therapeutic regimen designed to directly address the underlying genetic cause of the disease. Most children with SMA have 2 copies of *SMN2* gene and have a 97% probability of developing SMA based upon copy number alone (Feldkötter et al 2002). The majority of patients with SMA have normal strength at birth but

exhibit progressive weakness with the onset of symptoms being observed before 6 months of age (Shababi et al 2014, Finkel et al 2014).

OAV101 is a recombinant biological product comprised of replication-incompetent recombinant self-complementary AAV9 capsid shell containing the complimentary deoxiribonucleic acid (cDNA) of the human *SMN* gene. The *SMN* gene is under the control of the CMV enhancer/CB as well as 2 AAV ITRs derived from AAV2 DNA. One of the 2 AAV ITRs has been modified to promote intramolecular annealing of the transgene, thus forming a double-stranded transgene ready for transcription. This modified ITR, termed a "self-complementary" (sc) ITR, has been shown to significantly increase the speed at which the transgene is transcribed, and the resulting human *SMN* protein is produced. Recombinant self-complimentary adeno-associated virus can be employed because of the small size of the *SMN* gene, which enables efficient packaging and gene transfer with lower viral titers, compared with prototype single-stranded AAV vectors. All DNA from the wild-type AAV9 has been removed and replaced with the genes described above (the 2 ITRs are from AAV2).

Intravenous OAV101 can transduce neurons, muscle, and vascular endothelium, all of which have been proposed as target cells for SMA treatment. In pivotal toxicology studies, the main target organs of toxicity were limited to the heart and liver in mice, and the brain, dorsal root ganglia (DRG), and associated tissues (spinal cord, peripheral nerves), trigeminal ganglion (TG), liver, and heart in cynomolgus monkeys.

Liver findings in mice were comprised of hepatocellular hypertrophy, Kupffer cell activation, and scattered hepatocellular necrosis, while in NHP the findings were limited to single cell necrosis of hepatocytes associated with slight mononuclear cell infiltrates. In both species, these microscopic findings may have correlated with increased liver enzyme activity. The pathogenesis of OAV101 related liver findings has not been specifically studied but is potentially related to an innate and/or adaptive immune response to the viral capsid and/or transgene product which is prominently distributed to the liver. OAV101 related findings in the heart include ventricular inflammation, edema, and fibrosis, and atrial thrombosis and inflammation in mice. In monkeys, slight mixed cell infiltrates and minimal hemorrhage were noted in the right atrium of 1 animal 6 weeks post IT injection at 3e13 vg/animal, with no observed alteration of cardiac troponin. The pathogenesis of these heart findings in animals and potential translatability to humans is unclear.

Compared to the natural history of SMA, patients treated with OAV101 IV in a completed clinical study showed significant improvements in survival, attainment of developmental motor milestones, respiratory and motor function, and ability to thrive. Results obtained 24 months after OAV101 infusion showed that efficacy was durable and either consistent or improved compared to earlier analyses conducted when patients had reached at least 13.6 months and 20 months of age. In a Phase 3 completed clinical study, the co-primary efficacy results demonstrated that OAV101 has significant therapeutic benefits in patients with SMA with biallelic mutation of the *SMN1* gene and 1 or 2 copies of the *SMN2* gene who were < 6 months of age at the time of gene replacement therapy. The therapeutic benefit of OAV101 was again demonstrated for survival, the achievement of motor milestones, respiratory and motor function, and the ability to thrive. Consistent with findings in previous studies, the available data from currently ongoing IV studies of OAV101 have also demonstrated clear evidence of

clinically meaningful efficacy in this otherwise devastating neurodegenerative disease with an acceptable safety profile.

SMA is now recognized as a continuous spectrum of disease with severity determined by both genetic and environmental factors, including SMA-modifying therapy (e.g., nusinersen and risdiplam) and supportive care. As treatment is now available that changes the disease course, with older patients now having preserved motor neuron function that can be rescued by gene therapy compared to SMA patients in the pre-treatment era. This Phase IIIb open-label study will be conducted in SMA participants that weigh between 8.5 kg and 21 kg, inclusive. This study builds on the established efficacy and safety profile of OAV101 and aims to gather additional safety and efficacy information in a cohort of heavier children not previously studied in OAV101 clinical trials.

1.2 Purpose

The purpose of the study is to evaluate the safety, tolerability, and efficacy of IV administration of OAV101 in participants with SMA with bi-allelic mutations in the *SMN1* gene weighing ≥ 8.5 kg to ≤ 21 kg, during a 12-month period.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
● The primary objective of this study is to assess the safety and tolerability of IV OAV101 over a 12-month period in participants with SMA weighing ≥8.5 kg to ≤ 21 kg.	● Evaluation of treatment emergent AEs and SAEs ● Evaluation of important identified and important potential risks ● Evaluate changes from baseline in vital signs, cardiac safety assessments, and clinical laboratory results
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
● Determine the efficacy of IV OAV101 at 6 and 12 months post dose in participants with SMA weighing ≥ 8.5 kg to ≤ 21 kg, as measured by secondary endpoints.	● Achievement of development motor milestones according to the World Health Organization-Multicentre Growth Reference Study (WHO-MGRS) and Bayley Scale of Infant and Toddler Development - Third Ed (Bayley-III) criteria (Section 16.1) ● holds head erect for at least 3 seconds without support ● sits with slight support 30 seconds ● sitting without support ● sits without support 30 seconds ● hands-and-knees crawling ● pulls to stand ● standing with assistance ● walking with assistance ● standing alone ● walking alone ● Change from baseline in Hammersmith Functional Motor Scale - Expanded (HFMSE), as appropriate according to participant age. ● Change from baseline in Revised Upper Limb Module (RULM), as appropriate according to participant age.

Objective(s)	Endpoint(s)
[redacted]	

2.1 Primary estimands

The clinical question of interest: What is the safety of single administration of IV OAV101 treatment in SMA participants that weigh ≥ 8.5 to ≤ 21 kg?

The primary estimand is described by the attributes listed below.

The population of interest is participants with SMA that weigh ≥ 8.5 to ≤ 21 kg

The primary variables include:

1. Treatment emergent AEs and SAEs
2. Important identified and important potential risks
3. Change from baseline in vital signs, cardiac safety assessments, and clinical laboratory results

The treatment of interest is IV OAV101.

The remaining intercurrent events include receiving prohibited concomitant medications. Loss to follow-up due to reasons other than death will not impact 1 or 2 above primary variables; for primary variable 3it will be handled by a hypothetical strategy.

The summary measures include incidence and severity for treatment emergent AEs and SAEs as well as important identified and important potential risks and mean for changes from baseline in vital signs and clinical laboratory results.

2.2 Secondary estimands

The secondary clinical question of interest: What is the efficacy of single administration of IV OAV101 treatment in SMA participants that weigh ≥ 8.5 to ≤ 21 kg?

The secondary estimand is described by the attributes listed below.

The population of interest is patients with SMA that weigh ≥ 8.5 to ≤ 21 kg.

The secondary variables include:

1. Change from baseline in Hammersmith Functional Motor Scale - Expanded (HFMSE), as appropriate according to participant age.

2. Change from baseline in Revised Upper Limb Module (RULM), as appropriate according to participant age.
3. Achievement of developmental motor milestones according to the World Health Organization-Multicentre Growth Reference Study (WHO-MGRS) and Bayley Scales of Infant and Toddler Development - Third Ed (Bayley-III) criteria.
    - holds head erect for at least 3 seconds without support
    - sits with slight support 30 seconds
    - sitting without support
    - sits without support 30 seconds
    - hands-and-knees crawling
    - pulls to stand
    - standing with assistance
    - walking with assistance
    - standing alone
    - walking alone

The treatment of interest is IV OAV101.

The remaining intercurrent events include receiving concomitant medications. Loss to follow-up due to reasons other than death will be handled by a hypothetical strategy for the change from baseline variables and by a composite strategy for milestones.

The summary measures include mean for changes from baseline in HFMSE and RULM as well as incidence for developmental motor milestone achievement.

3 Study design

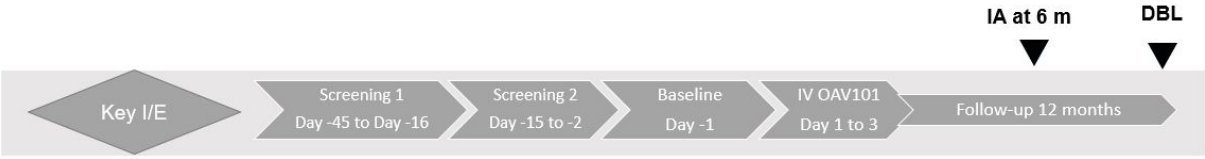
This is an open-label, single arm, multi-center study to evaluate the safety, tolerability and efficacy of IV OAV101 in SMA participants. The study will enroll participants that weigh ≥ 8.5 to ≤ 21 kg. Approximately 24-30 participants may be enrolled and distributed between 6 and 10 participants per cohort in each of the three brackets in order to achieve an approximately even weight distribution (≥ 8.5-13kg, > 13-17kg, > 17-21kg).

Participants who meet eligibility criteria at screening and baseline visits will receive a single-dose of IV OAV101 on Day 1 (Treatment period) at the approved dose of 1.1e14 vg/kg and will be followed for a period of 12 months. The study will include a screening period of up to 45 days in which there will be 2 screening visits, during which, eligibility will be assessed (Screening 1), weight will be collected for dose calculation (Screening 2), and baseline assessments will be performed prior to treatment. For the study duration, participants will complete visits as defined in the Schedule of Assessments (Table 8-1). On Day -1, participants will be admitted to the hospital for pre-treatment baseline procedures including prednisolone treatment per study protocol. On Day 1, participants will receive a single IV infusion of OAV101 and will undergo in-patient safety monitoring over the next 48 hours. Participants may be discharged 48 hours after the infusion, based on Investigator judgment. Section 6.7 outlines details regarding study drug preparation and administration.

Safety monitoring will be performed on an ongoing basis per protocol requirement and will be evaluated by the clinical and safety team as well as DMC. An interim analysis for safety and efficacy may be performed once the last participant completes 6-months of follow-up, and will include all available data up until that data cut-off. Final analysis will be planned after 12 months visits (EOS).

After study completion eligible participants will be invited to enroll into Long Term follow-up study to collect additional safety and efficacy data.

Figure 3-1 Study design



Remote procedures

At the Investigator's direction and based on benefit-risk considerations of the participant's clinical condition, qualifying participants may be offered the option to have certain clinical trial procedures according to Table 8-1 Assessment schedule performed at a remote location.

Procedures will be performed remotely under the oversight of the Investigator, who retains accountability for the oversight and all efficacy and safety decisions with delegation of tasks to an off-site healthcare professional.

The remote procedures will be offered in certain countries and sites as determined by Novartis based on national and local regulations.

The off-site healthcare professionals update/add role as applicable in line with glossary will be provided by a third-party vendor sourced by Novartis. Where a site wishes to use off-site healthcare professionals update/add roles as applicable in line with glossary that are not provided by Novartis this must be agreed with Novartis before use.

In addition to procedures performed by the off-site healthcare professional, the on-site staff will perform certain procedures remotely using tele-visits.

4 Rationale

4.1 Rationale for study design

This Phase IIIb open-label study builds on the established efficacy and safety profile of OAV101. The study is designed as a prospective open-label trial in order to characterize the safety of OAV101 in children ≥ 8.5 kg and ≤ 21 kg with symptomatic SMA. The open-label design is expected to facilitate enrollment [redacted]

The study includes 2 screening visits to facilitate assessment of eligibility (anti-AAV9 antibody titers), decrease burden of clinical and laboratory baseline evaluations, and weight-based dose calculation closer to infusion day. The second screening visit will be used for weight eligibility

and dose calculation. The study will administer one-time OAV101 and monitor participants in an inpatient setting for a minimum of 48 hours after administration to carefully monitor the emergence of acute AEs. Participants will be followed up to 12 months, which is considered adequate to characterize safety given clinical experience (Section 4.6) and sufficient to evaluate efficacy.

Inclusion of children ≥ 8.5 kg and ≤ 21 kg allows for careful assessment of safety and clinical response in a population that has not been previously included in OAV101 clinical trials. The study is broad in the inclusion of participants that are treatment naive and "switchers" (e.g treatment experienced) reflecting the real-world use of OAV101. The study excludes participants who have pre-existing AAV9 immunity and thus may be at risk for lack of efficacy. In order to reduce safety confounders and mitigate known OAV101 safety risks the study excludes participants with underlying liver disease, active infections, and immunizations planned before or after administration of OAV101. Please refer to Section 6.2 for more information.

4.1.1 Rationale for choice of background therapy

The study allows for standard of care non-disease modifying SMA therapy, including respiratory and nutritional support, physical therapy, and prevention of infection therapies in accordance to treatment guidelines and local practice. This will further mitigate safety and efficacy confounders.

4.2 Rationale for dose/regimen and duration of treatment

OAV101 will be administered in this trial as a single IV infusion and will undergo in-patient safety monitoring over the next 48 hours. Participants will receive a dose of 1.1e14 vg/kg. The total volume is determined by participant body weight.

4.3 Rationale for use of prednisolone

An immune response to the AAV9 capsid may occur after administration of OAV101. This can lead to elevations in liver transaminases. To dampen the immune response and in accordance to the market authorization, all participants will receive corticosteroids 24 hours prior to the infusion of OAV101 and for at least 30 days post-infusion (including the day of OAV101 administration). The participant vaccination schedule will be adjusted to accommodate corticosteroid administration. Pre- and post-infusion corticosteroids regimen is indicated in Section 6.2

4.5 Purpose and timing of interim analyses

An interim analysis may be performed once the last participant reaches the 6-month follow-up and will include all available data up until that data cut-off. The interim analysis is intended to provide an early safety readout from the study. No study design change or adaptation will be implemented based on the outcome of the interim analysis.

4.6 Risks and benefits

Evidence from the completed and ongoing clinical studies continue to demonstrate the efficacy of OAV101. Substantial clinical efficacy of OAV101 across multiple endpoints-survival, motor function, developmental motor milestones, and ventilatory and nutritional endpoints has been established and confirmed in first-in-human and confirmatory studies. Long-term follow-up studies continue to support the durability of OAV101 efficacy, and participants continue to exhibit the achievement of additional milestones. Data spans pre-symptomatic and symptomatic participants.

Appropriate eligibility criteria and clinical safety monitoring criteria are included in this protocol. The risk to participants in this trial will be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring and evaluation by an independent DMC.

The safety profile of OAV101 is described in the Investigator Brochure. The risks and benefits are derived from:

1. Non-clinical toxicology studies
2. Clinical studies for the treatment of symptomatic and pre-symptomatic participants with SMA who have 1, 2 or 3 copies of the *SMN2* gene and bi-allelic *SMN1* gene deletions at the proposed therapeutic dose of 1.1e14 vg/kg and the dose being proposed in this study
3. Long term follow-up study of participants who were administered OAV101 in clinical trials
4. US managed access program in participants with serious or life-threatening disease
5. Long-term registry of participants diagnosed with SMA
6. Post-marketing safety monitoring

The following are important identified and important potential risks associated with OAV101:

- Hepatotoxicity
- Thrombocytopenia
- Cardiac adverse events
- Dorsal root ganglia toxicity
- Thrombotic microangiopathy

Further details are outlined in the Investigator Brochure.

Risk of immunosuppression

All participants in the study will receive prophylaxis immunosuppression with prednisolone or equivalent corticosteroid to mitigate safety risks associated with inflammation (Section 4.3). The chronic use of corticosteroids may be associated with hypothalamic-pituitary-adrenal axis suppression, Cushing's syndrome and hyperglycemia which can be mitigated with adequate

tapering. Increased susceptibility to new infections or exacerbation and dissemination of latent infections, as well as elevated blood pressure, salt and water retention, hypokalemia, and gastrointestinal perforation have been reported. Risks will be mitigated by close monitoring, and implementation of standard prophylaxis and tapering protocol as detailed in Section 6.2

Risk of phlebotomy (maximum volume over what period of time)

European Medicines Agency (EMA) Guidelines for Drawing Blood and Best practices in Phlebotomy in pediatric participants will be followed.

Drug-drug interaction

OAV101 is a gene replacement therapy product for one-time administration, which delivers a transgene construct expressing the *SMN* protein. Pharmacokinetic drug-drug interactions are not expected with OAV101. There might be pharmacodynamic drug-drug interactions with other therapeutic agents for the treatment of SMA, e.g., an additive effect on *SMN* protein levels and associated pharmacodynamic responses.

In summary, clinical data strongly suggest OAV101 is safe and well tolerated with an acceptable benefit/risk profile when administered to participants with SMA with 2 or 3 survival motor neuron 2 (*SMN2*) gene copies or a clinical diagnosis of SMA.

4.7 Rationale for public health emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic, COVID-19 or natural disaster, mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Study Population

Approximately 24-30 participants with SMA with bi-allelic mutations in the *SMN1* gene weighing ≥ 8.5 kg and ≤ 21 kg, at the time of Screening Visit 2, will be enrolled.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Written informed consent/assent obtained prior to any assessment performed
2. Symptomatic SMA diagnosis based on gene mutation analysis with bi-allelic *SMN1* mutations (deletion or point mutations) and any copy of *SMN2* gene.
3. Weight ≥ 8.5 kg and ≤ 21 kg at the time of Screening Visit 2
4. Naive to treatment or have discontinued an approved drug/therapy
5. Up-to date on recommended childhood vaccinations and RSV prophylaxis with palivizumab (also known as Synagis), per local standard of care

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

1. Previous OAV101 use or previous use of any AAV9 gene therapy
2. BMI < 3rd percentile based on WHO Child Growth Standard
3. Participant with history of aspiration pneumonia or signs of aspiration (e.g., coughing or sputtering of food) within 4 weeks prior to screening
4. Anti-AAV9 antibody titer > 1:50 as determined by ligand binding immunoassay at the time of screening
5. History of gene therapy, hematopoietic transplantation, or solid organ transplantation
6. Inability to take corticosteroids
7. Concomitant use of immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, or immunosuppressive therapy within 3 months prior to gene replacement therapy (e.g., cyclosporine, tacrolimus, methotrexate, rituximab cyclophosphamide, IV immunoglobulin)
8. Requiring invasive ventilation, tracheostomy or awake non-invasive ventilation (standard of care nocturnal BiPAP is not considered exclusionary)
9. Administration of vaccines 2 weeks prior to infusion of OAV101
10. Awake hypoxemia (O2 saturation <95%) or awake oxygen saturation level decrease between screening and dosing that is clinically significant, as per investigator judgment.
11. Clinically significant neurologic or neuromuscular conditions other than SMA as determined by the principal Investigator
12. Clinically significant abnormalities in laboratory test results at Screening as determined by the Investigator
13. Hepatic dysfunction (i.e. AST, ALT, bilirubin, GGT or GLDH, > ULN) at Screening (with the exception of isolated AST elevation: in the absence of other liver laboratory abnormalities, isolated AST elevation is not considered exclusionary)
14. Excluding SMA, any medically unstable condition considered clinically significant by the Investigator, including cardiomyopathy, hepatic dysfunction, kidney disorder, endocrine disorder, GI disorders, metabolic disorders, severe respiratory compromise and significant brain abnormalities at either Screening or Baseline that, in the opinion of the Investigator, would interfere with the overall interpretation of safety or efficacy of the study
15. Presence of a confirmed or suspected active infectious process from screening and up to dose administration
16. If previously treated with disease modifying therapy, participants are excluded if they received
    - less than 3 doses of nusinersen (Spinraza®)
    - nusinersen (Spinraza®) within 4 months prior to Screening
    - risdiplam (Evrysdi®) within 15 days prior to Screening (washout period of at least 5 half-lives before Screening)
17. Use of other investigational drugs within 5 half-lives of enrollment/initiation of study treatment (select as appropriate) within 30 days (e.g., small molecules) / or until the expected pharmacodynamic effect has returned to baseline (e.g., biologics), whichever is longer; or longer if required by local regulations.
18. History of hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes.

19. Documented any parental consanguinity.

6 Treatment

6.1 Study treatment

The biological product is a non-replicating recombinant AAV9 containing the cDNA of the human *SMN* gene under the control of the CMV enhancer/CB promoter. The AAV ITR has been modified to promote intramolecular annealing of the transgene, thus forming a double-stranded transgene ready for transcription. This modified ITR, termed a "self-complementary" (sc) ITR, has been shown to significantly increase the speed of which the transgene is transcribed, and the resulting protein is produced. The biological product, called OAV101, expresses the human *SMN* protein in transduced cells.

Table 6-1 Investigational Drug

	Investigational Product
Product Name	OAV101 (AVXS-101)
Unit Dose	1.1e14 vg/kg
Route of Administration	Intravenous infusion
Physical Description	OAV101 is a clear, colorless to faint white solution.

6.1.1 Investigational and control drugs

See Table 6-1.

6.1.2 Additional study treatments

No other treatment beyond investigational drug is included in this trial.

6.1.3 Supply of study treatment

US and non-EU countries where in-country depot is not required: IMP is manufactured and supplied by the Sponsor. The vials are packaged in a clinical carton (1 vial per carton) and shipped out of the Sponsor facility directly to sites. The IMP is stored at a temperature ≤ -60°C and shipped under dry ice. Once received at the clinical site, the material is placed in cold storage (2-8°C) to thaw.

EU countries: IMP is manufactured by the Sponsor and supplied to EU Contract Manufacturing Organization. The vials are packaged in a clinical carton (1 vial per carton) and shipped out of the EU CMO facility directly to the clinical sites. The IMP is stored at a temperature ≤ -60°C and shipped under dry ice. Once received at the clinical site, the material is placed in cold storage (2-8°C) to thaw.

Ex-US non-EU countries where in-country depot is required: IMP is manufactured by the Sponsor and supplied to in-country depot. The vials are packaged in a clinical carton (1 vial per carton) and shipped out of the in-country depot directly to the clinical sites. The IMP is stored at a temperature ≤ -60°C and shipped under dry ice. Once received at the clinical site, the material is placed in cold storage (2-8°C) to thaw.

6.1.4 Treatment arms/group

Single treatment arm OAV101 IV.

6.1.5 Treatment duration

OAV101 will be administered as a one-time IV infusion over approximately 60 minutes.

6.2 Other treatment(s)

In accordance to this protocol, all study participants will receive immunomodulatory therapy with prednisolone. Immunomodulatory therapy is intended to mitigate safety risks associated with immune response to the AAV9 capsid that may occur after administration of OAV101. Immune responses may lead to elevations in liver transaminases, elevations of Troponin I, or decreased platelet counts. Where feasible, the participant's vaccination schedule should be adjusted to accommodate concomitant corticosteroid administration prior to and following OAV101, specifically vaccinations should be withheld 2 weeks pre and 4 weeks post OAV101 administration. Prior to initiation of the immunomodulatory regimen and prior to administration of OAV101, the participant must be checked for symptoms of active infectious disease of any nature.

Starting 24 hours prior to infusion of OAV101 it is required to initiate an immunomodulatory regimen with corticosteroids following the schedule below.

Table 6-2 Pre and post-infusion corticosteroid use

Pre-infusion	24 hours prior to OAV101 infusion	Prednisolone orally 1 mg/kg/day or equivalent
Post-infusion	At least 30 days (including the day of OAV101 administration)	Prednisolone orally 1 mg/kg/day or equivalent
Tapering	Once liver function tests return to baseline or after Day 30 if no liver function test elevation observed	Decrease dose by 0.25 mg/kg per week

Continue prednisolone 1 mg/kg/day until liver function tests return to baseline. For participants that require steroid dosing longer than 60 days total (including the weaning period) consider hepatology and infectious diseases specialty evaluation to address risk of opportunistic infections and recommendations for infectious prophylaxis.

6.2.1 Concomitant therapy

The Investigator should instruct the participant and his/her parents/caregivers to notify the study site about any new medications he/she takes after the participant was enrolled into the study.

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) that are ongoing or administered after the participant was enrolled into the study must be recorded on the appropriate CRFs.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication (Section 5.2 and Section 6.2.2). If in doubt, the Investigator should contact the Novartis medical monitor before enrollment of a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

Participants are encouraged to follow all routinely scheduled immunizations, recommended by local health authorities and consistent with Section 6.2.2, throughout the study. Vaccinations that include palivizumab prophylaxis (also known as Synagis) to prevent RSV infections are also recommended in accordance with the guidance of local health authorities.

6.2.2 Prohibited medication

Except for concomitant medication allowed per protocol (see Section 6.2.1) and/or any non-excluded medications which may be required to treat AEs, no medication other than study treatment will be allowed from the date the informed consent/assent is signed until all of the study completion evaluations have been performed.

Concomitant use of any of the following medications are prohibited:

- Concomitant medication with the intent to treat SMA
- Any investigational medication other than OAV101
- Use of non-live vaccines 4 weeks after infusion of OAV101; unless required for treatment of adverse events.
- Live vaccines are prohibited while receiving corticosteroids
- The use of immunosuppressive therapies, including but not limited to, for example, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, IVIG, rituximab, and adalimumab; unless required for treatment of adverse events

Given the nature and profile of the treatment, i.e., gene therapy, there are no PK drug interactions expected.

The Investigator should instruct the participant/caregiver to notify the study site about any new treatments the participant takes after the start of study treatment. All prohibited medications and significant non-drug therapies administered after the participant starts study treatment must be recorded in the eCRF.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened, as a result of a screen failure. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent/assent form, the participant is assigned to the next sequential Participant No. available.

The Investigator or designated staff will contact the IRT and provide the requested identifying information to register the participant. Once assigned, the Participant No. must not be reused for any other participant and the Participant No. for that individual must not be changed unless the participant is re-screened.

If the participant fails to be randomized or start treatment for any reason, the reason will be entered into the appropriate eCRF page and IRT should be notified as soon as possible. Re-screening is allowed once for participants that were initially screen failures for any reason (Section 8.1.1). All eligibility criteria must be re-checked and met prior to enrollment of the participant into the study. A new participant No. should be assigned for all re-screened participants.

A new ICF/ assent will need to be signed if the investigator chooses to re-screen the participant after a participant has screen failed, and the participant will be assigned a new Participant No.

6.3.2 Treatment assignment, randomization

IRT will be used for this trial. This is an open-label trial and randomization numbers will not be used. At screening visit 1, the site will log into IRT and input the participant number from RAVE and participant's weight. The site will log into IRT at Screening Visit 2 and enter participant's weight. The depot will be notified of the participant's weight and quantity of kits will be selected to ship to site based on the participant's weight. Once kits are selected, IRT will be updated with medication numbers assigned for shipment. Once the site receives drug they will need to confirm shipment via IRT. Please see Pharmacy Manual for details regarding drug shipment confirmation. The Investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria.

6.4 Treatment blinding

This is an open-label trial.

6.5 Dose escalation and dose modification

Investigational or other study treatment dose adjustments and/or interruptions are not permitted. The IV dosage is determined by participant body weight with a nominal recommended dose of 1.1e14 vg/kg.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

OAV101 will be administered as a single IV injection. If dose is not fully completed the site personnel will need to reflect total volume administered as well as the date and time of administration in the CRF page.

6.6.2 Recommended treatment of adverse events

The Investigator will use his/her medical judgement in accordance with standard of care to treat adverse events. Medication and/or intervention used to medically manage AEs must be recorded on the appropriate CRF.

6.7 Preparation and dispensation

As per Section 4.7, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits,

delivery of prednisolone directly to a participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate). In the event the Investigator decides that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to supply the prednisolone even without performing an on-site visit, prednisolone will be dispatched from the site to the participant's home and remains under the accountability of the Investigator. Each shipment/provisioning will be approximately 2 months' supply. In this case, regular phone calls or virtual contacts per schedule of assessment (Table 8-1) will occur between the site and the participant for instructional purposes, safety monitoring, drug accountability, investigation of any adverse events, ensuring participants continue to benefit from treatment and discussion of the participant´s health status until the participants can resume visits at the study site.

Study drug preparation

Preparation of OAV101 will be done aseptically under sterile conditions at the site per Pharmacy manual and will be received ready for infusion at the bedside.

OAV101 will arrive as outlined in the Pharmacy Manual. The total vector genome dose will be calculated based on the participant's body weight; sites will receive a participant-specific dose for each participant enrolled.

The dose-delivery vessel will be delivered in the appropriate setting with immediate access to acute critical care management. The vessel will be delivered in accordance with the Pharmacy Manual.

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section.

Study drug administration

OAV101 infusion will be administered under sterile conditions in an appropriate inpatient setting (e.g., interventional suite, operating room, dedicated procedure room) with immediate access to acute critical care management. OAV101 will be delivered as a single treatment through a venous catheter inserted into a peripheral limb vein (arm or leg) at a dose of 1.1e14 vg/kg. OAV101 should be slowly infused over approximately 60 minutes, dependent upon volume required, utilizing an infusion set and pump in accordance with the Pharmacy Manual.

Following administration of gene replacement therapy, participants should return to an appropriate designated setting to ensure close monitoring of vital signs and AEs. Vital signs will be continuously monitored throughout the gene replacement therapy infusion. Participants should be maintained in an appropriate inpatient setting for 48 hours after the start of gene replacement therapy.

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the participant by contacting the IRT and obtaining the medication number(s).

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

OAV101 kits will be stored in a locked, limited access room under the responsibility of the Investigator or other authorized persons (e.g., pharmacists) in accordance with local regulations, policies, and procedures. Control of storage conditions, especially control of temperature (e.g., refrigerated/freezer storage) and information on in-use stability and instructions for handling prepared OAV101 should be managed in accordance with the Pharmacy Manual.

OAV101 will be supplied to each site for each individual study subject after confirmation of weight at Screening Visit 2. Instructions for preparation of dose are detailed in the Pharmacy Manual. The OAV101 dose will be administered via a syringe and should be delivered by the pharmacist or designated study staff member to the procedure room, and administered IV to the patient within 8 hours from preparation.

Any quality issue noticed with the receipt or use of OAV101 (e.g., deficiency in condition, appearance, pertaining to documentation, labeling, expiration date, etc.) should be promptly reported to the Sponsor in accordance with procedures outlined in the Pharmacy Manual.

Under no circumstances will the Investigator supply OAV101 to a third party, allow OAV101 to be used other than as directed by this clinical trial protocol, or dispose of OAV101 in any other manner.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

7 Informed consent procedures

Eligible participants may only be included in the study after IRB/IEC- approved informed consent has been provided by a legally acceptable representative(s) or parent of the participant (country specific regulations may apply).

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her understanding.

Informed consent (video), and assent (7-11 years), if applicable, must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

Novartis will provide to Investigators, in a separate document, a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the Investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about known adverse events associated with study drug can be found in the IB. This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the study drug that is identified between IB updates will be communicated as

appropriate, for example, via an Investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

1. Global Model Parent Legal Guardian ICF
    - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on coded data collected during this study
    - A subsection that requires a separate signature for the 'Optional Consent for Autopsy' to allow, in the event of the death of a patient, the investigator site to arrange an autopsy and for the details of the autopsy and the autopsy report to be shared with the Sponsor
    - In case Home Nursing is implemented during the COVID-19 pandemic, a separate Home Nursing consent document must be used in addition to the main ICF (in accordance to local regulations)
    - A subsection for 'Optional Video Recording' to confirm Developmental Motor Milestones
2. Global Model Child Assent Form

[redacted]

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

Participants might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

The study includes the option for the participant to have certain study procedures performed offsite by an off-site healthcare professional instead of at the study site, for which a separate signature is required if the participant agrees. It is required as part of this protocol that the Investigator presents this option to the participant, as permitted by national and local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

As per Section 4.7, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Health Authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists type and timing of all assessments. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or within the specified visit window. Missed or rescheduled visits should not lead to automatic discontinuation. Participants who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, the AE and concomitant medications recorded on the CRF.

As per Section 4.7, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the Investigator as the situation dictates. If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g., tele consult) or visits by site staff/ home nursing staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

Table 8-1 Assessment Schedule

Period	Screening		Baseline	Treatment			Follow up Visits										
Visit Name	**Screening Visit 1**	**Screening Visit 2**	**Baseline**	**Day 1**	**Day 2**	**Day 3**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 13**	**Week 26**	**Week 39**	**Week 52 / EOS[1]**
Days	**-45 -0 +5**	**-15 ±2**	**-1**	**1**	**2 to 2**	**3 to 3**	**8 ±2**	**15 ±2**	**22 ±2**	**29 ±2**	**43 ±5**	**57 ±5**	**71 ±5**	**92 ±14**	**183 ±14**	**274 ±14**	**365 ±21**
Informed consent	X																
Inclusion / Exclusion criteria	X	X	X														
Height and Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination[2]	S		S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Neurological Examination	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																	
SMA Medical History	X																
Medical History	X	X															
Demography	X																
Hematology[3]	X		X		X[4]		X	X	X	X[5]	X	X	X[5]	X	X	X	X
Chemistry/Liver Function Testing	X		X				X	X	X	X	X	X	X	X	X	X	X
Coagulation panel		X															
Troponin-I		X					X			X		X		X	X		X
Virus Serology[6]	X																

Period	Screening		Baseline	Treatment			Follow up Visits										
Visit Name	Screening Visit 1	Screening Visit 2	Baseline	Day 1	Day 2	Day 3	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 10	Week 13	Week 26	Week 39	Week 52 / EOS[1]
Days	-45 -0 +5	-15 ±2	-1	1	2 to 2	3 to 3	8 ±2	15 ±2	22 ±2	29 ±2	43 ±5	57 ±5	71 ±5	92 ±14	183 ±14	274 ±14	365 ±21
[redacted]																	
DNA		X															
Urinalysis			X			X											
Electrocardiogram (ECG)	X		X				X			X		X		X	X		X
Echocardiogram	X						X			X		X		X	X		X
Prophylactic Prednisolone			X	X	X	X	X	X	X	X	X	X					
OAV101 Infusion				X													
IRT contact	X	X		X													X
HFMSE[9,10]		X								X				X	X	X	X
RULM[9,10]		X								X				X	X	X	X
Bayley Scales (Bayley-III) and WHO-MGRS Developmental Milestone Checklist[10]		X								X				X	X	X	X

Period	Screening		Baseline	Treatment			Follow up Visits										
Visit Name	Screening Visit 1	Screening Visit 2	Baseline	Day 1	Day 2	Day 3	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 10	Week 13	Week 26	Week 39	Week 52 / EOS[1]
Days	-45 -0 +5	-15 ±2	-1	1	2 to 2	3 to 3	8 ±2	15 ±2	22 ±2	29 ±2	43 ±5	57 ±5	71 ±5	92 ±14	183 ±14	274 ±14	365 ±21
[redacted]																	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study completion information																	X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[1] If discontinuation, all efforts should be made to complete the EOS assessments prior to study discontinuation.
[2] S = assessment to be recorded in source documentation only
[3] complete white blood count with differential
[4] Hematology assessment at Day 2 should be performed locally before discharge of the patients; further, platelets should be closely monitored following the first week after infusion.
[5] Hematology assessments at Week 4 and Week 10 are only applicable for Germany
[6] HIV antibody, Hepatitis C antibody, Hepatitis B surface antigen (HBsAG)
[redacted]
[9] HFMSE and RULM will not be administered until patient reaches 24 months of age
[10] physical assessments may occur over the span of more than 1 day within the visit window, but must not exceed 4 days
[redacted]

8.1 Screening

8.1.1 Information to be collected on screening failures

Participants who sign an informed consent form and subsequently found to be ineligible prior to enrollment will be considered a screen failure. The reason for screen failure should be entered on the applicable eCRF. The following eCRF pages must also be completed for screen failure participants if applicable and available:

- Informed consent
- Demography
- Inclusion/Exclusion Criteria
- Diagnosis_SMA
- Assessments
- Withdrawal of consent
- Rescreen
- Anti-AAV9 Antibody Testing (Blood)
- 5q SMA Genetic Testing (SMN1 and SMN2)
- AE page if seriousness criteria is Death

In addition, anti-AAV9 Antibody testing results and 5q SMA Genetic Testing (SMN1 and SMN2) will be entered into the appropriate Novartis database.

No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see SAE section for reporting details, Section 10.1.2) or protocol-related adverse event.

The Screening assessments will be performed from the time of the ICF signature.

The exact sequence of Screening assessments is at the discretion of the Site. It is recommended to obtain the anti-AAV9 antibody screening results first.

For participants who fail eligibility during the screening process for a temporary condition (e.g. viral illness, concomitant medication, or laboratory values, etc.) respective eligibility assessments can be repeated within the screening window up to two times; however, each case must be discussed and agreed with the Sponsor. Repeated assessments must be documented and eCRFs need to be completed for any additional visit.

Participants who fail eligibility for a temporary condition exceeding the screening window may be re-screened once. Re-screened participants will need to be re-consented and a new Participant number will be assigned. Re-screening tests should be repeated as per inclusion/exclusion requirements and re-screening should be documented in medical records.

Participants who fail upper weight eligibility at Screening Visit 2 cannot be re-tested or re-screened.

8.2 Participant demographics/other baseline characteristics

8.2.1 Demographics/medical history

Demographics (including age, sex)/medical history information will be collected at screening and captured in the eCRF.

Any relevant medical history, including relevant hospitalizations from time of birth /current medical conditions (until date of signature of informed consent) will be recorded in the eCRF. Where possible, the diagnosis and not symptoms should be recorded.

All prescription medications, over-the-counter drugs and significant non-drug therapies prior to the start of the study must be documented. See the Section 6.2.1 Concomitant Therapy for further details on what information must be recorded on the appropriate page of the eCRF.

8.2.2 SMA medical history

Familial history of SMA including affected siblings or parent carriers will be collected. Any relevant SMA medical history, including SMA type and number of *SMN2* gene copies (if available), will be recorded in the eCRF.

8.2.3 Physical examination

Physical examinations will be conducted by the Investigator or designee as specified in the Table 8-1. The Day 1 physical examination will be performed prior to the start of gene replacement therapy infusion. Physical examinations include a review of the following systems: (HEENT), lungs/thorax, cardiovascular, abdomen, musculoskeletal, neurologic, dermatologic, lymphatic, and genitourinary.

Physical examination data will be captured on source documentation.

8.2.4 Neurological examination

Neurological examinations will be conducted by the Investigator or designee as specified in the Table 8-1. Specifically, the neurological exam should include detailed, age-appropriate sensory testing (such as examination of proprioceptive, vibratory, tactile and pain sensation) at each visit. Any clinically significant sensory abnormal finding will be recorded in eCRF.

Further clinical evaluation of sensory abnormalities will include nerve conduction studies per local standard of care including but not limited to sural sensory nerve action potential (SNAP).

8.2.6 Virus serology

The administration of an AAV vector has the risk of causing immune-mediated hepatotoxicity. For participants who have HIV or positive serology for hepatitis B or C, administration of the AAV vector may represent an unreasonable risk; therefore negative serology testing must be confirmed at screening, prior to treatment. These samples will be collected in accordance with the Table 8-1 and shipped in accordance with the laboratory manual provided by the central laboratory.

8.3 Efficacy

The efficacy assessments described below have been selected in order to evaluate the effect of OAV101 on SMA.

8.3.1 Hammersmith Functional Motor Scale-Expanded (HFMSE)

See Section 8.5.1.1 for details.

8.3.2 Revised Upper Limb Module (RULM)

See Section 8.5.1.2 for details.

8.3.3 Developmental milestone checklist

See Section 8.5.1.3 for details.

8.3.4 Video evidence

Video evidence is optional. Parent(s)/legal guardian(s) may provide home videos at any time during the study that demonstrate achievement or maintenance of Developmental Motor Milestone in an effort to confirm compelling, demonstrable, documented evidence of efficacy.

Completion of the Developmental Milestone Checklist for home videos uploaded is required to document achievement of developmental motor milestones between visits. The Developmental Milestone Checklist will contain the date of home video recording.

Novartis will provide a secure process to upload, transfer and store videos through a contracted third-party vendor that will compile as per the sponsor requirements. A secure, encrypted transfer and storage solution will be provided to properly protect the identities of the patient and caregivers on the videos, which may be shared with regulatory agencies, the medical community, and/or in appropriate venues to discuss the results of this clinical trial. Any videos received will be treated as confidential data and will be either the sole property of Novartis or will be permanently licensed to Novartis to use and disclose.

8.3.6 Appropriateness of efficacy assessments

Efficacy assessments for developmental milestones and motor assessments are standard for this indication/participant population.

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed (Table 8-1).

Safety parameters include demographics/medical history, physical and neurological examinations, vital signs, height and weight measurements, 12-lead ECGs, echocardiograms, laboratory assessments, and AE monitoring.

For details on AE collection and reporting, refer to Section 10.1.

As per Section 4.7, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur based on the Table 8-1 assessment schedule for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

If participants cannot visit the site for safety lab assessments through central labs, local lab collection may be used and results will be entered in the eCRF.

8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to Investigators in the laboratory manual.

Safety samples that can be collected remotely will be collected and analyzed in line with the study laboratory manual. Where samples are collected and analyzed at a local laboratory instead of the central laboratory, Novartis will ensure the results reported are equivalent to central laboratory collection and analysis.

If participants cannot visit the site for safety lab assessments conducted through central labs, local lab collection may be used during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits.

If participants cannot visit the site for protocol specified safety lab assessments, an alternative lab (local) collection site may be used.

8.4.1.1 Hematology

Hematology analysis will include a complete blood count with differential and platelet count. Samples will be collected and shipped in accordance with the laboratory manual provided by the central laboratory. Blood samples for hematology analysis will be collected as specified in the Table 8-1.

Hematology analysis will include the following:

- Hematocrit
- Hemoglobin
- MCH
- MCHC
- MCV
- Platelets
- Red blood cells
- White blood cells
- Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands)

To monitor platelet counts, hematology analyses required during in-patient dosing, as determined by the Investigator, and on Day 2 prior to discharge, will be performed as per investigational site standard procedures at the local laboratory. Investigators will receive hematology results from all other study visits from the central laboratory. Further, platelet counts should be closely monitored in the week following infusion and on a regular basis afterwards.

In the event that clinically significant and/or moderate or severe thrombocytopenia and anemia are noted, further evaluation to diagnose Thrombotic Microangiopathy (TMA) should be conducted in accordance of standard of care. If a clinical diagnosis of TMA is made, a complete complement panel should be obtained per standard of care.

8.4.1.2 Coagulation panel

Coagulation testing including prothrombin time (PT) and International Normalized Ratio (INR), and activated partial thromboplastin time (aPTT) will be performed prior to OAV101 dosing (Table 8-1).

8.4.1.3 Blood chemistry

Samples will be collected and shipped in accordance with the laboratory manual provided by the central laboratory. Blood samples for chemistry analysis will be collected as specified in the Schedule of Assessments (Table 8-1).

Chemistry analysis will include the following:

- Alkaline phosphatase
- ALT
- AST
- GGT
- LDH
- G-LDH
- Bicarbonate
- Calcium
- Phosphorus
- Chloride
- Sodium
- Potassium
- Creatinine
- Creatine kinase
- Direct Bilirubin
- Indirect Bilirubin
- Total Bilirubin
- BUN or Urea
- Glucose

Troponin I will be collected as specified in the Schedule of Assessments (Table 8-1) as applicable.

Investigators will receive chemistry results from all trial visits from the central laboratory.

If liver aminotransferase elevations occur, the process outlined in Section 10.2.1 should be followed.

8.4.1.4 Urinalysis

Urine samples will be collected in accordance with the laboratory manual provided by the central laboratory at study visits in accord with the Schedule of Assessments (Table 8-1).

8.4.2 Electrocardiogram (ECG)

8.4.2.1 12-Lead electrocardiogram

A 12-lead ECG will be performed at times indicated in the Schedule of Assessments.

In the case of a series of assessments, ECG should be first assessment obtained while participant is at rest. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling.

The Fridericia QT correction formula (QTcF) must be used for clinical decisions.

Unless auto-calculated by the ECG machine, the Investigator must calculate QTcF at the Screening and/or Baseline visit(s) (as applicable) to assess eligibility according to the following formula:

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

Triplicate 12-lead ECGs are to be collected with ECG machines available at the site. Each ECG tracing must be labeled with study number, participant initials, participant number, date and time, and filed in the study site source documents. Investigator should document clinical evaluation in source.

The ECG will be interpreted locally by a pediatric cardiologist or designee for immediate safety evaluation. The ECG tracings or ECG machine data will also be collected for centralized review. In the event that a clinically significant ECG abnormality is identified at the site (e.g., severe arrhythmia, conduction abnormality of QTcF > 500 ms), a copy of the assessment is sent to the central ECG laboratory for expedited review and the ECG is repeated to confirm the diagnosis. If the participant is hemodynamically compromised, the investigator or a medically qualified person must initiate appropriate safety procedures without delay.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. All ECGs, including unscheduled safety ECGs with clinically relevant findings collected during the study need to be transmitted to the central ECG laboratory for review.

Clinically significant ECG findings at baseline must be discussed with Novartis before administration of study treatment.

Clinically significant abnormalities must be recorded on the relevant section of the medical history/Current medical conditions/AE eCRF as appropriate.

8.4.2.2 Echocardiogram

A standard transthoracic ECHO will be performed at times indicated in the Schedule of Assessments (Table 8-1); these will be interpreted locally by a cardiologist or a designee for immediate safety evaluation. The ECHOs will also be collected for centralized review by a cardiologist. The Novartis physician or designee will be notified of any safety concerns from the centralized review.

8.4.3 Vital signs

Vital sign parameters include blood pressure, respiratory rate, pulse, temperature, and oxygen saturation level. Vital signs will be obtained as specified in the Table 8-1. On Day 1, vital signs will be recorded pre-dose and monitored during and after the infusion.

Height and weight will be measured (supine or standing) at each study visit (Table 8-1). Screening weight shall be obtained at screening visit 2. On Day 1, weight and height will be measured pre-dose.

8.4.4 Other safety evaluations

Sural sensory nerve action potential (sural SNAP) is a conduction study commonly used to evaluate suspected peripheral neuropathies and will be performed in case sensory abnormalities, to complement neurologic examination (Section 8.2.4). Results will be read locally and must be captured in eCRF and as adverse event when criteria met per Section 8.2.4. Central review to ensure consistent implementation and quality control of the neurophysiology data will be performed by an external expert. For details on SNAP assessments and quality checks, the sensory nerve conduction studies manual should be consulted.

8.4.5 Appropriateness of safety measurements

Safety assessments such as AEs, clinical laboratory assessments, ECGs, and vital signs are standard for this indication/participant population.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

As per Section 4.7, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, COA data (e.g., neuromuscular module and multi-dimensional fatigue scale) may be collected remotely (e.g., web portal, telephone interviews) depending on local regulations, technical capabilities, and following any applicable training in the required process.

8.5.1.1 Hammersmith Functional Motor Scale-Expanded (HFMSE)

HFMSE was devised for use in children with SMA Type 2 and Type 3 to give objective information on motor ability and clinical progression (Glanzman et al 2011).

The HFMSE (2019 edition) assessment will be administered by the qualified site clinical evaluator (e.g., licensed physical or occupational therapist, or national equivalent) in accordance with the Schedule of Assessments (Table 8-1) for all participants ≥ 24 months of age. Participants < 24 months of age at time of visit will begin having HFMSE assessments as such time that 24 months of age is reached. The HFMSE is a short SMA-specific 33-item questionnaire that is easily administered by trained clinical evaluators. It requires minimal equipment, and is designed to factor in patient fatigue. 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 level of ability.

8.5.1.2 Revised Upper Limb Module (RULM)

RULM is a validated, SMA specific assessment that measures motor performance in the upper limbs from childhood through adulthood in ambulatory and non-ambulatory individuals with SMA, and weaker individuals who have a floor effect or very low score on the Hammersmith Functional Motor Scale (HFMS) (Mazzone et al 2017). The RULM has a total 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. The test is performed unilaterally using the limb preferred by the participant. The RULM will be administered by a site trained clinical evaluator (eg, licensed physical or occupational therapist, or national equivalent) in accordance with the Schedule of Assessments for all participants ≥ 24 months of age. Participants < 24 months of age at time of visit will begin having RULM assessments as such time that 24 months of age is reached.

For participants between 24-30 months of age the following two test items will not be administered and a Can Not Test (CNT) will be entered due to developmental limitations: (C)- tracing a path and (H)- tearing a paper. These items will be added into the assessment at ≥30 months of age.

8.5.1.3 Developmental milestone checklist

Developmental motor milestones will be assessed using relevant definition obtained from the World Health Organization Multicentre Growth Reference Study (WHO-MGRS) and Bayley Scales of Infant and Toddler Development - Third Ed (Bayley-III).

The Developmental Milestone Checklist will be completed by the qualified and trained site clinical evaluator (e.g., licensed physical or occupational therapist, or national equivalent) for all participants according to the Schedule of Assessments (Table 8-1).

Table 8-2 Developmental Milestone Checklist and Performance Criteria

Current Status Achieved	Developmental Motor Milestones: Bayley Scales of Infant and Toddler Development® Third edition (Bayley 2006) / WHO MGRS (2006)
YES/NO	Holds head erect for at least 3 seconds without support (Bayley GM #4)
YES/NO	Sits with slight support: 30 seconds (Bayley GM #19))
YES/NO	Sitting without support (WHO MGRS)
YES/NO	Sits without support: 30 seconds (Bayley GM #26)
YES/NO	Hands-and-knees crawling (WHO MGRS)
YES/NO	Pulls to stand (Bayley GM #35)
YES/NO	Standing with assistance (WHO MGRS)
YES/NO	Walking with assistance (WHO MGRS)
YES/NO	Standing alone (WHO MGRS)
YES/NO	Walking alone (WHO MGRS)
Developmental Milestone	**Performance Criteria**
Head control (Bayley, Gross Motor Item #4)	Child holds head erect for at least 3 seconds without support.
Sits with support (Bayley, Gross Motor Item #19)	Child sits with slight support for at least 30 seconds. Child may lose balance once or twice but is able to self-right (with your slight support).
Sitting without support (WHO MGRS)	Child sits up straight with the head erect for at least 10 seconds. Child does not use arms or hands to balance body or support position.

Sits without support: 30 seconds (Bayley, Gross Motor Item #26)	Child sits alone without support for at least 30 seconds. Child may lose balance once or twice but is able to self-right (does not fall over).
Hands-and-knees crawling (WHO MGRS)	Child alternately moves forward or backward on hands and knees. The stomach does not touch the supporting surface. There are continuous and consecutive movements, at least 3 in a row.
Pulls to Stand (Bayley, Gross Motor Item #35)	Child raises self to standing position using chair or other convenient object for support.
Standing with assistance (WHO MGRS)	Child stands in upright position on both feet, holding onto a stable object (e.g., furniture) with both hands without leaning on it. The body does not touch the stable object, and the legs support most of the body weight. Child thus stands with assistance for at least 10 seconds.
Walking with assistance (WHO MGRS)	Child is in upright position with the back straight. Child makes sideways or forward steps by holding onto a stable object (e.g., furniture) with 1 or both hands. One leg moves forward while the other supports part of the body weight. Child takes at least 5 steps in this manner.
Standing alone (WHO MGRS)	Child stands in upright position on both feet (not on the toes) with the back straight. The legs support 100% of the child's weight. There is no contact with a person or object. Child stands alone for at least 10 seconds.
Walking alone (WHO MGRS)	Child takes at least 5 steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object.

[redacted]

[redacted]

8.5.5 Pharmacokinetics

Not applicable.

[redacted]

[redacted]

DNA samples for genetic confirmation of SMA (mandatory)

The study includes a mandatory genetic research component.

Although participants are selected based on diagnostic testing results, it is possible that the diagnostic testing results needs to be confirmed during study process. The DNA sample collected may be used for genetic confirmation of SMA diagnosis and also be used for exon 7 modifier testing (current planned SMA genetic testing may not be able to detect *SMN1* point mutation).

The focus of the analysis is open and not pre-defined.

[redacted]

Laboratory manuals will be provided with detailed information on sample collection, handling, and shipment.

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

Since this is a single dose study, discontinuation of study treatment is not applicable.

Because the study treatment is a single administration gene therapy, stopping or reversing the study treatment is not possible. Participants who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see 'Withdrawal of Informed Consent' section). Where possible, they should return for the Week 52/EOS assessments indicated in the Assessment Schedule (Table 8-1). If they fail to return for these assessments for unknown reasons, every effort (e.g., telephone, e-mail, letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

In the event of study discontinuation, the EOS study should be completed. At a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments/medications
- AEs, including SAEs

9.1.1.1 Replacement policy

No participant replacement will be done for this study.

9.1.2 Withdrawal of informed consent

Participants may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a participant:

- Does not want to participate in the study anymore,

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

In this situation, the Investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw his/her consent and record this information.

Where consent to the use of personal and coded data is not required, participant therefore cannot withdraw consent. They still retain the right to object to the further use of personal data.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the EOS assessments prior to study discontinuation. A final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table.

9.1.3 Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the Investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from DMC after review of safety and efficacy data
- Discontinuation of study drug development by Novartis
- Regulatory Authority recommendation

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a prematurely withdrawn participant. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The Investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their Study Completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The Investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

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.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2*):*

1. Severity grade
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.

All adverse events must be treated appropriately.

6. Its outcome (i.e. recovery status or whether it was fatal)

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued until end of study.

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent (e.g., continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease.

On the basis of important identified and potential risks associated with OAV101, AESIs are determined and categorized as follows. These will be summarized based on Standardized MedDRA terminology:

- Hepatotoxicity
- Thrombocytopenia
- Cardiac adverse events
- Dorsal root ganglia toxicity
- Thrombotic microangiopathy

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the International Conference on Harmonisation ICH-E2D Guidelines 2003).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect

- requires in-patient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the participant's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the International Conference on Harmonisation ICH-E2D Guidelines 2003).

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours obtaining knowledge of events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each site. Information about all SAEs is collected and recorded on the electronic SAE form with paper backup; all applicable sections of the form must be completed in order to provide a clinically thorough report.

SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately without undue delay, but under no circumstances later than within 24 hours of the Investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the investigator for health authority

reporting. Novartis may need to issue an Investigator Notification to inform all Investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Clinical Trial Regulation 536/2014 (if submitted under EU CTR or) Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries. Any SAEs experienced after the 30 day period after the last study visit should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of OAV101, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Table 16-1 in Appendix 16.1 for complete definition and management of liver laboratory abnormalities.

Table 16-1 should be followed up by the Investigator or designated personnel at the trial site, as summarized below.

If elevated, repeated liver chemistry tests (i.e. ALT, AST, TBIL, Fractionated BIL, INR, and GLDH) will be performed within 48-72 hours to confirm elevation. If results will not be available from the central laboratory, then repeated testing should be performed at a local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate eCRF page. If liver function tests are elevated, follow-up requirements include (refer to Table 16-2 and Table 16-3):

- Hospitalization of the participant, if appropriate
- Causality assessment of the liver event
- Thorough investigation and follow-up of the liver event, which may include, based on Investigator's discretion: serology tests, laboratory tests for other causes of hepatitis, including viral hepatitis, imaging such as ultrasound/Fibroscan, and pathology assessments.
- Obtaining a more detailed history of signs and symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use, including nonprescription medications (e.g. acetaminophen); and herbal and dietary supplement preparations
- Exclusion of underlying liver disease
- Considering pediatric gastroenterology or hepatology consultation

All follow-up information and procedures performed must be recorded as appropriate in the CRF.

10.2.2 Post-mortem data collection

In the event of a fatal outcome, and if parental consent is obtained, autopsy should be performed when possible, for any participant who receives gene replacement therapy. The autopsy will be performed by the clinical site local pathologist, hospital, or other applicable location. Autopsy should be performed per local standard of care and local regulations, and with particular attention to CNS (e.g., DRG), liver, and cardiac examination.

Declining autopsy will not prevent patients from participating in the trial.

10.2.3 Data Monitoring Committee

This study will include a DMC which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will assess at defined intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify, or terminate a trial.

Specific details regarding composition, responsibilities, data monitoring, and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC.

11 Data Collection and Database management

11.1 Data collection

Designated Investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the Investigator staff.

The Investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the Investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated Investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the ATC classification system. Medical history/current medical conditions and adverse events will be coded using the MedDRA terminology.

Dates of screenings, screen failures, treatment and study completion, as well as drug confirmation will be tracked using an IRT. The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. electronic CRFs (eCRFs)) with the Investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by the CRAs.

The Investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the participant's file. The Investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

12.1 Analysis sets

The FAS and Safety Set both comprises all participants that received any study drug.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by weight bracket (≥ 8.5-13 kg, > 13-17 kg, > 17-21 kg) and overall for the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term by weight bracket and overall.

12.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of administration in minutes will be summarized by means of descriptive statistics using the safety set.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the ATC classification system.

12.4 Analysis of the primary endpoint(s)/estimand(s)

12.4.1 Definition of primary endpoint(s)

The primary endpoints include:

1. Incidence and severity of treatment emergent AEs and SAEs
2. Incidence of important identified and important potential risks
3. Change from baseline in vital signs, clinical laboratory, and procedure (e.g. ECG, echocardiogram) results

12.4.2 Statistical model, hypothesis, and method of analysis

Incidence and severity for treatment emergent AEs and SAEs as well as important identified and important potential risks will be summarized by weight bracket and overall in the safety set. The number and proportion of participants reporting a treatment emergent AE or SAE will be reported. Summaries will also be provided by MedDRA System Organ Class and Preferred Term.

Changes from baseline in vital signs and clinical laboratory results will be summarized descriptively by weight bracket and overall in the safety set. Mean, standard deviation, median, minimum, and maximum will be presented. For each applicable timepoint, only participants with a baseline and a measurement for that timepoint will be included in the summary.

No hypothesis testing will be performed.

12.4.3 Sensitivity analyses for primary endpoint/estimand

Given the descriptive nature of the summary of primary safety endpoints, no sensitivity analysis is planned.

12.4.4 Supplementary analysis

No supplementary analysis is planned.

12.4.5 Supportive analyses

No supportive analysis is planned as the analysis by weight bracket is already included in the primary analysis.

12.5 Analysis of secondary endpoints/estimands

The secondary endpoints include:

1. Changes from baseline in HFMSE and RULM

2. Percent of participants achieving development motor milestones according to the WHO-Multicentre Growth Reference Study (WHO-MGRS) and Bayley Scale of Infant and Toddler Development - Third Ed (Bayley-III) criteria

These endpoints will be presented by weight bracket and overall.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

For secondary endpoints, changes from baseline in HFMSE and RULM will be summarized descriptively; in addition, mixed models with repeated measurement will be fitted that include the change from baseline as the dependent variable, and fixed effects of weight bracket, visit, and their interaction. The least squares (LS) means and 95% 2-sided confidence intervals will be reported for each scheduled visit. The number and proportion of participants achieving each WHO-MGRS & Bayley Scale of Infant and Toddler Development developmental motor milestone will be presented. Summaries will be presented by weight bracket as well as overall.

12.5.2 Safety endpoints

Summary of adverse events, vital signs, and clinical laboratory results are described in Section 12.4. ECG and echocardiogram results will be summarized descriptively by weight bracket and overall.

12.7 Interim analyses

An interim analysis may be performed once the last participant reaches the 6-month time point, and will include all available data up until that data cut-off. The interim analysis is intended to provide an early safety readout from the study. No study design change or adaptation will be implemented based on the outcome of the interim analysis.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

The size of approximately 24 participants is considered reasonable to provide descriptive safety information across 3 weight brackets ≥ 8.5 kg and ≤ 21 kg. A sample size of approximately 24-30 participants will provide 90% probability to observe at least one event if the underlying incidence of the event is 9%.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations

(including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the Investigator and IRB/IEC

Before initiating a trial, the Investigator/institution must obtain approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the Investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last participant last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g., clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial Investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust QMS that includes all activities involved in quality assurance and quality control, to ensure compliance with written SOPs as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of Investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an Investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information,

observation would be incidentally collected, the Investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

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16 Appendices

16.1 Appendix

Appendix 1: Clinically notable laboratory values and vital signs

Appendix 2: Liver monitoring guidelines

Appendix 3: Performance criteria for Bayley scales infant and toddler development (version III) developmental milestones

Appendix 4. Performance criteria for World Health Organization (WHO) developmental milestones

16.1.1 Clinically notable laboratory values and vital signs

Potentially clinically relevant laboratory abnormalities

Age-appropriate, normal laboratory values and clinical measurements should be used in pediatric population. Laboratory tests are commonly interpreted in relation to established reference intervals. These limits serve to differentiate between normal and pathological findings, and to gauge the severity of any abnormal increases or decreases. As far as laboratory parameters are known to characteristically vary with age, pediatric test results are usually interpreted in relation to these physiological dynamics. Reference intervals for pediatric patients have been calculated by partitioning data from a healthy reference population into age groups, so that the corresponding subset-specific percentiles would form step functions of age (Hirschmann et al 2017).

Vital signs

Within vital signs data, height and weight are commonly collected along with heart rate, respiratory rate, and blood pressure. The exam and vital sign data can be interpreted only with a thorough understanding of normal values. In pediatrics, normal respiratory rate, heart rate, and blood pressure have age-specific norms (Flynn et al 2017, Fleming et al 2011).

16.1.2 Liver monitoring guidelines

Table 16-1 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers For ALT and total bilirubin normal at baseline:	ALT >3 × ULN Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome) Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and Total bilirubin > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) Any clinical event of jaundice (or equivalent term) Any adverse event potentially indicative of a liver toxicity

Table 16-2 Follow up requirements for liver laboratory triggers - ALT, AST, TBL

ALT	**TBL**	**Liver Symptoms**	**Action**
ALT increase without bilirubin increase:			

ALT	TBL	Liver Symptoms	Action
ALT > 3 x ULN	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	● Review compliance with immunomodulatory therapy (Protocol Section 6.2) ● Measure ALT, AST, TBIL,Fractionated BIL, INR, and GLDH in 48-72 hours. ● Follow-up for symptoms.
ALT > 5 x ULN	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	● Review compliance with immunomodulatory therapy (ProtocolSection 6.2) ● Measure ALT, AST, TBIL, Fractionated BIL, INR, albumin, CK, and GLDH in 48-72 hours. ● Follow-up for symptoms. ● Initiate close monitoring (hospitalization when appropriate) and workup for competing etiologies[a] ● Exclude underlying liver disease ● Detailed history of concomitant medications (e.g acetaminophen) ● Consult pediatric Gastroenterologist[b]
ALT increase with bilirubin increase:			
ALT > 3 x ULN	TBL > 2 x ULN (or INR > 1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	
ALT > 3 x ULN	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	

[a] Work-up for competing etiologies may include (but not limited to) viral Hepatitis Panel (IgM anti-HAV; HBsAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA), Viral panel (CMV, EBV, HSV), autoimmune hepatitis (ANA, ASMA titers)

[b]Consider appropriate imaging and liver biopsy in consultation with Pediatric Gastroenterologist

Table 16-3 Follow up requirements for liver laboratory triggers - isolated hyperbilirubinemia

Criteria	*Actions required*	*Follow-up monitoring*
Total Bilirubin (isolated)		
>1.5 – 3.0 ULN	● Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)	● Repeat LFT within 48-72 hours ● Hospitalize if clinically appropriate ● Establish causality ● Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 x ULN	● Hospitalize the participant ● Establish causality ● Record the AE and contributing factors(e.g. conmeds, med hx, lab)in the appropriate CRF	ALT, AST, total bilirubin, Alb, PT/INR, until resolution (frequency at investigator discretion)

Criteria	*Actions required*	*Follow-up monitoring*
Total Bilirubin (isolated)		
Any AE potentially indicative of a liver toxicity	● Hospitalization if clinically appropriate ● Establish causality ● Record the AE and contributing factors(e.g., conmeds, med hx, lab)in the appropriate CRF	Investigator discretion

Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, pediatric gastroenterologist or hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

16.1.3 Performance criteria For Bayley scales infant and toddler developmental motor milestones (Bayley-III)

Developmental Milestone	Performance Criteria
Head Control – Gross Motor Subtest Item #4	Child holds head erect for at least 3 seconds without support
Rolls from Back to Sides – Gross Motor Subtest Item #20	Child turns from back to both right and left sides
Sits Without Support – Gross Motor Subtest Item #26	Child sits alone without support for at least 30 seconds
Stands With Assistance – Gross Motor Subtest Item #33	Child supports own weight for at least 2 seconds
Crawls – Gross Motor Subtest Item #34	Child makes forward progress of at least 5 feet by crawling on hands and knees
Pulls to Stand – Gross Motor Subtest Item #35	Child raises self to standing position using chair or other convenient object for support
Walks With Assistance – Gross Motor Subtest Item #37	Child walks by making coordinated, alternated stepping movements
Stands Alone – Gross Motor Subtest Item #40	Child stands alone for at least 3 seconds after you release his or her hands
Walks Alone – Gross Motor Subtest Item #42	Child takes at least 3 steps without support, even if gait is stiff-legged and wobbly

16.1.4 Performance criteria For World Health Organization (WHO) developmental motor milestones

Gross Motor Milestone	Performance Criteria
Sitting without support	Child sits up straight with the head erect for at least 10 seconds. Child does not use arms or hands to balance body or support position.
Hands-and-knees crawling	Child alternately moves forward or backward on hands and knees. The stomach does not touch the supporting surface. There are continuous and consecutive movements, at least 3 in a row.
Standing with assistance	Child stands in upright position on both feet, holding onto a stable object (e.g., furniture) with both hands without leaning on it. The body does not touch the stable object, and the legs support most of the body weight. Child thus stands with assistance for at least 10 seconds.

Walking with assistance	Child is in upright position with the back straight. Child makes sideways or forward steps by holding onto a stable object (e.g., furniture) with 1 or both hands. One leg moves forward while the other supports part of the body weight. Child takes at least 5 steps in this manner.
Standing alone	Child stands in upright position on both feet (not on the toes) with the back straight. The legs support 100% of the child's weight. There is no contact with a person or object. Child stands alone for at least 10 seconds.
Walking alone	Child takes at least 5 steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object.

WHO = World Health Organization

Source: World Health Organization Multicentre Growth Reference Trial Group (WHO 2006)