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COAV101A1IC01 / NCT05073133

Clinical Trial Protocol

Amendment 1

A Phase IV Open-label, single-arm, single-dose, multicenter study to evaluate the saFEty, toLerability and efflcacy of gene replacement therapy with intravenousOAV101(AVXS101) in pediatric patients from Latin America with spinal muscular atrophy (SMA) – OFELIA

Document type: Clinical Trial Protocol
Version number: 1.0
Clinical Trial Phase: IV
Release date: 24/Mar/2022

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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
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BiPAP	Bi-Level Positive Airway Pressure
BMI	Body Mass Index
CB	Chicken-β-Actin-Hybrid
cDNA	Complementary Deoxyribonucleic Acid
CFR	Code of Federal Regulations
CK-MB	Creatinine Kinase-MB
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
FEES	Flexible Endoscopic Evaluation of Swallowing
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
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
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
MAP	Managed Access Program
MedDRA	Medical dictionary for regulatory activities
[redacted]	[redacted]
mg	milligram(s)
[redacted]	[redacted]
NfL	Neurofilament light chain
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PRO	Patient Reported Outcomes
PT	Preferred Term
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
RSV	Respiratory Syncytial Virus
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)
SoC	System organ Class
SoA	Schedule of Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction

TEAE	Thromboembolic Adverse Events
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

Amendment Summary of Changes

It is listed below the summary of changes of amendment 1

- Numbering correction in the Protocol summary section exclusion criteria
- Removal of Canada as a participant country
- Adjustment of project title considering the removal of Canada
- [redacted]
- Protocol improvements to confirm that the participants may be discharged 12-48 hours after the infusion, based on Investigator judgment
- Protocol improvements to confirm that the safety profile of OAV101 is described in the Investigator Brochure (IB) or package insert
- Numbering adjustment performed for items 6.1.2 Additional Study Treatment and 6.1.3 Supply of study treatment
- Adjustment in the item 8-1 Assessment Schedule – visit window

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
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate
Endpoints	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 endpoints 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
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
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

Protocol summary

Protocol number	COAV101A1IC01
Full Title	A Phase IV Open-label, single-arm, single-dose, multicenter study to evaluate the saFEty, toLerability and effIcacy of gene replacement therapy with intravenous OAV101 (*A*VXS-101) in pediatric patients from Latin America with spinal muscular atrophy (SMA) - OFELIA
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 4
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 ≤ 24 months and weighing ≤ 17 kg, over a 18-month period post infusion.
Primary Objective(s)	The primary objective of this study is to assess the safety and tolerability of IV OAV101 over a 18-month period in patients with SMA weighing less or equal of 17 kg at the time of dose Endpoints: • 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 Objectives	To determine the efficacy of IV OAV101 at 6, 12- and 18-months post infusion in participants with SMA ≤ 24 months and weighing ≤ 17kg as measured by change from baseline in: Achievement of developmental motor milestones according to the World Health Organization-Multicentre Growth Reference Study (WHO-MGRS)

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 ≤ 24 months that weigh ≤ 17 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 18 months. The study will include a standard screening period that can last up to 20 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 (SoA). 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 study team together with Data Monitoring Committee (DMC) as described in the charter. An interim analysis for safety and efficacy maybe 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 18 months visits (EOS). After study completion eligible participants will be invited to enroll into a Registry study (RESTORE) study to collect additional safety and efficacy data.
Study population	Participants ≤24 months of age with SMA with bi-allelic mutations in the SMN1 gene weighing ≤17kg, at the time of dosing.
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 SMN2 gene. 3. Age ≤ 24 months of age at time of treatment

*Patients should follow all criteria of the label locally approved by Health Authorities.	3. Weight ≤17 kg at the time of Screening Period 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 use of OAV101 or 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 (eg, coughing or sputtering of food) within 4 weeks prior to Screening 4. Participant dependent on gastrostomy feeding tube for 100% of nutritional intake. 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 (eg, cyclosporine, tacrolimus, methotrexate, rituximab cyclophosphamide, IV immunoglobulin) 8. Requiring invasive ventilation, tracheostomy or daytime 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. AST, ALT, bilirubin, GGT or GLDH, ≥ ULN; CTCAE ≥ 1) 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 visits 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. Previously treated with nusinersen (Spinraza®) within 4 months prior to Screening 17. Previously treated with risdiplam (Evrysdi™) within 15 days prior to Screening (washout period of at least 5 half-lives before Screening) 18. Use of other investigational drugs within 5 half-lives of enrollment/initiation of study treatment (select as appropriate) within 30 days (eg, small molecules) / or until the expected pharmacodynamic effect has returned to baseline (eg, biologics), whichever is longer; or longer if required by local regulations. 19. History of hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes. 20. Documented any parental consanguinity (1st degree 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 definitions obtained from the following: • WHO Multicentre Growth Reference Study (WHO-MGRS)
[redacted]	[redacted]

Key safety assessments	Safety and tolerability of OAV101 treatment includes evaluation of AEs, laboratory data, vital signs, and ECG and echocardiogram.
Data analysis	The primary endpoints include: 1. Incidence and severity of treatment emergent AEs and SAEs 2. Incidence of adverse events of special interest (AESI). 3. Change from baseline in vital signs, clinical laboratory, and procedure (eg ECG, echocardiogram) results Incidence and severity for treatment emergent AEs and SAEs as well as important identified and important potential risks will be summarized 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 (eg ECG, echocardiogram) results will be summarized descriptively 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. The number and proportion of patients achieving each Developmental Motor Milestone will be presented. An interim analysis may be performed once the last participant reaches the 6 and 12-month time point and will include all available data up until that data cut-off. There is no formal sample size calculation performed for this study. The primary objective is to evaluate descriptively the safety and tolerability of IV OAV101 over a 18 month post infusion period in participants with SMA weighing equal or less than 17kg. No hypothesis testing will be performed.

	The sample size is based on recruitment estimatives and clinical drug availability. Based on this assumption, it is anticipated that approximately 15 participants will be enrolled in this study. From a medical perspective, this number is considered reasonable to provide descriptive safety information. If the true incidence rate of an AE is 14%, then the probability of seeing at least one AE with a sample size of 15 participants is approximately 90%.
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, no sitters, the majority of whom have SMA1, typically have 2 copies of *SMN2* (approximate age 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 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 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).

Studies using OAV101 show a robust postnatal rescue of SMNΔ7 mice with correction of motor function, neuromuscular electrophysiology, and survival after single administration (Foust et al 2010). 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 likely related to an innate and/or acquired 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 intrathecal (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 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 (eg, 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 IV open-label study will be conducted in SMA pediatric participants that weigh between 8.5 kg and 17 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 ≤ 24 months of age with SMA with bi-allelic mutations in the SMN1 gene weighing up to and equal to 17kg at the time of infusion, during a 18-month post-infusion 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)**
• To assess the safety and tolerability of IV OAV101 over a 18 month post-infusion period in participants with SMA weighing to ≤ 17 kg.	• Evaluation of treatment emergent AEs and SAEs • Evaluation of important identified and potential risks • Evaluate changes from baseline in vital signs, cardiac safety assessments, and clinical laboratory results

Objective(s)	Endpoint(s)
Secondary objective(s)	**Endpoint(s) for secondary objective**
• To evaluate the efficacy of IV OAV101 at 6, 12, and 18 months post-infusion in participants with SMA weighing ≤ 17 kg, as measured by the following: • World Health Organization-Multicentre Growth Reference Study (WHO-MGRS)	• Proportion of participants who achieve Development Motor Milestones according to the World Health Organization-Multicentre Growth Reference Study (WHO-MGRS) at 6, 12, and 18 months post-infusion

[redacted]

2.1 Primary Endpoint

The clinical question of interest: What is the safety of single administration of IV OAV101 treatment in SMA participants ≤ 24 months of age that weigh ≤ 17 kg?

The primary endpoint is described by the attributes listed below.

- Population: Participants ≤ 24 months of age with SMA that weigh ≤ 17 kg who meet inclusion/exclusion criteria
- Endpoint: Evaluation of AEs, laboratory data, vital signs, and ECG and echocardiogram.
- Binary indicator of having at least one occurrence of TEAE

- AESIs
- Change from baseline in vital signs, cardiac safety assessments, and clinical laboratory results
- Treatment of interest: Treatment strategy includes corticosteroids 24 hours prior to the infusion of OAV101 followed by IV OAV101 and corticosteroids for at least 30 days post-infusion (including the day of OAV101 administration).

Handling of intercurrent events:

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 3 it 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.

3 Study design

This is an open-label, single arm, multi-center study to evaluate the safety, tolerability, and efficacy of IV OAV101 in symptomatic SMA pediatric participants. The study will enroll participants that weigh ≤ 17 kg.

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 18months. The study will include a 20 day screening period 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 be completing 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. Participants may be discharged 12-48 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 safety team as well as DMC. An interim analysis for safety and efficacy will 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 once all participants have completed Month 18End of Study (EOS) assessments.

After study completion eligible participants will be invited to enroll into RESTORE registry study to collect additional safety and efficacy data.

4 Rationale

4.1 Rationale for study design

This Phase IV 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 pediatric participants ≤ 17kg with symptomatic SMA. [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 (Day 1). The second Screening visit (Screening 2) will be used for weight eligibility and dose calculation. The study will administer OAV101 and monitor participants in an inpatient setting for a minimum of 12-48 hours after administration to carefully monitor the emergence of acute AEs. Participants will be followed for up to 18 months, which is considered adequate to characterize safety given clinical experience (Section 4.6) and sufficient to evaluate efficacy.

Inclusion of pediatric participants ≤ 17kg and 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 AA9 immunity and who 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 before and after administration of OAV101.

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, occupational therapy, speech-language 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. Participants will receive a dose of 1.1e14 vg/kg. The total volume is determined by participant body weight. The participant will undergo in-patient safety monitoring for 48 hours post-infusion.

4.3 Rationale for use of prednisolone

An immune response to the AAV9 capsid may occur after administration of OAV101. 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

4.4 Purpose and timing of interim analyses

An interim analysis will be performed once the last participant reaches the 6-month and 12-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.

4.5 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 (IB) and or package insert . 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
- Sensory abnormalities suggestive of ganglionopathy
- Thrombotic microangiopathy

Further details are outlined in the IB.

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 mitigate 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. Drug-drug interactions are not expected with OAV101.

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 SMN2 copies or a clinical diagnosis of SMA.

4.6 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 15 pediatric participants ≤ 24 months of age with SMA with bi-allelic mutations in the SMN1 gene weighing ≤ 17 kg, at dosing, will be enrolled.

5.1 Inclusion criteria*

*Patients should follow all criteria of the label locally approved by Health Authorities.

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. Age ≤ 24 months of age at time of dosing

4. Weight ≤ 17 kg at the time of Screening Visit 2

5. Naive to treatment or have discontinued an approved drug/therapy

6. 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 (eg, coughing or sputtering of food) within 4 weeks prior to screening

4. Participant dependent on gastrostomy feed tube for 100% of nutritional intake

5. Anti-AAV9 antibody titer > 1:50 as determined by ligand binding immunoassay at the time of screening

6. History of gene therapy, hematopoietic transplantation, or solid organ transplantation

7. Inability to take corticosteroids

8. Concomitant use of immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, or immunosuppressive therapy within 3 months prior to gene replacement therapy (eg, cyclosporine, tacrolimus, methotrexate, rituximab cyclophosphamide, IV immunoglobulin)

9 Requiring invasive ventilation, tracheostomy or awake non-invasive ventilation (standard of care nocturnal BiPAP is not considered exclusionary)

10. Administration of vaccines 2 weeks prior to infusion of OAV101

11. Awake hypoxemia (O_2 saturation <95%) or awake oxygen saturation level decrease between screening and dosing that is clinically significant, as per investigator judgment.

12. Clinically significant neurologic or neuromuscular conditions other than SMA as determined by the principal Investigator

13. Clinically significant abnormalities in laboratory test results at Screening as determined by the Investigator

14. Hepatic dysfunction (i.e. AST, ALT, bilirubin, GGT or GLDH, ≥ ULN; CTCAE ≥ 1) at Screening (with the exception of isolated AST elevation: in the absence of other liver laboratory abnormalities, isolated AST elevation is not considered exclusionary)

15. 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

16. Presence of a confirmed or suspected active infectious process from screening and up to dose administration

17. If previously treated with disease modifying therapy, participants are excluded if they received

- nusinersen (Spinraza®) within 4 months prior to Screening 1.
- risdiplam (Evrysdi™) within 15 days prior to Screening 1 (washout period of at least 5 half-lives before Screening)

18. Use of other investigational drugs within 5 half-lives of enrollment/initiation of study treatment (select as appropriate) within 30 days (eg, small molecules) / or until the expected pharmacodynamic effect has returned to baseline (eg, biologics), whichever is longer; or longer if required by local regulations.

19. History of hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes.

20. Documented any parental consanguinity (1st degree 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

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).

6.1.3 Supply of study treatment

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

Open label, single treatment arm OAV101 IV.

6.1.5 Treatment duration

OAV101 will be administered as a 1-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 or elevations of Troponin I. Where feasible, the participant's vaccination schedule should be adjusted to accommodate concomitant corticosteroid administration prior to and following OAV101. In addition to consideration for corticosteroids, 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

Prednisolone treatment of 1 mg/kg/day will be continued post-infusion until liver function tests return to baseline.

For participants that require steroid dosing longer than 60 days total (including the weaning period) Pediatric GI/hepatology specialty evaluation will be considered to address the risk of opportunistic infections and to make 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), prednisolone, 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 intravenous immunoglobulins and 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/PD drug interactions expected.

The Investigator should instruct the participant/caregiver to notify the study site about any new treatments, including herbal and over the counter medications 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. 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.

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.

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

This is an open-label trial and randomization numbers will not be used.

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 at Screening Visit 2 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 the dose is not fully completed the site personnel will need to reflect the total volume administered as well as the date and time of administration in the eCRF.

6.6.2 Recommended treatment of adverse events

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

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 AEs, 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 and will be received ready for infusion at the bedside.

The total vector genome dose will be calculated based on the participant's body weight at Screening Period; 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.

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 (eg, 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 country label.

Following the administration of the 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 as described in *(Vital Signs/Weight and Height section under Safety Parameters)*. Participants should be maintained in an appropriate inpatient setting from 12 to 48 hours after the start of gene replacement therapy based on Investigator judgment.

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

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 (eg, pharmacists) in accordance with local regulations, policies, and procedures. Control of storage conditions, especially control of temperature (eg, refrigerated/freezer storage) and information on in-use stability and instructions for handling prepared OAV101 should be managed in accordance with the country label specifications.

OAV101 will be supplied to each site for each individual study subject after confirmation of weight at Screening Visit 2. 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 (eg, deficiency in condition, appearance, pertaining to documentation, labeling, expiration date, etc.) should be promptly reported to the Sponsor.

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.

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 AEs associated with study drug can be found in the IB or in the package insert. 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 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)

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

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 (eg 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 (eg 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 eCRF.

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 (eg 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													
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 12	Week 26	Week 52	Week 78 EOS
Days	-20 -0 +5	-14 ±2	-1	1	2 to 2	3 to 3	8 ±2	15 ±2	22 ±2	29 ±2	43 ±5	57 ±5	71 ±14	85 ±14	183 ±14	365 ±21	547 ±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
Vital Signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Neurological Examination	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
WHO		X												X	X	X	X
[redacted]																	
Videodeglutogram		X													X	X	X
[redacted]																	
SMA Medical History	X																
Medical History	X	X															
Demography	X																

Period	Screening		Baseline	Treatment													
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 12	Week 26	Week 52	Week 78 EOS
Days	-20 -0 +5	-14 ±2	-1	1	2 to 2	3 to 3	8 ±2	15 ±2	22 ±2	29 ±2	43 ±5	57 ±5	71 ±14	85 ±14	183 ±14	365 ±21	547 ±21
Hematology	X		X				X	X	X		X	X	X	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/Troponin T		X					X			X		X	X	X	X	X	X
Virus Serology	X												X	X	X	X	X
[redacted]																	
Urinalysis			X			X											
Electrocardiogram (ECG)	X		X				X			X		X	X		X	X	X
Echocardiogram	X						X			X		X	X	X	X		X
Prophylactic Prednisolone			X	X	X	X	X	X	X	X	X	X					
OAV101 Infusion				X													
Developmental Milestone Checklist		X								X			X	X	X	X	X
[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

8.1 Screening

8.1.1 Information to be collected on screening failures

Participants who sign an informed consent form and are 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 demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a SAE during the screening phase (see SAE section for reporting details, Section 10.1.2) or protocol-related AE.

The Screening assessments will be performed from the time of the ICF signature, as outlined in the protocol and SoA.

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.

Participants who fail eligibility during the screening process for a temporary condition (eg viral illness, concomitant medication, or laboratory values, etc.) may be re-screened at a later time. Participants who fail upper weight eligibility at Screening Visit 2 cannot be re-screened.

In case the screening window has expired, all screening procedures must be repeated. When all inclusion and exclusion criteria will have to be re-verified, a new Participant No. will be assigned. A participant initially excluded for a condition no longer exclusionary upon a protocol amendment may also be 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 copies (if available), will be recorded in the eCRF.

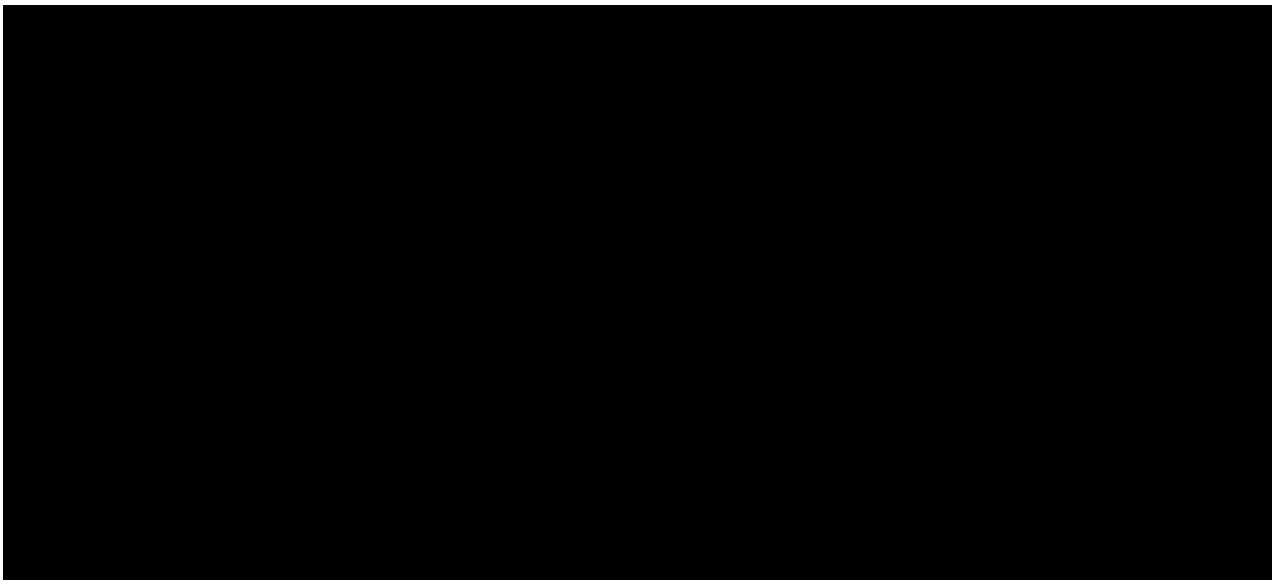
8.2.3 Physical examination

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.



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..

8.3 Efficacy

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

8.3.1 Developmental motor milestone checklist

See Section 8.5.1.1 for details.

8.3.2 Appropriateness of efficacy assessments

Efficacy assessments for developmental motor milestones is 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.

8.4.1 Laboratory evaluations

The site laboratory will be used for analysis of all specimens collected, except for AAV9 antibodies, that will use central laboratory. Details on the collections, shipment of samples and reporting of results by the central laboratory for AAV9 antibodies are provided to Investigators.

8.4.1.1 Hematology

Hematology analysis will include a complete blood count with differential and platelet count. Samples will be collected and processed in the local site 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)

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.

If clinically significant and/or moderate or severe thrombocytopenia and anemia are noted, further evaluation to diagnose 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 Blood chemistry

Samples will be collected and processes in the local site 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. In case Troponin I is not available at site, Toponin T can be performed. **If Troponin-T is collected at baseline then Tropinin T must be collected for follow up.**

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

8.4.1.3 Urinalysis

Urine samples will be collected in accordance with the local laboratory standards 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 the 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.

During feasibility, the ECG readout availability should be confirmed at the site for QTcF. If a site only has availability to readout in QTcB (Bazett) and NOT QTcF, the ECG machine must still be able to provide QT and RR interval values so the Investigator can perform the below QTcF (Fridericia) calculation to determine eligibility. 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 No., date and time, and filed in the study site source documents. The Investigator should document clinical evaluation in the source documents.

The ECG will be interpreted locally by a pediatric cardiologist or designee for immediate safety evaluation. 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. A

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 Novartis physician or designee will be notified of any safety concerns from the site 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 then monitored as specified in the Table 8-1.

Height and weight will be measured (supine or standing) at each study visit. Screening weight shall be obtained ≤ 14 days prior to Day 1. On Day 1, weight and height will be measured pre-dose.

8.4.4 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 (eg, neuromuscular module and multi-dimensional fatigue scale) may be collected remotely (eg web portal, telephone interviews) depending on local regulations, technical capabilities, and following any applicable training in the required process.

8.5.1.1 Developmental Motor Milestone checklist

Developmental Motor Milestones will be assessed using relevant definition obtained from World Health Organization Multicentre Growth Reference Study (WHO-MGRS).

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

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Table 8-2 Developmental Motor Milestone and Performance Criteria

Developmental Motor Milestone	Performance Criteria
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.
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.

Standing with assistance (WHO MGRS)	Child stands in upright position on both feet, holding onto a stable object (eg, 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 (eg, 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]

[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 assessments indicated in the Assessment Schedule. If they fail to return for these assessments for unknown reasons, every effort (eg 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 (eg 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.

No further assessments to be 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.

The sponsor will continue to retain and use all research results (data) that have already been collected for the study evaluation.

9.1.3 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, eg 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 AE is any untoward medical occurrence (eg any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

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

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 AEs 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 IB.

Abnormal laboratory values or test results constitute AEs 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.

Based on 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
- Sensory abnormalities suggestive of ganglionopathy
- 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, eg 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 within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each site.

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

within 24 hours of the Investigator receiving the follow-up information. 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 IB 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 regulatory requirements in participating countries.

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 liver function tests are elevated, the following will also be performed:

- Hospitalization of the participant, if appropriate
- Causality assessment of the liver event
- Thorough investigation and follow-up of the liver event. Laboratory investigations may include based on Investigator's discretion: serology and laboratory tests for other causes of hepatitis, including viral hepatitis
- Obtaining a more detailed history of signs and symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use, including nonprescription medications (eg acetaminophen); and herbal and dietary supplement preparations
- Exclusion of underlying liver disease

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

10.2.2 Post-mortem data collection

In the event of a fatal outcome, and if parental consent is obtained, an 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. The autopsy should be performed per local standard of care and local regulations, and with particular attention to CNS (eg, DRG), liver, and cardiac examination.

Declining an 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 Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions and AEs will be coded using the MedDRA terminology.

Dates of screenings, screen failures, treatment and study completion, as well as drug confirmation will be tracked by a system that 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. 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

The data will be analyzed by Novartis and/or a designated CRO.

Data from all participating centers will be combined, so that an adequate number of participants will be available for analysis.

Primary safety and efficacy analysis will be conducted on all participant data after all participants have completed the Month 18/EOS visit. A final CSR will be produced for the primary analysis of the study.

Any data analysis carried out independently by the Investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The Full Analysis Set (FAS) comprises all participants to whom study treatment has been assigned and who received at least one dose of study treatment. Participants will be analyzed according to the treatment they have been assigned to.

The Safety Set includes all participants who received at least one dose of study treatment. Participants will be analyzed according to the study treatment received.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively 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. For selected parameters, 25th and 75th percentiles will also be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class (SOC) and preferred term (PT).

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 actual, weight-adjusted dose, in vg/kg, of OAV101 administered during infusion will be summarized as well as duration of infusion, whether the entire volume was delivered, and whether the infusion was interrupted.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 supporting primary objectives

12.4.1 Definition of primary endpoint(s)

All safety data, including TEAEs, cardiac safety assessments, clinical laboratory measurements, vital signs, are considered primary endpoints.

12.4.2 Statistical model, hypothesis, and method of analysis

No statistical hypothesis testing will be performed.

Treatment-emergent AEs are defined as any event that begins or worsens in severity after infusion of OAV101 through to the last study visit. The incidence of TEAEs will be summarized according to MedDRA as follows: overall by SOC and PT, overall, by SOC, PT and severity, suspected treatment-related AEs by SOC and PT, SAEs by SOC and PT.

Adverse events of special interest (AESI) are defined by the important identified risk and important potential risk as presented in the effective Risk Management Plan (RMP). MedDRA search criteria to retrieve AEs indicative of these risks are updated on a regular basis at the

OAV101 program level. The incidence of treatment emergent AESIs will be summarized. Descriptive summary statistics for the change from baseline in cardiac safety assessments, clinical laboratory measurements, and vital signs will be summarized descriptively by visit/timepoint. Mean, standard deviation, median, minimum, and maximum will be presented. For each applicable visit/timepoint, only participants with a baseline and a measurement for that timepoint will be included in the summary. Categorical cardiac safety assessments, clinical laboratory measurements, and vital signs data will be presented as frequencies and percentages.

12.4.3 Handling of intercurrent events

For the analysis of TEAE (including AESI), the treatment effect will be based on a treatment policy strategy (i.e. the target of estimation is considered regardless of the occurrence of intercurrent events, and the endpoint mirrors the decision to treat a participant rather than the effect of the treatment itself).

The analysis of cardiac safety assessments, clinical laboratory measurements, vital signs will take into account the following intercurrent events using a hypothetical strategy:

- Intake of prohibited concomitant medications
- Discontinuation from the study due to reasons other than death

12.4.4 Handling of missing values not related to intercurrent event

All available data will be used in the analysis of safety data. No imputation will be done for missing safety data.

12.4.5 Sensitivity analyses

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

12.4.6 Supplementary analysis

Subgroup analyses

Subgroup analyses will be performed on the primary endpoints based on the participant's baseline status:

- Age

As the sample size is small, data will be only summarized within each subgroup. Analysis supporting secondary objectives

The secondary objective is:

- To evaluate the efficacy of IV OAV101 at 6, 12, and 18 months post-infusion in participants with SMA weighing ≤ 17 kg, as measured by the following:

WHO-MGRS

All secondary efficacy endpoints will be analyzed for the FAS.

12.4.7 Efficacy and/or Pharmacodynamic endpoint(s)

The number and proportion of participants achieving each WHO developmental milestone will be presented at 6-, 12-, and 18- months post-infusion.

The analysis will take into account the following intercurrent events using a composite strategy:

- Intake of prohibited concomitant medications
- Discontinuation from study due to reasons other than death

This means that if the any of the intercurrent events of interest occur the participant will be regarded as a non-responder from when the first intercurrent event of interest occurs.

12.4.8 Safety endpoints

For all safety analyses, the Safety set will be used.

The overall observation period will be divided into two mutually exclusive segments:

1. Pre-treatment period: from day of participant's informed consent to the day before infusion of OAV101
2. On-treatment period: from day of infusion of OAV101 through to the last study visit.

Adverse events

Details of the summary of AEs for the primary endpoint are detailed in Section 12.4.

In addition, separate summaries will be provided for death and other significant TEAEs leading to discontinuation.

All AEs, deaths, and SAEs (including those from the pre-treatment period) will be listed and those collected during the pre-treatment period will be flagged.

Vital signs

Details of the summary of AEs for the primary endpoint are detailed in Section 12.4.

12-lead ECG

Details of the summary of 12-lead ECG (cardiac safety assessment) for the primary endpoint are detailed in Section 12.4

1. PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs for each participant during the study. ECG data will be read and interpreted (locally).
2. Categorical Analysis of QT/QTc interval data based on the number of participants meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented.

All ECG data will be summarized by visit/timepoint.

Clinical laboratory results

Details of the summary of clinical laboratory results for the primary endpoint are detailed in Section 12.4.

In addition, shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

Grading of laboratory values will be assigned programmatically as per NCI CTCAE version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE version 4.03, results will be categorized as low/normal/high based on laboratory normal ranges.

The following listings/summaries will be generated separately for hematology, and biochemistry tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE version 4.03 grades if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE version 4.03:

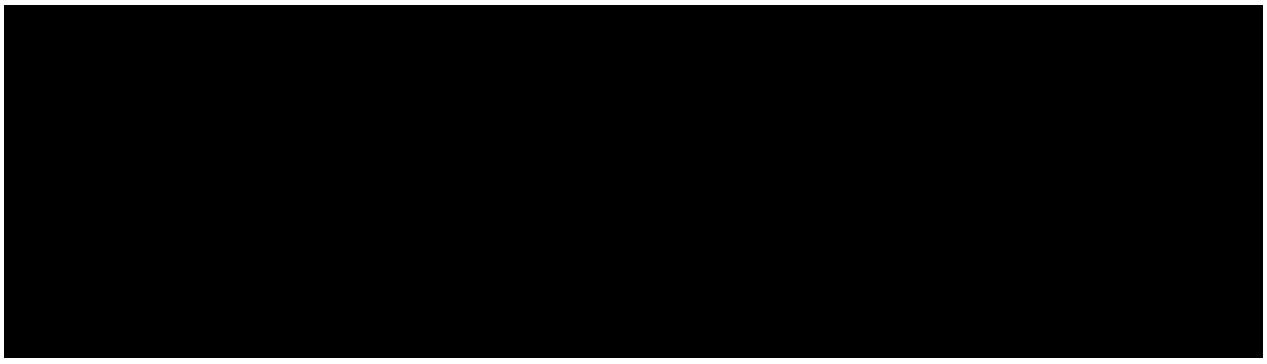
- Worst post-baseline CTCAE grade (regardless of the baseline status). Each participant will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE version 4.03 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE version 4.03:

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

Other safety evaluations

Details of the summary of echocardiogram (cardiac safety assessment) for the primary endpoint are detailed in Section 12.4.



12.6 Interim analyses

An interim analysis will be performed once the last participant reaches the 6 and 12-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.

12.7 Sample size calculation

12.7.1 Primary endpoint(s)

There is no formal sample size calculation performed for this study. The primary objective is to evaluate descriptively the safety and tolerability of IV OAV101 over a 18 month post infusion period in participants with SMA weighing equal or less than 17kg. No hypothesis testing will be performed.

The sample size is based on recruitment estimatives and clinical drug availability. Based on this assumption, it is anticipated that approximately 15 participants will be enrolled in this study. From a medical perspective, this number is considered reasonable to provide descriptive safety information.

If the true incidence rate of an AE is 14%, then the probability of seeing at least one AE with a sample size of 15 participants is approximately 90%.

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 (eg, 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 (eg 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 World Health Organization (WHO) developmental milestones

16.1.1 Clinically notable laboratory values and vital signs

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.

Vital sign	Value		Patient age at visit	
			< 18 years	≥ 18 years
Systolic blood pressure (mmHg)	High		≥ 95th percentile of the age and height group[1]	≥ 180 with increase from updated baseline[5] or ≥ 20 mmHg
	Low		≤ 5th percentile of the age and height group[1]	≤ 90 with decrease from updated baseline[5] or ≥ 20 mmHg
Diastolic blood pressure (mmHg)	High		≥ 95th percentile of the age and height group[1]	≥ 105 with increase from updated baseline[5] or ≥ 15 mmHg
	Low		≤ 5th percentile of the age and height group[1]	≤ 50 with decrease from updated baseline[5] or ≥ 15 mmHg
	High		≥ 38.4	≥ 39.1

Oral body temperature (°C)	Low		≤ 35.0	≤ 35.0
Pulse rate (bpm)[2]	High	12-18 months	> 140	≥ 120 with increase from updated baseline[5] or ≥ 15 mmHg
		18-24 hours	> 135	
		2-3 years	> 128	
		3-4 years	> 123	
		4-6 years	> 117	
		6-8 years	> 111	
		8-12 years	> 103	
		12-15 years	> 96	
		≥ 15 years	> 92	
	Low	12-18 months	< 103	≤ 50 with decrease from updated baseline[5] or ≥ 15 mmHg
		18-24 hours	< 98	
		2-3 years	< 92	
		3-4 years	< 86	
		4-6 years	< 81	
		6-8 years	< 74	
		8-12 years	< 67	
		12-15 years	< 62	
		≥ 15 years	< 58	
Weight	High		Increase from baseline[3] of ≥ 2 BMI-for-age percentile cetagories[4]	Weight increase from updated baseline[5] of ≥ 10%
	Low		Decrease from baseline[3] of ≥ 2 BMI-for-age percentile cetagories[4]	Weight decrease from updated baseline[5] of ≥ 10%
Respiratory rate (breath per minutes)[2]	High	12-18 months	> 46	≥ 30
		18-24 hours	> 40	
		2-3 years	> 34	
		3-4 years	> 29	
		4-6 years	> 27	
		6-8 years	> 24	
		8-12 years	> 22	
		12-15 years	> 21	
		≥ 15 years	> 20	
	Low	12-18 months	< 28	≤ 10
		18-24 hours	< 25	
		2-3 years	< 22	
		3-4 years	< 21	

		4-6 years	< 20	
		6-8 years	< 18	
		8-12 years	< 16	
		12-15 years	< 15	
		≥ 15 years	< 13	

bpm=beats per minute
[1] Blood pressure percentiles were calculated for each blood BP record using the method described in Appendix B of National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004
[2] Fleming et al 2011
[3] Baseline BMI-for-age weight status categories are underweight (less than the 5th percentile), healthy weight (5th percentile to less than the 85th percentile), overweight (85th to less than the 95th percentile) and obese (equal to our greater than 95th percentile).
[4] BMI-for-age percentiles categories (P3, P5, P10, P25, P50, P75, P85, P90, P95, P91) are obtained from the WHO Growth Charts (http://www.who.int/childgrowth/en/); For patients less than 2 years old, growth charts are based on recumbent length instead of height, which is not collected in the study. As an approximation, height collected in the study is considered as equal to the recumbent length
[5] Updated baseline was the last value collected before the 18th birthday.

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 > 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,Fraction

	ALT	TBL	Liver Symptoms	Action
				ated 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 (Protocol Section 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 > 8 x ULN	Normal	None	
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)
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 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 (eg, 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 (eg, 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)