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OAV101

Clinical Trial Protocol COAV101B12302 / NCT05386680

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

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List of abbreviations

AAV	Adeno-associated Virus
AAV9	adeno-associated virus serotype 9
ACEND	Assessment of Caregiver Experience in Neuromuscular Disease
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ASO	Antisense oligonucleotide
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
Beta-hCG	Blood beta-human chorionic gonadotropin
BIL	Bilirubin
BMI	Body Mass Index
[redacted]	[redacted]
C-SSRS	Columbia Suicide Severity Rating Scale
CB	Chicken-β-Actin-Hybrid
cDNA	Complementary Deoxyribonucleic Acid
CE	Clinical Evaluator
CFR	Code of Federal Regulations
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CI	confidence interval
CK	Creatine Kinase
ClinRO	Clinician Reported Outcomes
CMO&PS	Chief Medical Office and Patient Safety
CMV	Cytomegalovirus
CNS	Central Nervous System
CO	Country Organization
COA	Clinical Outcome Assessment
COVID-19	Coronavirus disease of 2019
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSF	Cerebrospinal fluid
[redacted]	[redacted]
CSR	Clinical study report
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DRG	Dorsal Root Ganglia
EBV	Epstein Barr Virus
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessment
eCRF	electronic Case Report Form

eCRS	electronic Case Retrieval Strategy
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOS	End of Study
eSAE	Electronic Serious Adverse Event
ESE2	Exonic splicing enhancer 2
eSource	Electronic Source
eTMF	Electronic trial master file
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEV1	forced expiratory volume in the first second
FIVC	forced inspiratory vital capacity
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLDH	Glutamate Dehydrogenase
HAV	Hepatitis A Virus
HBc	Hepatitis B core
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B Virus
hCG	human chorionic gonadotropin
HCO3	Bicarbonate
HCV	Hepatitis C Virus
HEENT	Head, Eyes, Ears, Nose and Throat
HEV	Hepatitis E
HFMSE	Hammersmith Functional Motor Scale Expanded
HIV	Human immunodeficiency virus
HSV	Herpes Simplex 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
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IT	intrathecal
ITR	Inverted terminal repeats
IUD	Intrauterine device

IV	intravenous
kg	kilogram(s)
LDH	lactate dehydrogenase
LFT	Liver function test
LLN	lower limit of normal
LP	lumbar puncture
LS	least squares (LS)
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
[redacted]	[redacted]
mL	milliliter(s)
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
[redacted]	[redacted]
ObsRO	Observer Reported Outcomes
PA	posterior to anterior
PICU	Pediatric intensive care unit
PIP	Paediatric Investigation Plan
PNCR	Pediatric Neuromuscular Clinical Research
PT	prothrombin time
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
rAAV	Recombinant adeno-associated virus
[redacted]	[redacted]
RNA	Ribonucleic acid
RULM	Revised Upper Limb Module
SAE	Serious Adverse Event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SMA	Spinal muscular atrophy
SMN	Survival of Motor Neuron
SMN1	Survival of Motor Neuron 1
SMN2	Survival of Motor Neuron 2
SmPC	Summary of Product Characteristics
SNAP	Sensory nerve action potential
SOC	System organ class
SOP	standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total bilirubin
ULN	upper limit of normal

US	United States
vg	vector genome
WBC	White blood cells
WHO	World Health Organization
WOB	work of breathing
WoC	Withdrawal of Consent

Glossary of terms

(5q)SMA	Spinal muscular atrophy caused by bi-allelic defects in the survival motor neuron 1 (*SMN1*) gene on chromosome 5q13.2 leading to a deficiency in the *SMN1* protein
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)
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
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over 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
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
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 source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants
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
Estimand	As defined in the ICH E9(R1) addendum, estimand is 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 participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.

Investigational drug/ treatment	The drug whose properties are being tested in the study
Investigational Product/ Investigational Medicinal product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference (such as an active comparator) in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Medication number	A unique identifier on the label of medication kits
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.
Off-site healthcare Professional (OHP)	A qualified healthcare professional, such as include those used in the study e.g. Nurse, Phlebotomist, Physician, who performs certain protocol procedures for the participant in an off-site location such as a participant's home.
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" terminology is used in the protocol whereas term "Subject" is used in data collection
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.
[redacted]	[redacted]
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.
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Remote	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location
Run-in Failure	A participant who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to participant's intervention or other treatment)
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
Start of study treatment	The start of the clinical trial is defined as the signature of the informed consent by the first participant Per EU Regulation 536/2014 the start of a clinical trial means the first act of recruitment of a potential participant for a specific clinical trial, unless defined differently in the protocol. However, for Novartis trials under EU CTR, please do not define differently in the protocol
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant

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
Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant is not at the investigative site where the investigator will conduct the trial.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
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 consent (WoC) / Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and/or biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

Amendment 1 (17-May-2023)

Amendment rationale

The purpose of this amendment is to expand the age group for inclusion in the study from 2 to 12 years of age, to 2 to < 18 years of age to cover the full pediatric age range and for consistency with the study population age range of Novartis' ongoing Phase 3 study (COAV101B2301) in treatment naïve patients age 2 to < 18 years.

In addition, the risk language has been revised to include the theoretical risk of tumorigenicity due to the very low potential incorporation of AAV vector DNA into chromosomal DNA that has been noted based on published literature for AAV-based therapies, in Section 4.5; also, the liver safety monitoring for elevated levels has been updated (Table 16-1) to apply more stringent monitoring to ensure a timely follow-up and to align with FDA guidance for drug induced liver toxicity (FDA 2009) in protocol Section 10.2.1 and Section 16.2.2.

Other major changes to the protocol are listed below.

Changes to the protocol

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

- Title:
  - Dose in vector genomes has been corrected to include superscript text.
  - The upper age limit has been expanded and is now <18 years.
- Summary:
  - In patient monitoring timeline has been updated from 24-48 hours to at least 48 hours to align with recommendations in Section 6.7.3 and Section 8.3.3.11
  - Anti-AAV9 eligibility criterion has been aligned with Section 5.2
- Section 2 Objectives and Endpoints:
  - [redacted]
  - Secondary estimands have been added for better clarity.
- Section 3 Study Design:
  - In patient monitoring timeline has been updated from 24-48 hours to at least 48 hours to align with recommendations in Section 6.7.3 and Section 8.3.3.11
- Section 4.5 Risks and Benefits:
  - Theoretical risk of tumorigenicity added. The risk language has been revised to include the theoretical risk of tumorigenicity due to the very low potential

incorporation of AAV vector DNA into chromosomal DNA that has been noted based on published literature for AAV-based therapies.
    - Risk terminology has been updated to "transient thrombocytopenia" to align with eCRS.
    - Maximum blood volume withdrawn for patients has been added. In line with EU Regulation No 536/2014 (European Commission 2017).
- Section 4.6 Rationale for Public Health Emergency Mitigation Procedures:
    - Rationale for Public Health Emergency mitigation procedures – wording revision to align with the latest Novartis Protocol template.
- Section 5 Study Population:
    - The total population age group has expanded from 2-12 years to 2-<18 years. The sample size remains the same at approximately 28 patients. Age of participants enrolled will be stratified as 2-5 years or 6-< 18 years, with approximately 12 subjects in each stratum.
- Section 5.1 Inclusion Criteria:
    - Inclusion criterion #3 has been amended to include patients from 2 to < 18 years of age to cover the full pediatric age range and for consistency with the study population age range for another Novartis ongoing Phase 3 COAV101B2301 trial in treatment naïve patients aged 2 to <18 years. Sample size assumptions remain unchanged.
- Section 5.2 Exclusion Criteria:
    - Exclusion criterion #6 has been clarified to specify exclusion of 'clinically significant' abnormal results to allow investigator discretion in case of minimally abnormal coagulation results.
    - Exclusion criterion #14 has been edited to apply if an infection is present within 30 days prior of OAV101 versus "at any time" during screening and additionally for febrile illnesses "within two weeks prior to Screening visit 1" to conform to program standards.
    - Exclusion criterion #23 has been clarified in order to specify that 'systemic' immunosuppressive therapy is excluded.
    - Exclusion criterion #26 has been edited to remove 'and/or sponsor' as the sponsor will not make decisions on eligibility.
- Table 6-1 Investigational Drug:
    - More details regarding the investigational drug have been added to align with the latest Novartis protocol template.
- Section 6.2.1.1 Permitted concomitant therapy requiring caution and/or action:
    - Instances of 'should' have been changed to 'must' as vaccination guidance is mandatory to adhere to.
- Section 6.2.2 Prohibited medication:
    - Instances where prohibited concomitant medications may be allowed, have been clarified. Prohibited medications are still allowed post-treatment, if medically indicated.

- Table 8-1 Assessment Schedule:
  - Footnote 11 has been edited to clarify hospitalization.
  - The timepoint for the last actimetry assessment was corrected from W52 to W42 to mark the beginning of the last recording period.
  - Footnote 18 was aligned with changes in Section 8.4.1.1 to align with the SmPC for Zolgensma (OAV101 IV). To align with the SmPC for Zolgensma (OAV101 IV).
  - Added D1 call in IRT.

- Section 8.4.1.1 Hematology:
  - The wording for close monitoring of platelet counts has been changed from "the week following infusion" to "the first two weeks following infusion [...] until platelet counts return to baseline" to align with the SmPC for Zolgensma® (OAV101 IV).
- Section 8.4.1.7 Urine beta-human chorionic gonadotropin pregnancy test (Qualitative):
  - Sentence "Results of hCG dipstick testing will be captured on source documentation only" has been added to add clarification on how results will be documented.
- Section 8.4.5.2 Sensory Nerve Action Potential (SNAP)
  - Deleted text that sensory nerve action potentials provide information from motor nerves to correct an error. Deleted text on asymptomatic patients undergoing SNAP post-treatment because this is not applicable, therefore was removed for clarity.
- Section 8.4.5.4 Vital Signs
  - Vital signs monitoring are explained in more detail for clarity.

- Section 10.1.1 Adverse events:
  - Updated the adverse events of special interest to reflect the risks in Section 4.5

- Section 10.2.1 Liver Safety Monitoring:
  - 'Fibroscan' has been edited to 'elastography' to use the generic name of the procedure.
  - Timing of liver safety monitoring follow up for elevated levels (Table 16-1) is changed from "72 hours from test results" to "within 48-72 hours" Liver safety monitoring follow up timelines were updated to align with the FDA guidance for drug-induced liver toxicity.

[redacted]

- Section 11.3 Site Monitoring:
  - Instructions on retention of records & documents added to align with the latest Novartis protocol template.

[redacted]

- Section 16.2.2 Follow-up requirements for liver laboratory triggers ALT and AST, with and without TBL:
  - Timing of liver safety monitoring follow up indicated in Table 16-1 is changed from "72 hours from test results" to "within 48-72 hours" to apply more stringent monitoring and to align with FDA guidance for drug induced liver toxicity (FDA 2009) to ensure timely follow-up
  - Recommended laboratory work-up for competing liver etiologies have been clarified to list the specific recommended laboratory tests.

IRBs/IECs

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

Protocol summary

Protocol number	C0AV101B12302
Full Title	Phase IIIb, open-label, single-arm, multi-center study to evaluate the safety, tolerability and efficacy of OAV101 administered intrathecally (1.2×10^{14} vector genomes) to participants 2 to < 18 years of age with spinal muscular atrophy (SMA) who have discontinued treatment with nusinersen (Spinraza®) or risdiplam (Evrysdi®)
Brief title	Safety, tolerability and efficacy study of OAV101 administered intrathecally to participants 2 to <18 years of age with spinal muscular atrophy (SMA) who have discontinued treatment with nusinersen (Spinraza®) or risdiplam (Evrysdi®)
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Biological
Study type	Interventional
Purpose	To characterize the safety, tolerability and efficacy of OAV101 (1.2×10^{14} vector genomes) administered by one-time lumbar intrathecal (IT) injection over a 52-week period, in participants who have discontinued treatment with nusinersen (Spinraza®) or risdiplam (Evrysdi®).
Primary Objective(s)	The primary objective of this study is to characterize the safety and tolerability of OAV101 IT over a 52-week period in patients with SMA aged 2 to < 18 years who have discontinued treatment with nusinersen (Spinraza®) or risdiplam (Evrysdi®). The primary endpoints for the primary objective are: the number and percentage of participants reporting adverse events (AEs), related AEs, serious AEs and adverse events of special interest (AESIs) over a 52-week period.
Secondary Objectives	The secondary objective of this study is to assess the efficacy of OAV101 IT on motor function and caregiver impact over a 52-week period in patients with SMA aged 2 to < 18 years who have discontinued treatment with nusinersen (Spinraza®) or risdiplam (Evrysdi®). The secondary endpoints for the secondary objective questions of interest are: ● What is the change from baseline to Week 52 visit in the Hammersmith Functional Motor Scale Expanded (HFMSE) total score? ● What is the change from baseline to Week 52 visit in the Revised Upper Limb Module (RULM) total score? ● What is the change from baseline to Week 52 visit in Assessment of Caregiver Experience in Neuromuscular Disease (ACEND) instrument score?

Study design	This is an open-label, single arm, multi-center study. Approximately 28 participants aged 2 to < 18 years will be enrolled stratified as 2 to 5 years and 6 to < 18 years. The study is comprised of 3 periods, Screening (up to 45 days), Treatment (1 day), and Follow-up (52 weeks). During the Screening period and on Day -1 (Baseline), eligibility will be assessed, including confirmation that nusinersen (Spinraza®) or risdiplam (Evrysdi®) have not been used for the defined period (4 month and 15 days prior to Day -1 respectively). On Day - 1 (Baseline) participants will be admitted to the hospital for pre-treatment baseline procedures. Prednisolone (or equivalent) will be given and continued as per the study protocol. Participants who meet eligibility criteria at Screening and Baseline will receive a single dose of OAV101 (1.2×10^{14} vector genomes) by lumbar IT injection on Day 1 (Treatment) and will then undergo in-patient safety monitoring over at least the next 48 hours, after which the participant may be discharged according to Investigator judgement. During Follow-up, safety monitoring will continue as per the visits defined in the Assessment Schedule. Safety for participants enrolled will be evaluated by the study team together with the Data Monitoring Committee (DMC) as described in the DMC charter. Final analysis will be performed after all participants have completed Week 52 or discontinued prior to Week 52. At the end of study, participants will be invited to enroll in a Novartis-sponsored long-term follow-up study to monitor long-term safety and efficacy.
Rationale	The data from this study will expand on the data generated from other studies of OAV101 IT in the treatment naive SMA population. Specifically, data from this study may provide safety, tolerability, and efficacy evidence in support of management and monitoring for patients with SMA who discontinue nusinersen (Spinraza®) or risdiplam (Evrysdi®) to receive OAV101 IT.
Study population	Participants with SMA with bi-allelic mutations in the survival of motor neuron 1 (*SMN1)* gene, and any number of copies of survival of motor neuron 2 (*SMN2)* gene, aged 2 to <18 years will be enrolled. The population will be stratified by age (2 to 5 years and 6 to <18 years with approximately 12 subjects in each stratum). Participants must be able to sit independently, but never have taken steps independently and must have received at least four loading doses of nusinersen (Spinraza®) or at least 3 months of risdiplam (Evrysdi®) to be eligible for this study.
Key Inclusion criteria	● Written informed consent ● SMA diagnosis based on gene mutation analysis with bi-allelic *SMN1* mutations and any copy of *SMN2* gene ● Aged 2 to <18 years (screening visit must occur before the patient's 18th birthday) at time of Screening Visit 1 ● Have had at least four loading doses of nusinersen (Spinraza®) or at least 3 months of treatment with risdiplam (Evrysdi®) at Screening ● Must be able to sit independently but must never have taken steps independently ● Diagnosed through newborn or neonatal screening or patients clinically diagnosed must have age of clinical symptom onset < 18 months ● Meets age-appropriate institutional criteria for use of anesthesia/sedation ● Female participants who are sexually active or have reached menarche must have a negative pregnancy test at Screening. Those

	females who are sexually active must also agree to use highly effective methods of contraception.
Key Exclusion criteria	● Excluding SMA, any medical condition considered clinically significant ● Positive for human immunodeficiency virus (HIV), hepatitis B or hepatitis ● Anti Adeno Associated Virus Serotype 9 (AAV9) antibody titer using an immunoassay is reported as elevated at Screening (reference to >1:50 or a validated result consistent with being elevated) ● Clinically significant abnormalities in test results during screening period and/or at Baseline ● Platelet count less than the lower limit of normal (LLN), or platelet transfusion within 1 month at Screening Visit 1 ● Clinically significant abnormal coagulation panel results at Screening ● Hepatic dysfunction (i.e. alanine aminotransferase (ALT), total bilirubin (TBL), gamma-glutamyl transferase (GGT) or glutamate dehydrogenase (GLDH) > upper limit of normal (ULN) at Screening (with the exception of isolated AST elevation: in the absence of other liver laboratory abnormalities, isolated elevated AST is not considered exclusionary) ● Contraindications for lumbar puncture procedure ● At Baseline (Day-1), participants are excluded if they received: ● nusinersen (Spinraza®) within 4 months at Baseline ● risdiplam (Evrysdi®) within 15 days at Baseline ● Vaccinations 2 weeks prior to administration of OAV101 ● Hospitalization for a pulmonary event, or for nutritional support within 2 months prior to Screening or inpatient major surgery planned. ● Presence of the following: ● An active infectious process requiring systemic antiviral or antimicrobial therapy up to 30 days prior to OAV101 administration, or ● An active but untreated viral or bacterial infectious process up to 30 days prior to administration of OAV101, or ● Any febrile illness up to 30 days prior to administration of OAV101 ● Requiring invasive ventilation, awake noninvasive ventilation for > 6 hours during a 24-hour period, noninvasive ventilation for >12 hours during a 24-hour period or requiring tracheostomy, at Screening and up to OAV101 administration ● Concomitant use of any of the following medication categories within 90 days prior to administration of OAV101 ● Ongoing systemic immunosuppressive therapy (e.g., corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, intravenous immunoglobulin, rituximab), plasmapheresis, immunomodulators (e.g., adalimumab) ● History of hypersensitivity to any of the study treatments or its excipients or drugs of similar chemical classes
Study treatment	OAV101
Treatment of interest	Single IT administration of OAV101 at a dose of 1.2×10^{14} vector genomes
Key efficacy assessments	● HFMSE total score

	● RULM total score ● ACEND instrument total score
Key safety assessments	● Adverse event monitoring ● Physical examination, inlcuding neurological examination ● Vital signs ● Laboratory values (hematology, chemistry including liver function tests (LFTs) and troponin I, coagulation, urinalysis) ● Electrocardiogram ● Echocardiogram ● Columbia Suicide Severity Rating Scale (C-SSRS) ● Pregnancy tests as applicable
Other assessments	[redacted]
Data analysis	The primary estimand is described by the following attributes: ● Population: Patients with SMA aged 2 to <18 years who were treated with OAV101 IT administration after the discontinuation of nusinersen (Spinraza®) or risdiplam (Evrysdi®). ● Endpoint (the primary variable): AEs, related AEs, serious adverse events (SAEs) and AESIs. ● Treatment of interest: OAV101 IT Handling of intercurrent events (including receiving prohibited concomitant medications): Treatment policy strategy, i.e., reporting all observed AEs, related AEs, SAEs (including death) and AESIs during the trial period, regardless whether intercurrent events occurred or not. Loss to follow-up does not impact primary estimand under treatment policy strategy. Summary measures: The number and percentage of participants reporting AEs, related AEs, SAEs and AESIs will be summarized by strata and overall. Summaries will also be provided by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term. The secondary endpoints include change from baseline to Week 52 in the HFMSE total score, change from baseline to Week 52 in the RULM total score and change from baseline to Week 52 in the ACEND instrument score. Change from baseline to Week 52 in the HFMSE total score, change from baseline to Week 52 in the RULM total score and change from

	baseline to Week 52 in the ACEND instrument total score will be summarized descriptively; in addition, mixed models with repeated measurement with age, visit, and their baseline value as covariants will be used. The least squares (LS) means and 95% 2-sided confidence intervals will be reported for each scheduled visit. A final analysis will be performed after all participants have completed Week 52 or discontinued prior to Week 52. [redacted]
Key words	Spinal muscular atrophy, OAV101, gene therapy

1 Introduction

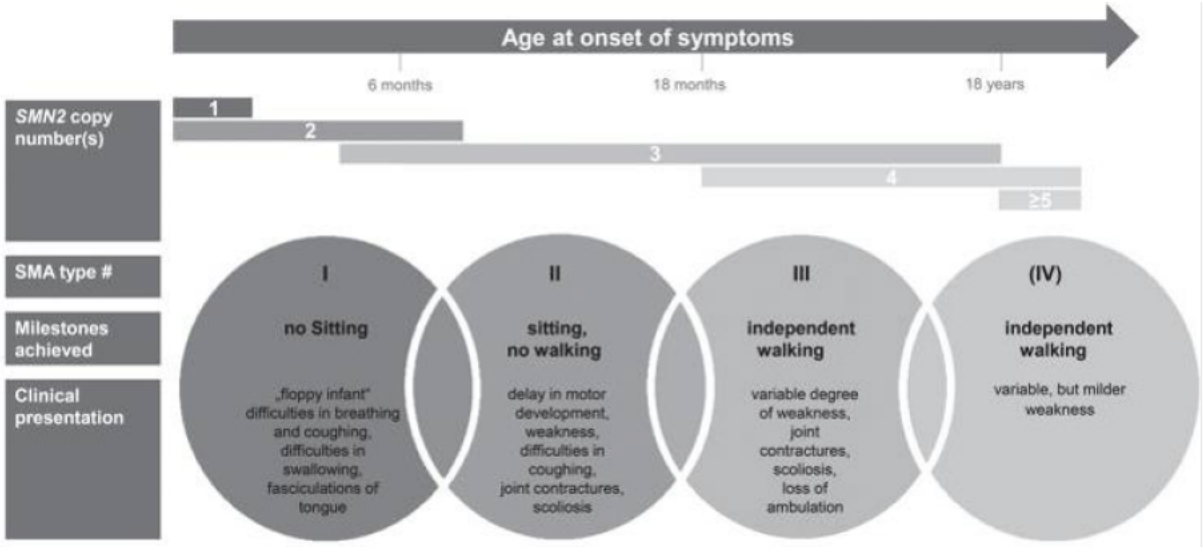
1.1 Background

Spinal Muscular Atrophy (SMA) is a neurogenetic disorder caused by a loss or mutation in the survival motor neuron 1 gene (*SMN1*) on chromosome 5q13, which leads to reduced SMN protein levels and a selective dysfunction of motor neurons. SMA is an autosomal recessive, early childhood disease with an incidence of approximately 1:10,000 live births (Ogino et al 2004, Sugarman et al 2012). Prior to available treatments, SMA was the leading cause of infant mortality due to genetic disease (Kaufmann et al 2012). A small amount of SMN protein (approximately 10 – 15 % of total) is also produced by the *SMN2* gene. The *SMN2* gene is almost identical to *SMN1*, but only partially functional (Rochette et al 2001, Kolb and Kissel 2011). Disease severity and clinical prognosis generally inversely correlate with the variable number of copies of *SMN2*. In the most common and severe form of SMA (Type 1), hypotonia and progressive weakness are recognized in the first few months of life, leading to diagnosis by 6 months of age and then death due to respiratory failure by 2 years of age. Motor neuron loss in SMA Type 1 is profound in the early postnatal period (or may even start in the pre-natal period), whereas patients with Type 2 and 3 SMA adapt and compensate during development and persist into adult life.

In support of the hypothesis that gene copy numbers of *SMN2* primarily drive phenotypic presentation of SMA, a large review examined the association between *SMN2* copy number and SMA phenotype (Calucho et al 2018). The authors showed that 79% of patients with two copies of *SMN2* developed SMA Type I, 16% developed SMA Type 2 and 5% developed SMA Type 3; 54% of patients with three copies of *SMN2* developed SMA Type 2, 31% developed SMA Type 3 and 16% developed SMA Type 1; and among patients with four copies of *SMN2*, most had mild SMA variants with only 1% developing SMA Type 1 and 11% developing SMA Type 2. In keeping with the importance of SMN production by *SMN2*, few individuals with *SMN1* mutations and ≥6 copies of *SMN2* develop symptoms and those who are affected develop only milder forms of SMA; while patients with one copy of *SMN2* often present with more severe forms of SMA (Bernal et al 2010, Riessland et al 2017).

SMA 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 spinal muscular atrophy (Kolb and Kissel 2011, Mercuri et al 2012). SMA Type 1 patients present with symptoms within the first 6 months of life and by definition never attain independent sitting. SMA Type 1 is the leading genetic cause of infant death. In contrast, SMA Type 2 manifests within the first 18 months of life and follows a slower disease progression as compared to SMA Type 1. Children with SMA Type 2 are able to maintain sitting unassisted but never walk independently and have a life expectancy of 20-40 years of age. SMA Type 3 patients attain the ability to walk unaided (Type 3a have onset <3 years of age; Type 3b have onset > 3 years of age), but untreated many of those patients will lose this ability at older age. SMA Type 4 is an adult onset form of the disease. Figure 1-1 summarizes SMA subtypes and associated clinical features as well as the relationship of the SMA subtypes to *SMN2* copy numbers.

Figure 1-1 **Clinical classifications according to onset, milestones achieved, and clinical presentation - typically associated *SMN2* copy numbers are displayed**



Schorling et al 2020

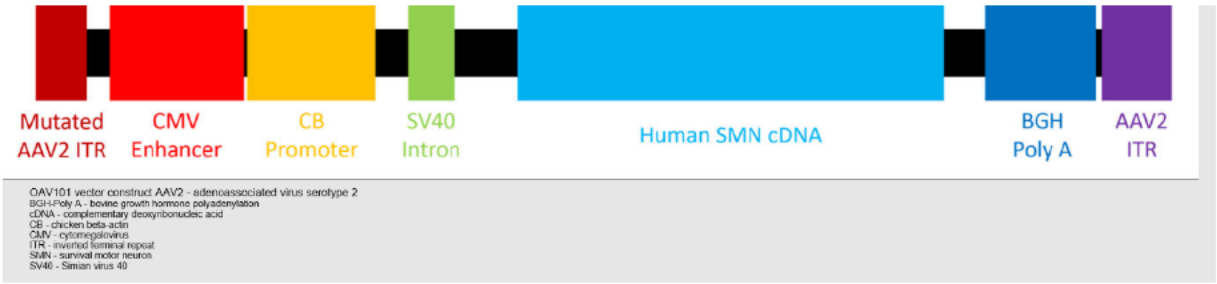
Irrespective of phenotypic classification, expert consensus is that all patients with biallelic pathogenic *SMN1* variants and up to 4 *SMN2* copies should receive SMN dependent therapy (Glascock et al 2018, Glascock et al 2020). Therapeutically increasing SMN levels leads to the most striking results in patients with SMA Type 1 (Mercuri et al 2018a, Pane et al 2019, Pechmann et al 2019, Aragon-Gawinska et al 2020). These results are thought to be mainly due to early intervention, preventing neurodegeneration and the associated progressive deterioration that is seen in all Type 1 SMA infants. These patients now experience improvement in their functional abilities and attain developmental milestones that had never previously been achieved in this population (Mercuri et al 2018a, Pane et al 2019, Pechmann et al 2019, Aragon-Gawinska et al 2020). A proportion of these infants acquire the ability to sit independently, and treatment can enable them to stand (usually with support), depending on how soon treatment is initiated after onset of symptoms. In children with SMA Type 2, treatment also clearly reduces progression of the disease compared with the natural history. For these patients, developing the ability to walk is a possibility.

Currently there are several treatments approved for treatment of SMA with different mechanisms of action such as splicing enhancers (nusinersen (Spinraza®) and risdiplam (Evrysdi®)) that modulate splicing of the *SMN2* gene thus functionally converting the *SMN2* gene into *SMN1* gene and increase the level of SMN protein in the central nervous system (CNS), and gene therapy (Zolgensma IV) which replaces a mutated or deleted *SMN1* with a functional copy. Nusinersen (Spinraza®, Biogen), approved by the Food and Drug Administration (FDA) in 2016 and the European Medicines Agency (EMA) in 2017, is an antisense oligonucleotide (ASO) that enhances the inclusion of exon 7 in messenger ribonucleic acid (mRNA) transcripts of *SMN2*. Nusinersen (Spinraza®) binds to an intronic splice-silencing-site in intron 7 of *SMN2*

and thereby suppresses the binding of other splice-factors. This results in an increased proportion of *SMN2*-mRNA with included exon 7 and consecutively more functional full-length *SMN2* protein (Schorling et al 2020). Following four loading doses over 58 days, nusinersen (Spinraza®) must be administered indefinitely every 4 months via IT injection. Nusinersen (Spinraza®) is approved for pediatric and adult patients with SMA. Risdiplam (Evrysdi®, Roche), approved by FDA in 2020 and EMA in 2021, is a small molecule, pyridazine derivative, that modulates *SMN2* gene splicing, binding two sites in *SMN2* pre-mRNA: 50 splice site (50 ss) of intron 7 and exonic splicing enhancer 2 (ESE2) in exon 7. Risdiplam (Evrysdi®) is administered orally once a day and is approved for treatment of SMA in patients 2 months of age and older in the US. Unlike OAV101, which is a one-time gene therapy, nusinersen (Spinraza®) and risdiplam (Evrysdi®) require lifelong treatment in order to sustain effectiveness. Therefore, OAV101, which targets the main source of SMN protein and provides sustained and uninterruptible SMN protein levels, may offer an important treatment option to patients who are unwilling or unable to commit to a chronic, lifelong therapy. Additionally, individuals with SMA may discontinue nusinersen (Spinraza®) or risdiplam (Evrysdi®) due to other reasons (e.g., suboptimal efficacy, safety, compliance, burden). Data collected in the real-world show that a population of patients who discontinue nusinersen (Spinraza®) exists already in SMA types 1-3. In a retrospective claims database analysis of over 300 patients, report of persistence rates of nusinersen (Spinraza®) use 12 months after treatment initiation is below 56% (Gauthier-Loiselle et al 2021). The SMA-related comorbidity profile was similar per SMA-type in subjects who discontinued and those who did not discontinue nusinersen (Spinraza®), but SMA-related comorbidities were increased in those patients with non-adherence for which logistical challenges were thought to play a role (Hache et al 2016,Gauthier-Loiselle et al 2021). Mean adherence rates were 71.84%, 74.37% and 75.57% for SMA Type 1, Type 2 and Type 3 respectively, and non-adherence also led to higher health care resource utilization days and higher health care costs per patient per year (Gauthier-Loiselle et al 2021). Given the shorter time that has lapsed since risdiplam (Evrysdi®) approval, similar data on patients who may discontinue risdiplam (Evrysdi®) is not yet available.

OAV101 gene therapy mechanism of action: OAV101 is a single treatment for patients with 5q SMA. OAV101 is a non-replicating recombinant adeno-associated virus serotype 9 (AAV9) containing the human SMN complementary deoxyribonucleic acid (cDNA) under the control of the cytomegalovirus (CMV) enhancer/chicken-β-actin-hybrid (CB) promoter (Figure 1-2). One of the two adeno-associated virus (AAV) inverted terminal repeats has been modified to promote intramolecular annealing of the transgene, thus forming a double-stranded transgene ready for transcription.

Figure 1-2 OAV101 vector construct



The mechanism of action of OAV101is designed to address the root cause of (5q)SMA by the delivery of a functional copy of the *SMN1* gene encoding for the SMN protein into target cells. The goal is to increase SMN protein levels in motor neurons prior to the development of irreversible injury and motor neuron loss, thereby modifying the patient's SMA phenotype to a milder course with improved quality of life and prolonged survival.

1.2 Purpose

The purpose of this study is to characterize the safety and tolerability of OAV101 IT in participants who have discontinued treatment with nusinersen (Spinraza®) or risdiplam (Evrysdi®). The data from this study will expand on the data generated from other studies of OAV101 IT in the treatment naive SMA population. Specifically, data from this study may provide evidence in support of management and monitoring for patients with SMA who discontinue nusinersen (Spinraza®) or risdiplam (Evrysdi®) to receive OAV101 IT. In addition to the collection of safety and tolerability data, efficacy will be assessed to support evaluation of OAV101 IT for the treatment of this SMA population. Participants will receive a single dose of OAV101 (1.2×10^{14} vector genomes) by lumbar IT injection after the defined period off nusinersen (Spinraza®) or risdiplam (Evrysdi®); and safety, tolerability, and efficacy will be evaluated over a 52-week period. Approximately 28 participants aged 2 to <18 years will be enrolled. Age of participants enrolled will be stratified as 2 to 5 years (inclusive of all 5-year-olds) and 6 to <18 years, with approximately 12 subjects in each stratum.

2 Objectives, endpoints and estimands

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To characterize the safety and tolerability of OAV101 IT over a 52-week period in patients with SMA aged 2 to < 18 years who have discontinued treatment with nusinersen (Spinraza®) or risdiplam (Evrysdi®).	• Number and percentage of participants reporting AEs, related AEs, SAEs, and AESIs
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the efficacy of OAV101 IT on motor function, and caregiver impact over a 52-week period in patients with SMA aged 2 to < 18 years who have discontinued treatment with nusinersen (Spinraza®) or risdiplam (Evrysdi®)	• Change from baseline to Week 52 visit in the HFMSE total score • Change from baseline to Week 52 visit in the RULM total Score

Objective(s)	Endpoint(s)
	• Change from baseline to Week 52 visit in Assessment of Caregiver Experience in ACEND instrument score

[redacted]

[redacted]

- Number and percentage of participants with suicidal ideation, suicidal behavior, or self-injurious behavior as assessed by the C-SSRS

[redacted]

2.1 Primary estimands

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results.

The primary clinical question of interest is: *What is the effect on safety and tolerability of OAV101 IT for patients with SMA* w*ho were discontinued from treatment with nusinersen (Spinraza®) or risdiplam (Evrysdi®).*

The primary estimand is described by the following attributes:

1. Population: Patients with SMA aged 2 to <18 years who were treated with OAV101 IT administration after the discontinuation of nusinersen (Spinraza®) or risdiplam (Evrysdi®).
2. Endpoint (the primary variable): AEs, related AEs, SAEs and AESIs.
3. Treatment of interest: OAV101 IT

Handling of intercurrent events (including receiving prohibited concomitant medications):

Treatment policy strategy, i.e., reporting all observed AEs, related AEs, SAEs (including death) and AESIs during the trial period, will be used regardless of whether intercurrent events occurred or not. Loss to follow-up does not impact primary estimand under treatment policy strategy.

Summary measures: The number and percentage of participants reporting AEs, related AEs, SAEs and AESIs will be summarized by strata and overall. Summaries will also be provided by MedDRA SOC and preferred term.

2.2 Secondary estimands

The secondary clinical question of interest is: *What is the effect on efficacy of OAV101 IT for patients with SMA who were discontinued from treatment with nusinersen (Spinraza®) or risdiplam (Evrysdi®).*

The secondary estimand is described by the following attributes:

1. Population: Patients with SMA aged 2 to < 18 years who were treated with OAV101 IT administration after the discontinuation of nusinersen (Spinraza®) or risdiplam (Evrysdi®).
2. Endpoint (the secondary variable): Change from baseline to Week 52 in the HFMSE total score, change from baseline to Week 52 in the RULM total score, and change from baseline to Week 52 in the ACEND instrument total score.
3. Treatment of interest: OAV101 IT

The intercurrent events will include receiving prohibited concomitant medications, study discontinuation due to any reason. All available assessments collected up to Week 52 visit / EOS visit regardless intercurrent events will be included in the analyses following a treatment policy strategy.

Summary measures: mean changes from baseline in HFMSE total score, RULM total score as well as ACEND instrumental total score.

3 Study design

This is a Phase IIIb open-label, single arm, multi-center study to evaluate the safety, tolerability and efficacy of OAV101 IT in patients with SMA aged 2 to < 18 years after the discontinuation of treatment with nusinersen (Spinraza®) or risdiplam (Evrysdi®). The study is comprised of 3 periods, Screening (includes Baseline), Treatment, and Follow-up (Figure 3-1).

Screening Period

Participants will undergo screening procedures for up to 45 days prior to OAV101 IT treatment (Screening Visit 1 and Screening Visit 2 as detailed in Table 8-1) during which time initial eligibility will be determined (pending confirmation of all criteria including time off nusinersen (Spinraza®) or risdiplam (Evrysdi®) treatment at Baseline).

The eligibility criterion relating to timeframe of nusinersen (Spinraza®) or risdiplam (Evrysdi®) discontinuation treatment will be confirmed at Baseline on Day -1.

On Day -1, eligible participants will be admitted to the hospital for pre-treatment Baseline procedures (Table 8-1) including prednisolone treatment per study protocol (or an equivalent corticosteroid, Section 6.2).

Treatment Period

On Day 1, participants meeting Screening and Baseline eligibility criteria will receive lumbar puncture with CSF withdrawal for analyses in accordance with the Assessment Schedule (Table 8-1) and receive a single IT injection of OAV101. Following OAV101 administration, participants will undergo in-patient safety monitoring over at least the next 48 hours (Table 8-1).

Follow-up Period

During the 52-week Follow-up Period safety and efficacy assessments will be performed in accordance with the Assessment Schedule (Table 8-1).

Final analysis will be performed after all participants have completed Week 52 or discontinued prior to Week 52. At the end of study, participants will be invited to enroll in a Novartis-sponsored long-term follow-up study to monitor long-term safety and efficacy.

Figure 3-1 Study design

4 Rationale

4.1 Rationale for study design

Table 4-1 Rationale for study design

Overall	This open-label, single arm, multi-center study design in pre-treated patients with SMA allows for collection of safety and tolerability data and descriptive evaluation of efficacy data, to characterize OAV101 IT in these patients in a clinical trial setting, mirroring the majority of anticipated use in the real world. An open label design with no internal control arm is most ethical for patients who have access to other SMN-targeting treatments, and most appropriate for the treatment exposed population as their safety and efficacy data may be confounded by previous treatment. These data will complement the results of a study in treatment naive patients to fully characterize OAV101 IT. Primary endpoint: the number and percentage of AEs, related AEs, SAEs and AESIs. Secondary endpoints: change from baseline in HFMSE total score, change from baseline in RULM total score, and change from baseline in ACEND instrument score at the end of the 52-week period. The assessments used are appropriate for this indication and study population.
Duration of study	A clinical study duration of 52 weeks provides the optimal time frame to characterize the safety and tolerability of OAV101 for IT administration in this study population, (See Section 4.5), striking a reasonable balance between the ability to assess safety in pre-treated patients and adherence to follow-up visits and caregiver burden. Clinical studies with OAV101 IV showed that safety and efficacy can be sufficiently assessed within this timeframe for patients with SMA. The assessment schedule is therefore based on a 52-week follow-up period.

Duration of prior SMA therapy	Participants included in this study are required to have had at least four loading doses of nusinersen (Spinraza®) or at least 3 months of treatment with risdiplam (Evrysdi®) prior to Baseline (Day-1). This is to ensure the participants are exposed to previous treatments of nusinersen (Spinraza®) or risdiplam (Evrysdi®), and for clinicians to determine a risk/benefit profile of OAV101 in treatment experienced patients.
Time off prior SMA therapy	Participants should have received their latest dose of prior medication at least 4 months prior to the Baseline Visit (Day -1) for nusinersen (Spinraza®) or at least 15 days prior to the Baseline Visit (Day -1) for risdiplam (Evrysdi®). For nusinersen (Spinraza®), a period of 4 months will allow participants to receive OAV101 at the same time when their next maintenance dose of nusinersen (Spinraza®) would have been due, though some participants may also have discontinued nusinersen (Spinraza®) prior to this. For risdiplam (Evrysdi®) (half-life 2 days), a period of 15 days will result in >99% of the drug being cleared from the plasma.

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, occupational, and speech-language therapies; other forms of supportive therapies are allowed but the frequency should remain the same during the clinical study, if possible. Prevention of infection therapies should be conducted in accordance with treatment guidelines and local practice.

Participants are expected to have access to respiratory equipment (e.g. cough assist machine) in the event they are required during the course of the study (e.g. develop a respiratory illness). The use of concomitant therapies or procedures must be documented on the appropriate Case Report Form (CRF) (see Section 6.2.1)

4.2 Rationale for dose/regimen and duration of treatment

OAV101 will be administered in this trial as a single IT injection as a nominal dose of 1.2 x 10^{14} vector genomes (vg). This dose was selected for assessment in this study based on the totality of clinical and nonclinical data, taking into consideration well established literature showing constant CSF volumes from 2 years of age into adulthood (Matsuzawa et al 2001). The AVXS-101-CL-102 trial explored the safety and efficacy of OAV101 IT in SMA type-2 patients between 6 months and 5 years of age at three doses; Dose A (N=3; 6.0 x 10^{13} vg), Dose B (N=25; 1.2 x 10^{14} vg) and Dose C (N=4; 2.4 x 10^{14} vg). Robust motor improvements were seen in the older ≥ 24 months to <5-year age group who were treated with dose B (1.2 x 10^{14} vg). These improvements were statistically significant and clinically meaningful; the estimated difference (95% confidence interval [CI]) relative to the Pediatric Neuromuscular Clinical Research (PNCR) dataset for the change in HFMSE from baseline to Month 12 was 5.5 (1.9, 9.0) points, with a p-value of 0.0027. In these older patients, 11/12 (91.7%) patients achieved the ≥3-point change in HFMSE, which is usually accepted to demonstrate clinically meaningful

improvement in the HFMSE (Krosschell et al 2011, Mercuri et al 2018b). Dose B demonstrated clear clinical efficacy in Study AVXS-101-CL-102. More information on safety of OAV101 IT can be found in the Investigator's Brochure. Based on the totality of available non-clinical and clinical data, the flat dose of 1.2 x10^{14} vg patient administered intrathecally is appropriate for the patient population in this study.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Not applicable

4.4 Purpose and timing of interim analyses/design adaptations

Interim analyses may be conducted for internal decision-making purposes, in response to health authority requests, and/or for purposes of scientific publication.

4.5 Risks and benefits

OAV101 IT can achieve sustained expression of SMN in motor neurons with one-time dosing, which can fulfil a clear unmet need in SMA patients unable to commit to chronic, lifelong therapy.

Uninterruptable and constant SMN protein production within motor neurons positively impacts the clinical phenotype by allowing motor development which leads to stability in motor function. Clinical data to date suggest OAV101 is well tolerated with an acceptable benefit/risk profile when administered to patients with 5qSMA with 2 or 3 survival motor neuron 2 *(SMN2*) copies or a clinical diagnosis of SMA. Safety and clinically meaningful efficacy with IT delivery of OAV101 was observed in the AVXS-101-CL-102 trial.

The AVXS-101-CL-102 trial explored the safety and efficacy of OAV101 IT in SMA Type-2 patients between 6 months and 5 years of age at three doses; Dose A (N=3; 6.0 x 10^{13} vg), Dose B (N=25; 1.2 x 10^{14} vg) and Dose C (N=4; 2.4 x 10^{14} vg). Robust motor improvements were seen in the older ≥ 24 months to <5-year age group who were treated with dose B (1.2 x 10^{14} vg). These improvements were statistically significant and clinically meaningful; the estimated difference (95% confidence interval [CI]) relative to the PNCR dataset for the change in HFMSE from baseline to Month 12 was 5.5 (1.9, 9.0) points, with a p-value of 0.0027. In these older patients, 11/12 (91.7%) patients achieved the ≥3-point change in HFMSE, which is usually accepted to demonstrate clinically meaningful improvement in the HFMSE (Krosschell et al 2011, Mercuri et al 2018b). Dose B demonstrated clear clinical efficacy in Study AVXS-101-CL-102 study.

Each of the following is an important identified or important potential risk associated with OAV101:

- Hepatotoxicity
- Transient thrombocytopenia
- Thrombotic microangiopathy
- Cardiac adverse events

- Dorsal root ganglia toxicity
- Theoretical risk of tumorigenicity due to vector integration

The risk to participants in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring. Refer to the Investigator's Brochure for summary of OAV101 safety data.

Theoretical risk of tumorigenicity due to vector integration

There is a theoretical risk of tumorigenicity due to integration of AAV vector DNA into the genome.

OAV101 is composed of a non-replicating AAV9 vector whose DNA persists largely in episomal form. Rare instances of random vector integration into human DNA are possible with recombinant AAV. The clinical relevance of individual integration events is unknown, but it is acknowledged that individual integration events could potentially contribute to a risk of tumorigenicity.

Risk of immunosuppression

All participants in the study will receive prophylaxis immunosuppression with prednisolone or an equivalent corticosteroid to mitigate safety risks associated with inflammation. The chronic use of corticosteroids may be associated with hypothalamic-pituitary-adrenal axis suppression, Cushing's syndrome and hyperglycemia which can be mitigated with adequate tapering. Increased susceptibility to new infections or exacerbation and dissemination of latent infections, as well as elevated blood pressure, salt and water retention, hypokalemia, and gastrointestinal perforation have been reported. Risks will be mitigated by close monitoring, and implementation of standard prophylaxis and tapering protocol as detailed in Section 6.2.

Risk of phlebotomy

European Medicines Agency (EMA) Guidelines for blood testing in pediatric participants will be followed (EMA 2001). Maximum 18 ml of blood will be collected at each visit requiring a blood sample for children aged 6 to 18 years. Maximum 10 ml of blood will be collected at each visit requiring a blood sample for children aged 2 to 5 years.

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.

[redacted]

The test to measure [redacted] to determine participant eligibility [redacted] for this purpose. Thus, while the test can be utilized to measur [redacted]
Therefo
benefit-risk of OAV101 in participants with [redacted] has not been determined.

Summary

In summary, available data suggest OAV101 IT one-time administration can provide a stable source of SMN protein via replacement of *SMN1*, and has the potential to improve the SMA-related comorbidity profile in these patients, as well as removing issues such as compliance and long-term burden associated with chronic therapies.

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, or natural disaster, mitigation procedures to ensure participant safety and trial integrity may be implemented. Notification of the Public health emergency as declared by local or regional authorities should be discussed among investigators and Novartis. All procedures adapted to the situation must be submitted, if required as per local regulations, through a protocol amendment for approval by local or regional Health Authorities and Ethics Committees prior to implementation of mitigation procedures.

5 Study Population

Approximately 28 participants with SMA with bi-allelic mutations in the *SMN1* gene aged 2 to < 18 years (screening visit must occur before the patient's 18th birthday) will be enrolled stratified as 2 to 5 years and 6 to < 18 years with approximately 12 subjects in each stratum. Participants must have received at least four loading doses of nusinersen (Spinraza®) or at least 3 months of risdiplam (Evrysdi®) for the treatment of SMA.

5.1 Inclusion criteria

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

1. Written informed consent must be obtained before any assessment is performed
2. SMA diagnosis based on gene mutation analysis with bi-allelic *SMN1* mutations and any copy of *SMN2* gene
3. Aged 2 to <18) years of age at time of Screening Visit 1
4. Have had at least four loading doses of nusinersen (Spinraza®) or at least 3 months of treatment with risdiplam (Evrysdi®) at Screening
5. Must be able to sit independently but must never have taken steps independently
   - *Definition of sitting independently: 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 (*Wijnhoven et al 2004*).*
6. Diagnosed through newborn or neonatal screening or patients clinically diagnosed must have age of clinical symptom onset < 18 months
7. Meets age-appropriate institutional criteria for use of anesthesia/sedation as assessed by the physician responsible for administering anesthesia/sedation
8. Must obtain bilateral radial and sural nerve SNAPs at Screening
9. Female participants who are sexually active or have reached menarche must have a negative pregnancy test at Screening. Those females who are sexually active must also

agree to use highly effective methods of contraception (implants, injectables, oral contraceptives [hormonal], intrauterine devices (IUDs), total abstinence) as well or limit sexual activity to surgically sterilized or contraception-practicing partners during the trial and for 24 months after the administration of the investigational product. Female participants must agree to refrain from egg freezing and egg donation until 24 months after dosing. Note: In case of use of oral contraceptives, females should have been stable on the same pill for a minimum of 3 months before OAV101 administration. If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the informed consent form (ICF).

10. Males capable of fathering a child must agree to use barrier contraception (combination of a condom and spermicide) or be abstinent for 6 months after OAV101 administration. In addition, male patients must agree to refrain from sperm donation or 12 months after OAV101 administration.

5.2 Exclusion criteria

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

1. Excluding SMA, any medical condition considered clinically significant by the Investigator, including permanent ventilatory support, cardiomyopathy, hepatic dysfunction, kidney disorder, endocrine disorder including diabetes mellitus, gastrointestinal disorders, metabolic disorders, severe respiratory compromise and significant brain abnormalities at either Screening or Baseline visits
2. Positive for Human Immunodeficiency Virus (HIV), Hepatitis B or Hepatitis C
3. Anti Adeno Associated Virus Serotype 9 (AAV9) antibody titer using an immunoassay is reported as elevated at Screening (reference to > 1:50 or a validated result consistent with being elevated)
4. Platelet count less than the lower limit of normal at Screening
5. Platelet transfusion within 1 month prior to Screening Visit 1 and up to administration of OAV101
6. Clinically significant abnormal coagulation panel results at Screening
7. Hepatic dysfunction (i.e. ALT, TBL, GGT or GLDH > ULN) at Screening (with the exception of isolated aspartate aminotransferase (AST) elevation: in the absence of other liver laboratory abnormalities, isolated elevated AST is not considered exclusionary)
8. Clinically significant abnormalities in test results during screening period and/or at Baseline as determined by the Investigator
9. Contraindications for lumbar puncture procedure (including but not limited to cutaneous infection at the treatment site, and signs or symptoms of increased intracranial pressure), active administration of any intrathecal therapy, presence of an implanted shunt for the drainage of CSF, presence of implanted CNS catheter, or any impediment to CSF access
10. Conditions, as determined by the investigator, that would interfere with the intrathecal administration/lumbar puncture procedure (e.g., severe scoliosis)
11. At Baseline (Day -1), participants are excluded if they received:
    - nusinersen (Spinraza®) within 4 months at Baseline

- risdiplam (Evrysdi®) within 15 days at Baseline

12. Vaccinations 2 weeks prior to administration of OAV101
13. Participants will be excluded for hospitalization for a pulmonary event, or hospitalization for nutritional support within 2 months prior to Screening and up to administration of OAV101. In addition, patients will not be eligible if during Screening, inpatient major surgery is planned at any time during the 52-week follow up period of the study
14. Presence of any of the following:
    - An active infectious process requiring systemic therapy intended to eliminate the infection up to 30 days prior to administration of OAV101
    - An active but untreated viral or bacterial infectious process up to 30 days prior to administration of OAV101
    - Any febrile illness up to 30 days prior to administration of OAV101
15. Clinical or radiological signs of aspiration within 4 weeks prior to Screening Visit 1 and up to administration of OAV101
16. Requiring invasive ventilation, awake noninvasive ventilation for > 6 hours during a 24-hour period, noninvasive ventilation for > 12 hours during a 24-hour period or requiring tracheostomy at Screening and up to administration of OAV101
17. Awake hypoxemia (defined as O_2 saturation <95% in room air) at Screening and up to administration of OAV101
    - NOTE: For altitudes >1000 m, awake hypoxemia is defined as O_2 saturation <92% in room air
18. BMI < 3rd percentile at Screening if considered clinically significant by the investigator based on the WHO Child Growth Standards (WHO 2022a) and WHO Growth reference data for 5-19 years (WHO 2022b).
19. Inability to tolerate corticosteroids administered by mouth or gastrostomy tube
20. History of gene therapy, hematopoietic transplantation, or solid organ transplantation
21. Current or scheduled participation in another investigational trial in which the participant receives treatment, or use of other investigational drugs within 30 days prior to Screening Visit 1, 5 half-lives prior to Screening Visit 1 or during the screening period (small molecules), or until the expected pharmacodynamic effect has returned to baseline (e.g. for biologics), whichever is longer; or longer if required by local regulations.
    - NOTE: Participation in observational cohort studies or non-interventional studies in which the participant does not receive treatment or undergo procedures which may compromise this study data integrity may be allowed following Sponsor approval.
22. Plan to take any other investigational therapies relating to SMA while participating in this study
23. Concomitant use of any of the following medication categories within 90 days prior to administration of OAV101:
    - Ongoing systemic immunosuppressive therapy (e.g.,corticosteroids [except prophylactic use before OAV101 IT injection], cyclosporine, tacrolimus,

methotrexate, cyclophosphamide, intravenous immunoglobulin, rituximab), plasmapheresis, immunomodulators (e.g., adalimumab)

24. History of hypersensitivity to any of the study treatments or its excipients or drugs of similar chemical classes
25. History of untreated or uncorrected vitamin deficiencies which can produce sensory neuropathies such as pyridoxine deficiency (Vitamin B6)
26. Any medication deemed by Principal Investigator to pose an unacceptable safety risk for gene therapy administration
27. Clinically significant sensory abnormalities in the neurological examination at Screening

6 Treatment

The investigational drug, OAV101, will be prepared by Novartis and supplied to the study-site pharmacist or equivalent per local practice. The pharmacist (or equivalently trained individual per local practice) will prepare the appropriate dosage (detailed instructions will be provided in the Pharmacy Manual).

6.1 Study treatment

For this study, the terms "investigational drug" or "study treatment" refers to OAV101 administered as a single IT dose of 1.2 x 10^{14} vector genomes. The investigational drug OAV101 will be prepared and supplied by Novartis. See the Pharmacy Manual for OAV101 storage, preparation, and administration procedures.

6.1.1 Investigational and control drugs

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 inverted terminal repeats (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

Treatment title	OAV101 (formerly AVXS-101)
Treatment description	1.2 x 10^{14} vector genomes in 3 ml, one time
Type	Biologic
Dose Formulation	Solution
Route of Administration	Intrathecal injection
Use	Experimental
IMP	Yes
Sourcing	Provided centrally by the sponsor or locally by designee
Packaging and Labeling	Study treatment will be provided in a single vial carton. Each vial carton will be labeled as required per country requirement.

6.1.2 Additional study treatments

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

6.1.3 Treatment arms/group

Single treatment arm with OAV101 IT.

6.1.4 Treatment duration

OAV101 IT is a one-time, single dose treatment for SMA.

6.2 Other treatment(s)

In accordance with this protocol, all study participants will receive immunomodulatory therapy with prednisolone or equivalent.

The Investigator must promote compliance with the administration of prednisolone (or equivalent) by instructing the participant/caregiver to administer as prescribed and by stating that compliance is necessary for the participant's safety.

Immunomodulatory therapy is intended to mitigate safety risks associated with immune response to the AAV9 capsid that may occur after administration of OAV101.

Immune responses may lead to elevations in liver transaminases, elevations of Troponin I or decreased platelet counts.

Prior to initiation of the immunomodulatory regimen and prior to administration of OAV101, the participant must be checked for symptoms of active infection and/or febrile illness of any nature.

Starting approximately 24 hours prior to OAV101 IT injection, prednisolone will be instituted according to the schedule in Table 6-2 below.

Table 6-2 Prednisolone prophylaxis

Period	Dosing schedule	Dose
[redacted]	[redacted]	Prednisolone [redacted]
[redacted]	[redacted]	Prednisolone [redacted]
[redacted]	[redacted]	[redacted]
[redacted]		

For participants who require steroid dosing longer than 60 days total (including the tapering period) consider hepatology and infectious diseases specialty evaluations to address risk of opportunistic infections and recommendations for infectious prophylaxis. The prescribed dose regimen of prednisolone and all subsequent dose changes must be recorded in the respective eCRF page.

6.2.1 Concomitant therapy

The Investigator should instruct the participant and his/her parent(s)/caregiver(s) to notify the study site about any new medications taken by the participant after enrollment into the study. All medications, procedures, and significant non-drug therapies administered after the participant was enrolled into the study must be recorded on the appropriate CRFs, including nusinersen or risdiplam.

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.

Prior medications excluded according to the criteria in Section 5.2 will be recorded within 90 days prior to Screening and all prior medications will be recorded on the eCRF at all visits prior to Baseline. If the participant's last dose of nusinersen or risdiplam was beyond 90 days prior to Screening, this must still be recorded on the eCRF.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Participants are encouraged to follow all routinely scheduled immunizations, recommended by local health authorities and consistent with Section 6.2.2, throughout the study. Where feasible, the participant’s vaccination schedule should be adjusted to accommodate concomitant corticosteroid administration prior to and following OAV101, specifically vaccinations must be withheld 2 weeks pre OAV101 administration, and live vaccines must not be administered while receiving corticosteroids.

Participants and caregivers should be advised to follow local site guidelines on vaccination against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). For participants who are required to receive vaccination for SARS-CoV-2, the vaccination series (if multi-dose regimen) must be completed at least 2 weeks prior to OAV101 administration. For participants already in the study, potential benefits for vaccination against SARS-CoV-2 should be assessed on a case-by-case basis and is at the discretion of the Investigator. If a live/attenuated SARS-CoV-2 vaccine becomes available, participants are advised to complete the vaccination series prior to enrolling in the study, and such vaccines are prohibited while receiving corticosteroids. Vaccinations must be recorded as a concomitant medication.

6.2.2 Prohibited medication

Except for concomitant medication allowed per protocol (see Section 6.2.1) and/or any non-excluded medications which may be medically indicated, no medication other than study treatment will be allowed from the date the informed consent 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, including nusinersen and risdiplam beyond the cut-off time.

- Any investigational medication other than OAV101
- Plasmapheresis and immunomodulators (except prednisolone or equivalent, for prophylaxis or treatment of adverse events), unless medically indicated.
- Use of non-live vaccines 4 weeks after injection of OAV101; unless medically indicated
- Live vaccines are prohibited while receiving corticosteroids. Participants are advised to complete all age-appropriate inoculations with live vaccines prior to enrolling in the study if possible.
- The use of immunosuppressive therapies, including but not limited to, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, intravenous immunoglobulins, rituximab, and adalimumab; unless medically indicated.
- Hepatotoxic agents, unless medically indicated.

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

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

6.3 Preparation and dispensation

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

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

Investigator staff will identify the study medication kits to dispense to the participant by contacting the Interactive Response Technology (IRT) and obtaining the medication number(s).As per Section 4.6, 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, at-home visits may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate). In this case, regular phone calls or virtual contacts per the Assessment Schedule (Table 8-1) will occur between the site and the participant for instructional purposes, safety monitoring, drug accountability, investigation of any adverse events, ensuring participants continue to benefit from treatment and discussion of the participant´s health status until the participants can resume visits at the study site.

OAV101 will arrive as outlined in the Pharmacy Manual. A single administration of OAV101 will be prepared by an appropriately trained pharmacist (or equivalent). Preparation of OAV101 will be done aseptically under sterile conditions at the site per Pharmacy Manual. OAV101 IT will be administered in the appropriate setting with immediate access to acute critical care management. The investigational delivery system will be prepared and used in accordance with the Pharmacy Manual.

6.3.1 Handling of study treatment and other treatment

6.3.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified in the Pharmacy Manual.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization (CO) Quality Assurance. Please refer to procedures as outlined in the Pharmacy Manual.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The designated site personnel must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial.

At the conclusion of the study, and as appropriate during the course of the study, the designated site personnel will return the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

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

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

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

6.3.1.2 Handling of other treatment

Not applicable

6.4 Participant numbering, treatment assignment, randomization

6.4.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened, as a result of screen failure. The

Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

The Investigator or designated staff will contact the IRT and provide the requested identifying information to register the participant. Once assigned, the Participant No. must not be reused for any other participant and the Participant No. for that individual must not be changed unless the participant is re-screened. The site should select the eCRF book with a matching Participant Number from the EDC system to enter data. If the participant fails to be treated for any reason, the IRT must be notified within 2 days that the participant was not treated. Re-screening is allowed once for participants that were initially screen failures for any reason. 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 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.

6.4.2 Treatment assignment, randomization

This is an open-label study where all eligible participants will receive OAV101 IT. No randomization will be performed.

6.5 Treatment blinding

Not applicable

6.6 Dose escalation and dose modification

Investigational or other study treatment dose adjustments and/or interruptions are not permitted. OAV101 is administered once intrathecally at a fixed dose of 1.2×10^{14} vector genomes.

6.6.1 Definitions of dose limiting toxicities (DLTs)

Not applicable

6.6.2 Dose modifications

Not applicable

6.6.3 Follow-up for toxicities

Not applicable

6.7 Additional treatment guidance

6.7.1 Treatment compliance

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

6.7.2 Administration procedures

For details on sedation/anesthesia, setting, and IT administration, please refer to the Pharmacy Manual.

6.7.3 Post-administration monitoring

Following OAV101 administration participants will return to a designated pediatric intensive care unit (PICU) bed, or other appropriate setting, with close monitoring of vital signs. Concomitant medications and all adverse events/serious adverse events will also be monitored and documented following dosing procedures. Participants will be kept in the PICU patient room or other appropriate setting with immediate access to acute critical care management for at least 48 hours for closer monitoring of mental status. If there are suspected complications related to post- LP as assessed by the Investigator and/or proceduralist, local standard practice should be followed. Optional assessments will be based on local and institutional standards, and may include safety assessments such as magnetic resonance imaging (MRI) of brain and spine (Table 8-1). Other assessments should be performed as deemed necessary based on the Investigator and/or proceduralist discretion. Reports will be retained as source data and adverse events will be entered in the eCRF if applicable.

For full details on post-administration procedures please refer to the Pharmacy Manual.

6.7.4 Recommended treatment of adverse events

The Investigator will use his/her medical judgement in accordance with standard of care to treat adverse events. Medication and/or intervention used to medically manage AEs must be recorded on the appropriate CRF. At present there is insufficient information to provide specific recommendations regarding treatment of adverse events other than prednisolone (or an equivalent) used to dampen the immune reaction directed against OAV101 (Table 6-2).

6.7.5 Emergency breaking of assigned treatment code

Not applicable

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation) Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent.

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 level of understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

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

Novartis will provide to Investigators, in a separate document, a proposed informed consent and assent forms that complies with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Good Clinical Practice (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 common side effects already known about the the investigational treatment can be found in the Investigator Brochure. This information will be included in the participant informed consent and should be discussed with the caregiver(s)/parent(s)/legal guardian and/or participant upon obtaining consent and also during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between Investigator's Brochure 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 caregiver(s)/parent(s) and/or participant.

The following informed consents are included in this study:

- Global Model Parent Legal Guardian ICF
  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on coded data collected during this study
  - A subsection that requires a separate signature for the 'Optional Consent for Autopsy' to allow, in the event of the death of a participant, 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 coronavirus disease of 2019 (COVID-19) pandemic, a separate Home Nursing consent document must be used in addition to the main ICF (in accordance to local regulations)
  - [redacted]
- Global Model Child Assent Form
- Global Model Adolescent Assent Form

- Global Pregnancy Follow-up Model ICF for Pregnant Participant
- Global Pregnancy Follow-up Model ICF for Pregnant Partner of Male Participants
- [redacted]
- [redacted]

Females of child-bearing potential are defined as all females physiologically capable of becoming pregnant. This includes female pediatric participants who are menarchal or who become menarchal during the study.

Serum pregnancy test will be performed for all females of child-bearing potential according to the protocol assessment schedule (See Table 8-1).

All menarchal females and their parents/caregivers should be informed about the potential risks of pregnancy and the need to prevent pregnancy during the study.

Male participants must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

[redacted]

It is important to be sensitive in introducing this issue, as understanding and comprehension of puberty, sexual activity, pregnancy and contraception is influenced by age, as well as factors such as precocity, socio(educational) economic and familial background. These discussions with the participant and her parents/caregivers are therefore best performed by investigators familiar with the pediatric participant and her family and should be guided by requirements of the local regulatory authorities. These discussions should take into account the socio-economic, cultural factors and religious beliefs of the adolescent participant and her family. The investigator should also discuss the management of the pregnancy test results with the participant and her parents/caregivers. The privacy of the participant should be considered in accordance with the local law and ethics.

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

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g., telephone, videoconference) if allowable by a local Health Authority.

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

8 Visit schedule and assessments

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

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. The efficacy assessments HFSME and RULM may occur over more than 1 day within the visit window, but must not exceed 4 days. Missed or rescheduled visits should not lead to automatic discontinuation. Participants who discontinue from the study or withdraw their consent/oppose the use of their data/biological samples should be scheduled for a final evaluation visit if they agree 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 not previously reported must be recorded on the CRF.

The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

As per Section 4.6, 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, national and local regulations and depending on operational capabilities, phone calls, virtual contacts (e.g., tele consultation) or visits by site staff/ off-site healthcare professional(s) to the participant´s home, can replace certain protocol assessments, for the duration of the disruption until it is safe for the participant to visit the site again. If the Investigator delegates tasks to an off-site healthcare professional, the Investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The Investigator must oversee their conduct and remain responsible for the evaluation of the data collected.

Table 8-1 Assessment Schedule

Period	**Screening**		**Baseline**	**Treatment Period**			**Follow-up Period**											
Visit Name	**Visit 1**	**Visit 2**	**Baseline Visit**	**Day 1**	**Day 2**	**Day 3**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 22**	**Week 32**	**Week 42**	**Week 52/EOS** [1]
Days	**-45 -0 +15**	**-21 ±2**	**-1**	**1**	**2 to 2**	**3 to 3**	**8 ±2**	**15 ±2**	**22 ±2**	**29 ±2**	**43 ±2**	**57 ±2**	**71 ±2**	**85 ±7**	**155 ±7**	**225 ±7**	**295 ±14**	**365 ±21**
Informed consent/assent	X																	
Demography	X																	
Medical history/current medical conditions	X																	
[redacted]																		
Information to be collected on screening failures	X[4]	X[4]	X[4]															
IRT contact	X	X		X														
Inclusion / Exclusion criteria	X	X	X															
Sensory Nerve Action Potential (SNAP)/Electrophysiology	X	X[5]																
Chest X-ray	X																	
[redacted]																		
Prophylactic prednisolone			X[6]	X	X	X	X	X	X	X	X	X[7]						
OAV101 IT administration				X[8]														

Period	**Screening**		**Baseline**	**Treatment Period**			**Follow-up Period**											
Visit Name	**Visit 1**	**Visit 2**	**Baseline Visit**	**Day 1**	**Day 2**	**Day 3**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 22**	**Week 32**	**Week 42**	**Week 52/EOS[1]**
Days	**-45 -0 +15**	**-21 ±2**	**-1**	**1**	**2 to 2**	**3 to 3**	**8 ±2**	**15 ±2**	**22 ±2**	**29 ±2**	**43 ±2**	**57 ±2**	**71 ±2**	**85 ±7**	**155 ±7**	**225 ±7**	**295 ±14**	**365 ±21**
Post-administration monitoring[9]				X	X	X												
Prior medications	X	X	X[10]	X														
Concomitant medications and therapies				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X[11]	X[11,12]	X[11]	X[11]	X	X	X	X	X	X	X	X	X	X	X	X
BMI	X		X							X		X			X	X	X	X
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Height (Segmental by Tibial Length)	X		X							X		X			X	X	X	X
Neurological Examination[13]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination[14]	S		S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Adverse events/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Columbia Suicide Severity Rating Scale (C-SSRS)[15]			X				X	X	X	X	X	X	X	X	X	X	X	X
Hammersmith Functional Motor Scale Expanded (HFMSE)[16]	X		X							X		X		X	X	X	X	X
Revised Upper Limb Module (RULM)[16]	X		X							X		X		X	X	X	X	X

Period	**Screening**		**Baseline**	**Treatment Period**			**Follow-up Period**											
Visit Name	**Visit 1**	**Visit 2**	**Baseline Visit**	**Day 1**	**Day 2**	**Day 3**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 22**	**Week 32**	**Week 42**	**Week 52/EOS[1]**
Days	**-45 -0 +15**	**-21 ±2**	**-1**	**1**	**2 to 2**	**3 to 3**	**8 ±2**	**15 ±2**	**22 ±2**	**29 ±2**	**43 ±2**	**57 ±2**	**71 ±2**	**85 ±7**	**155 ±7**	**225 ±7**	**295 ±14**	**365 ±21**
[redacted]																		
ACEND			X							X		X		X	X	X	X	X
[redacted]																		
BLOOD: Serum beta-human chorionic gonadotropin pregnancy test (Quantitative). Female participants only[17]		X																

Period	**Screening**		**Baseline**	**Treatment Period**			**Follow-up Period**											
Visit Name	**Visit 1**	**Visit 2**	**Baseline Visit**	**Day 1**	**Day 2**	**Day 3**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 22**	**Week 32**	**Week 42**	**Week 52/EOS[1]**
Days	**-45 -0 +15**	**-21 ±2**	**-1**	**1**	**2 to 2**	**3 to 3**	**8 ±2**	**15 ±2**	**22 ±2**	**29 ±2**	**43 ±2**	**57 ±2**	**71 ±2**	**85 ±7**	**155 ±7**	**225 ±7**	**295 ±14**	**365 ±21**
URINE beta-human chorionic gonadotropin pregnancy test (Qualitative). Female participants only[17]				S						S	S	S	S	S	S	S	S	S
Hepatitis Panel	X																	
HIV Screen (Antigen/Antibody with reflex to confirmation)	X																	
Hematology	X		X		X[18]		X	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry	X		X				X	X	X	X	X	X	X	X	X	X	X	X
Troponin I	X		X				X			X		X		X				X
Coagulation Panel		X																
Urinalysis	X		X				X											
5q SMA Genetic Testing (SMN1 and SMN2)		X																
[redacted]																		

Period	**Screening**		**Baseline**	**Treatment Period**			**Follow-up Period**											
Visit Name	**Visit 1**	**Visit 2**	**Baseline Visit**	**Day 1**	**Day 2**	**Day 3**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 22**	**Week 32**	**Week 42**	**Week 52/EOS** [1]
Days	**-45 -0 +15**	**-21 ±2**	**-1**	**1**	**2 to 2**	**3 to 3**	**8 ±2**	**15 ±2**	**22 ±2**	**29 ±2**	**43 ±2**	**57 ±2**	**71 ±2**	**85 ±7**	**155 ±7**	**225 ±7**	**295 ±14**	**365 ±21**
Survival Motor Neuron (SMN) Testing [BLOOD]		X									X			X	X			X
[redacted]																		
Electrocardiogram (ECG)	X		X				X			X		X			X			X
Echocardiogram	X						X			X		X			X			X
[redacted]																		
Study completion information																		X

Period	Screening		Baseline	Treatment Period			Follow-up Period											
Visit Name	Visit 1	Visit 2	Baseline Visit	Day 1	Day 2	Day 3	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 10	Week 12	Week 22	Week 32	Week 42	Week 52/EOS [1]
Days	-45 -0 +15	-21 ±2	-1	1	2 to 2	3 to 3	8 ±2	15 ±2	22 ±2	29 ±2	43 ±2	57 ±2	71 ±2	85 ±7	155 ±7	225 ±7	295 ±14	365 ±21
Medical resource utilization							X	X	X	X	X	X	X	X	X	X	X	X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
1 If discontinuation, all efforts should be made to complete the End of Study (EOS) assessments prior to study discontinuation.
2 This assessment is conditional on availability
3 [redacted]
4 If applicable, reason for screen failure should be entered on the corresponding Case Report Form. Assessments and other eCRF pages must also be completed if data is available.
5 SNAP is not performed at Screening Visit 2 if a SNAP score was obtained at Screening Visit 1
6 Prophylactic prednisolone (or an equivalent) must be administered approximately 24 hours prior to OAV101 injection
7 Prophylactic prednisolone (or an equivalent) may need to be continued beyond Week 8 Visit as described in Section 6.2
8 Clinical and laboratory results must be consistent with institutional guidelines for lumbar puncture before proceeding with OAV101 IT administration.
9 Refer to Section 6.7.3 for details of post-administration monitoring and optional assessments such as MRI or other safety assessments, based on Investigator discretion
10 Exclusion criteria 11 and 12 must be confirmed for eligibility prior to OAV101 IT administration
11 Participants will be hospitalized on Day 1 for inpatient OAV101 IT administration on Day 1, and in-patient observation will continue through Day 1, Day 2, and through part of Day 3 (for at least 48 hours post-treatment).
12 Vital signs to be performed pre-dose and post-dose as described in Section 8.4.5.4
13 Refer to Section 8.4.5.1 for details
14 S = assessment to be recorded in source documentation only
15 C-SSRS is only to be performed in participants ≥ 7 years of age. For participants < 7 years old at Screening Visit 1 who will not turn 7 before the EOS Visit (Week 52), no C-SSRS assessment will be performed. For participants < 7 years old at Screening Visit 1 who will turn 7 before the EOS Visit (Week 52), C-SSRS assessments will commence at the visit following the participant's 7th birthday.
16 Assessments may occur over more than 1 day within the visit window, but must not exceed 4 days
17 Female participants of child bearing potential
18 Hematology assessment at Day 2 should be performed locally; further, close monitoring of platelets should be performed locally as needed in the first two weeks following infusion.

[redacted]

Period	Screening		Baseline	Treatment Period			Follow-up Period											
Visit Name	Visit 1	Visit 2	Baseline Visit	Day 1	Day 2	Day 3	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 10	Week 12	Week 22	Week 32	Week 42	Week 52/EOS [1]
Days	-45 -0 +15	-21 ±2	-1	1	2 to 2	3 to 3	8 ±2	15 ±2	22 ±2	29 ±2	43 ±2	57 ±2	71 ±2	85 ±7	155 ±7	225 ±7	295 ±14	365 ±21
[redacted]																		

8.1 Screening

Screening

Written informed consent must be obtained prior to any screening procedures. Please refer to Section 7 for the Informed Consent procedures. After informed consent is collected, the participant must be registered in IRT, eligibility reviewed and, once eligible (all exclusion criteria must be confirmed at this point) study treatment can be pre-ordered. Assessments that confirm participant eligibility into the study will occur at Screening Visits 1 and 2 and at Baseline Visit (Table 8-1). The exact sequence of Screening assessments is at the discretion of the Site. It is recommended to obtain the anti-AAV9 antibody screening results first for timely completion of the eligibility assessment.

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

Participants who fail eligibility for a temporary condition exceeding the screening visit window will be considered screen failed and may be re-screened once. Re-screened participants must be re-consented and a new Participant number will be assigned (link to numbering section). All screening tests must be repeated as per inclusion/exclusion requirements and re-screening must be documented in the medical records.

8.1.1 Inclusion and exclusion criteria

The Investigator must ensure that all participants being considered for the study meet the inclusion criteria and do not meet any exclusion criteria. A relevant record (e.g., checklist) must be stored with the source documentation at the study site. Deviation from any entry criterion excludes a participant from enrollment into the study. The Investigator or his/her deputy must promote compliance to inclusion and exclusion criteria for the duration of the study.

8.1.2 Information to be collected on screening failures

Participants who sign an informed consent form and are subsequently found to be ineligible will be considered as screen failures. The reason for screen failure should be entered on the applicable CRF.

The following eCRF pages must also be completed for screen failure participants if applicable and data is available:

- Informed consent
- Demography
- Inclusion/Exclusion Criteria
- SMA diagnosis
- Assessments completed prior to screen failing

- Withdrawal of consent
- Rescreen
- Anti-AAV9 Antibody Testing (Blood)
- 5q SMA Genetic Testing (*SMN1* and *SMN2*)
- AE page if seriousness criteria is Death

No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see SAE Section 10.1.3 for reporting details) or protocol-related adverse event. Data and samples collected from participants prior to screen failure may still be analyzed.

8.1.3 Prior medications

Prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system.

8.1.4 Medical history and current medical conditions

Relevant medical history, hospitalizations, and current medical conditions will be recorded on the eCRF. Where possible, diagnoses and not symptoms will be recorded. Any event or change in the participant's condition or health status occurring *prior to* informed consent will be reported in the Relevant medical history / Current medical conditions section of the eCRF.

SMA HISTORY

SMA history may include the following:

- Type of *SMN1* pathogenic variants on each allele (e.g., deletion, point mutation)
- *SMN2* gene copy number
- Age at SMA symptom onset
- Date of SMA diagnosis
- Highest motor function achieved
- Type and frequency of physical therapy
- Number of hospitalizations for pneumonia with or without respiratory failure
- Familial history of SMA, including parent carriers and affected sibling(s)
- Prior SMA treatment, duration of treatment, and reason for discontinuation

8.1.5 Screening laboratory tests

Laboratory testing performed during the Screening Period is described in Table 8-1.

All laboratory results from Screening Visit 2 must be confirmed to be normal before proceeding with ordering drug in the system.

8.1.6 Virus serology

The administration of an AAV vector has the risk of causing immune-mediated hepatotoxicity. For participants who have active or chronic Hepatitis B or Hepatitis C, or known history of or

positive test for HIV, administration of the AAV vector is an unreasonable risk; therefore, status must be confirmed at screening, prior to treatment. Serology samples will be collected in accordance with Table 8-1 and shipped in accordance with the laboratory manual provided by the central laboratory.

8.1.7 Ventilatory support

Ventilatory support assessment will be performed by a pulmonologist (or appropriate individual as per standard institutional practice) and conducted as specified in Table 8-1. Prior to study entry, the Investigator or designee will review and document ventilator usage during the 2 weeks prior to Screening.

8.1.8 Radiological evaluations

Radiological examinations are performed to assess participants for disease complications in accordance with Inclusion/Exclusion criteria (Section 5).

8.1.8.1 Chest X-Ray

Both standard posterior to anterior (PA) and lateral chest X-rays will be performed at Screening Visit 1.

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8.2 Participant demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with eCRF. Participant race and ethnicity are collected and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities.

Participant demographics (including age, sex, race, and ethnicity if permitted) relevant medical history/current medical conditions (see Section 8.1.4) (until date of signature of informed consent) will be collected at Screening Visit 1 and captured 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 protocol Section 6.2.1 Concomitant

Therapy for further details on what information must be recorded on the appropriate page of the eCRF.

8.3 Efficacy

The primary endpoint in this study is safety. The secondary endpoint efficacy assessments, HFMSE and the RULM, are chosen based on their acceptability to health authorities, extensive validation and clinical and trial use, and proof of utility for efficacy assessment in other trials (Mercuri et al 2018b). [redacted]

The secondary efficacy endpoints rely on data collected by trained and qualified site clinical evaluators (physical or occupational therapist, or national equivalent) administering HFMSE and RULM during the screening period, and over a 52-week period after OAV101 administration.

8.3.1 Secondary efficacy assessments

8.3.1.1 HFMSE

HFMSE was devised for use in children with SMA Type 2 and Type 3 to give objective information on motor ability and clinical progression (Glanzman et al 2011) and has been used in a double blinded clinical trial of Type 2 SMA to demonstrate efficacy of SMN-targeting therapy (Mercuri et al 2012)

HFMSE is a SMA-specific 33-item assessment that is administered by clinical evaluators in a short period of time, requires minimal equipment, and is designed to factor in patient fatigue. Each motor skill item is scored on a 3-point Likert scale from 0 (no response) to 2 (full response), with a total score range of 0 to 66. A higher score indicates a higher ability level.

HFMSE assessment will be administered by a qualified site clinical evaluator (CE) in accordance with the Assessment Schedule (Table 8-1) for all participants. A CE is defined as a physical or occupational therapist, or national equivalent, and holds a valid physical or occupational therapy license in the state in which they are practicing, or country equivalent if outside the United States.

8.3.1.2 RULM

RULM is a validated, SMA-specific assessment that measures motor performance in the upper limbs from childhood through adulthood in ambulatory and never ambulatory individuals with SMA, and weaker individuals who have a floor effect or very low score on the Hammersmith Functional Motor Scale (HFMS) (Mazzone et al 2017). RULM administration is recommended for assessment of patients >2 years of age with the ability to sit by the SMArtCare-project (Pechmann et al 2019, Schorling et al 2020).

The revised version of the test consists of 19 scorable items: 18 items scored on a 0 (unable) to 2 (full achievement) scale, and one item that is scored from 0 (unable) to 1 (able). These item scores are summed to give a total score ranging from 0 to 37 points with lower scores reflecting poorer ability. RULM consists of upper limb performance items that are reflective of reachable

space and activities of daily living (i.e., raise a can to mouth as if drinking, take a coin and place it in a box, and remove the lid of a container).

RULM will be administered by a qualified site clinical evaluator (CE) in accordance with the Assessment Schedule (Table 8-1) for all participants starting at 30 months of age. A CE is defined as a physical or occupational therapist, or national equivalent, and holds a valid physical or occupational therapy license in the state in which they are practicing, or country equivalent if outside the United States.

8.3.1.3 ACEND instrument

The primary parent/caregiver of participants will complete the ACEND instrument according to the Assessment Schedule (Table 8-1). This assessment instrument has been designed to quantify the caregiver impact experienced by parents/caregivers of children affected with severe neuromuscular diseases, including children with SMA (Matsumoto et al 2011). ACEND instrument includes a total of seven domains assessing physical impact (including feeding/grooming/dressing, sitting/play, transfers, and mobility) and general caregiver impact (including time, emotion, and finance); each domain comprises several items. The total score for a domain with n items, where each item is assessed on an ordinal scale from 1 to z, is derived as follows: 100 multiplied by (Mean of the n items in the domain -1) divided by (z-1). This total score will be on a scale of 0 to 100 with a higher score indicating a greater impact on the caregiver.

8.3.2 Appropriateness of efficacy assessments

The secondary efficacy assessments in this study are appropriate for this indication and participant population. The rationale and support for HFMSE, RULM, and ACEND instrument as efficacy assessments are described in Section 8.3.1.1, Section 8.3.1.2, and Section 8.3.1.3, respectively.

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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 4.6, 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 for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again. If participants cannot visit the site for safety lab assessments through central labs, home-nursing may be deployed using central lab kits or local lab collection may be used and results will be entered in the eCRF.

8.4.1 Laboratory evaluations

Laboratory assessments will be performed according to the Assessment Schedule (Table 8-1). Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to Investigators in the laboratory manual.

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

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

All local labs should be reported on the respective eCRF page.

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate.

8.4.1.1 Hematology

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

Hematology analysis will include the following at all trial visits:

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

Transient decreases in platelet counts, some of which met the criteria for thrombocytopenia, were observed in OAV101 clinical studies with intravenous administration. In most cases, the lowest platelet value occurred the first week following OAV101 administration. Platelet counts should be obtained before OAV101 administration and should be closely monitored in the first two weeks following infusion and on a regular basis afterwards, weekly for the first month and every other week for the second and third months as specified in Table 8-1, until platelet counts return to baseline

To monitor platelet counts, hematology analyses are required on Day 2 prior to discharge and will be performed as per investigational site standard procedures at the local laboratory. As determined by the Investigator, further hematology tests should be done in the first two weeks following OAV101 administration as per investigational site standard procedures at the local laboratory. Local labs should be entered on the respective eCRF page. Investigators will receive hematology results from all other study visits from the central laboratory.

8.4.1.2 Coagulation panel

Coagulation testing including prothrombin time (PT), international normalized ratio (INR) and activated partial thromboplastin time (aPTT) will be measured at Screening Visit 2.

8.4.1.3 Clinical chemistry

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

Clinical chemistry is recommended to be evaluated in the non-fasted state.

If immediate/same-day chemistry analyses are required, as determined by Investigator, tests will be performed as per investigational site standard procedures at the local laboratory. Local labs should be recorded on the respective eCRF page. **If liver aminotransferase elevations occur post OAV101 administration, the process outlined in Section 10.2.1 should be followed.**

Chemistry analysis will include the following analytes:

- Albumin
- Alkaline phosphatase (ALP)
- ALT
- AST
- GGT
- Lactate dehydrogenase (LDH)
- Glutamate dehydrogenase
- serum HCO_{3-} (bicarbonate)
- Calcium
- Phosphorus
- Chloride
- Sodium
- Potassium
- Creatinine
- Creatine kinase
- Blood urea nitrogen
- TBL (NOTE: If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, the test should be repeated so that direct and indirect reacting bilirubin can be differentiated.)
- Direct bilirubin (if TBL is >1.5 x ULN)
- Indirect bilirubin (if TBL is >1.5 x ULN)
- Glucose

Residual serum (including from screen failures) may also be used towards the development of an in vitro test and/or a companion diagnostic assay.

8.4.1.4 Troponin I

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

If immediate/same-day Troponin I analyses are required, as determined by Investigator, tests will be performed as per investigational site standard procedures at the local laboratory. Local labs should be recorded on the respective eCRF page.

8.4.1.5 Urinalysis

Dipstick measurements for protein, blood, and WBC/leukocytes will be performed. If dipstick measurement results are abnormal, results will be sent to the central laboratory for microscopic evaluation in accordance with the Laboratory Manual.

8.4.1.6 Serum beta-human chorionic gonadotropin pregnancy test (Quantitative).

Serum beta-human chorionic gonadotropin (Beta-hCG) testing (Quantitative) will be performed at Screening Visit 2. Serum Beta-hCG testing will be performed on females of childbearing potential (See Section 8.4.3).

8.4.1.7 Urine beta-human chorionic gonadotropin pregnancy test (Qualitative).

All female participants who are sexually active or have reached menarche will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements. The cultural differences as well as standard of care approaches across participating countries must be taken into account in order to appropriately manage contraception and pregnancy considerations.

Urine human chorionic gonadotropin (hCG) dipstick testing will be performed on females of child-bearing potential. First-morning urine is the preferred specimen; however, any specimen is suitable for testing (See Section 8.4.3). Results of hCG dipstick testing will be captured on source documentation only.

8.4.2 Cardiac evaluations

8.4.2.1 Electrocardiogram

This study is centrally evaluated and thus, full details of all procedures relating to the ECG collection and reporting will be contained in the technical manual which is provided to the site by the core laboratory.

In the event that a clinically significant ECG abnormality is identified at the site (e.g., severe arrhythmia, conduction abnormality of QT interval corrected by Fridericia's formula (QTcF) > 500 ms), a copy of the assessment is sent to the core laboratory for expedited central review if applicable. The Investigator or a medically qualified person will repeat the ECG to confirm the diagnosis, and initiate further work-up as needed. If the participant is hemodynamically

compromised, the Investigator or a medically qualified person must initiate appropriate safety procedures without delay (e.g., cardioversion).

ECGs must be recorded (after 10 minutes rest in the supine position to ensure a stable baseline / according to the ECG investigator manual). The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling (add additional study specific assessments e.g., spirometry to the sequence) (Figure 8-1).

The QTcFmust be used for clinical decisions, e.g., at the Screening and Baseline visits(s) to assess eligibility. The Investigator must calculate QTcF if it is not auto-calculated by the ECG machine. Triplicate 12-lead ECGs are to be recorded approximately 2 minutes apart. The mean QTcF value for each visit will be calculated from the triplicate ECGs for each participant. For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. ECG safety monitoring, or a review process, should be in place for clinically significant ECG findings, at Baseline, before administration of treatment and during the study.

Additional unscheduled safety ECGs may be repeated at the discretion of the Investigator at any time during the study as clinically indicated.

Clinically significant abnormalities must be recorded on the relevant section of the CRFs as either medical history/current medical conditions or adverse events as appropriate.

Figure 8-1 Timing of study procedures

8.4.2.2 Echocardiogram

A standard transthoracic echocardiogram will be performed at times indicated in the Assessment Schedule (Table 8-1) and interpreted locally by a cardiologist or a designee for immediate safety evaluation. The echocardiogarms will also be collected for centralized review by a cardiologist.

8.4.2.3 Cardiac enzymes

Please see Section 8.4.1.4.

8.4.3 Pregnancy testing

For female participants who are sexually active or have reached menarche, quantitative beta-human chorionic gonadotropin testing in blood for pregnancy is required at Screening Visit 2 (See Section 8.4.1.6). For all female participants meeting this definition of child-bearing

potential, qualitative beta-human chorionic gonadotropin in urine will be performed at Day 1, Week 4, and at all subsequent visits during the trial (See Section 8.4.1.7). It is important that participants on Day 1 are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. Note that a positive urine test should be confirmed with a serum pregnancy test. In case of a positive test, the participant must contact the investigator immediately. In this fashion, the pregnancy discussion will become an additional point at each visit, serving to increase compliance with contraception.

Additional pregnancy testing may be performed if requested per local requirements. The cultural differences across participating countries need to be taken into account and it is acceptable to have both options simultaneously in the protocol to allow for cultural differences between participating countries.

Urine human chorionic gonadotropin (hCG) dipstick testing will be performed on females of child-bearing potential. First-morning urine is the preferred specimen; however, any specimen is suitable for testing. If participants cannot visit the site to have urine pregnancy dipstick testing, participants can perform the urine pregnancy test at home and report the result to the site. A communication process should be established with the participant so that the Site is informed and can verify the pregnancy test results (e.g., following country specific measures).

8.4.4 Suicidal ideation and behavior assessment

8.4.4.1 C-SSRS

The C-SSRS is a tool to assess suicidal ideation and behavior. C-SSRS should be completed as per the Assessment Schedule in Table 8-1 and at all unscheduled visits. Four constructs are measured: severity of ideation, intensity of ideation, behavior and lethality of actual suicide attempts. Binary (yes/no) data are collected for 10 categories, and composite endpoints based on the categories are followed over time to monitor participant safety (Posner et al 2011). It maps to the Columbia-Classification Algorithm for Suicide Assessment (C-CASA) and meets the criteria listed in the Food and Drug Administration (FDA) draft guidance for assessment of suicidality in clinical trials (FDA 2012). The C-SSRS will be used to monitor the participants throughout the study.

The C-SSRS is only to be performed in participants ≥ 7 years of age and is completed by proxy (caregiver). For participants < 7 years old at Screening Visit 1 who will turn 7 before EOS Visit (Week 52), C-SSRS assessment will commence at the visit following the participants 7th birthday.

The “baseline/screening” version of the C-SSRS assesses the lifetime suicidality, while the “since last visit” version assesses any new instances of suicidality.

If, at any time after screening and/or baseline, the score is “yes” on items 'active suicidal ideation with some intent to act, without specific plan' or 'active suicidal ideation with specific plan and intent' of the suicidal ideation section of the C-SSRS or “yes” on any item of the suicidal behavior section, the participant must be referred to a mental health care professional for further assessment and/or treatment. The decision on whether prednisolone (or equivalent)

treatment should be discontinued or tapered is to be taken by the investigator in consultation with the mental health professional to whom the participant is referred.

In addition, all life-threatening events must be reported as SAEs. For example, if a participant answers "yes" to one of the questions in the suicidal behavior section, an SAE must be reported if the event was life-threatening. All events of "Non-Suicidal Self-Injurious Behavior" (question also included in the suicidal behavior section) should be reported as AEs and assigned the appropriate severity grade.

8.4.5 Clinical safety evaluations

8.4.5.1 Neurological examination

A complete neurological examination is performed according to the Assessment Schedule (Table 8-1), with attention to exam features and participant symptoms consistent with a sensory neuropathy. The neurological exam should include detailed, age-appropriate sensory testing (such as examination of proprioceptive, vibratory, tactile and pain sensation) at each visit. An age appropriate sensory exam is important for sensory neuropathy detection.

Any clinically significant abnormal finding should be recorded as an AE in the eCRF.

Further clinical evaluation of somatic sensory abnormalities will be conducted per local standard of care, including but not limited to nerve conduction studies such as sensory nerve action potential (SNAP) and other optional assessments (e.g, MRI) that the Investigator may deem necessary for the evaluation.

8.4.5.2 Sensory Nerve Action Potential (SNAP)

Sensory nerve action potential (SNAP) is a conduction study commonly used to evaluate suspected peripheral neuropathies. The SNAP provides information on the sensory nerve axon and its pathway from the distal receptors in the skin to the dorsal root ganglia to evaluate the function, especially the ability of electrical conduction by the sensory nerves of human body. The SNAP represents the sum of single nerve fiber action potentials by electrically stimulating sensory fibers.

SNAP will be performed as per local and institutional guidelines at Screening and in the case of sensory abnormalities in the neurological examination, and can be initiated based on the clinical judgement at any time during the study. Orthodromic or antidromic SNAPs are acceptable depending on the institutional protocol. Performance of sensory nerve action potentials (SNAPs) should comply with professional society standards (Stålberg et al 2019, AANEM (2020)). The SNAP will be scored as "Present" or "Absent" or "Unable to obtain". Results will be entered in the eCRF and as an adverse event if applicable.

Pre-treatment: SNAP must be performed for all participants at Screening Visit 1. If the SNAP is scored as "Unable to obtain" at Screening Visit 1, then SNAP must be performed at Screening Visit 2. Bilateral radial and sural nerve SNAPs must each be obtained at least once at one of the two screening visits for trial eligibility. Rescheduling is warranted when any factor impedes the ability to obtain SNAP data.

If the SNAP is scored as "Absent" at any one of the pre-treatment visits, the clinician must assess whether the absent SNAP is supported by any clinically significant sensory abnormal finding(s) in the neurological examination.

Post-treatment: Post-treatment, SNAP must be performed if there are sensory abnormalities in the neurological examination. A complete neurological examination is performed at visits specified in Table 8-1, with attention to exam features and participant symptoms consistent with a sensory neuropathy (refer to Section 8.4.5.1).

Any participant with new post-treatment sensory symptoms with or without loss of a SNAP will receive a comprehensive assessment of the differential diagnosis. The differential diagnosis should include a careful assessment for sensory neuronopathy (sensory ganglionopathy). CSF testing and MRI imaging of brain, spinal cord, and dorsal root ganglia is encouraged. Sensory ganglionopathies are usually associated with diffuse SNAP abnormalities but may be patchy early, with upper limb involved before lower limb.

8.4.5.3 Physical examination

Physical examinations will be conducted according to the Assessment Schedule (Table 8-1). The Baseline (Day -1) physical examination will be performed prior to OAV101 administration.

A complete review of systems is performed at the time of each physical examination. Physical examinations will include each system: head, eyes, ears, nose and throat (HEENT), lungs/thorax, cardiovascular, abdomen, musculoskeletal, neurologic, dermatologic, lymphatic, and genitourinary.

Physical examination data will be captured on source documentation only.

Any clinically significant abnormal finding occurring after signing of the informed consent will be recorded as an AE.

8.4.5.4 Vital signs

Vital sign parameters include blood pressure, respiratory rate, pulse, temperature, and pulse oximetry.

Vital signs will be obtained at each visit. Vital signs on Day 1 (OAV101 administration) , with the exception of blood pressure, will be recorded pre-dose and then monitored every 15 (± 5) minutes for the first 1 hour, every 30 (± 10) minutes until 2 hours, every 2 hours (± 15 minutes) until 8 hours, and every 4 hours (± 30 minutes) until 24 hours. Blood pressure will be recorded pre-dose and every 8 hours through 24 hours. Patients must be kept in an appropriate setting for 48 to 72 hours for closer monitoring as per study protocol. After discharge, vital signs will be monitored as specified in Table 8-1. Vitals should be measured according to the site's standard operating procedure.

Any clinically significant abnormal finding occurring after signing of the informed consent will be recorded as an AE.

8.4.6 Anthropometry

8.4.6.1 Body height (segmental tibial length)

Direct measurement of recumbent length or height may be challenging in children and adolescents with physical disabilities due to joint contractures, muscular weakness, scoliosis, or poor cooperation. Since participants in the trial are never ambulatory, use the tibial length for segmental height assessment in all participants (Preedy VR 2012, Samson-Fang and Bell KL 2013, Mokhy et al 2020). Tibial length measurement does not require specialized equipment, is not impacted on by knee and ankle contractures and the landmarks are relatively easy to palpate.

- Use a flexible tape measure that does not stretch.
- Tibial length is the distance from the superomedial edge of the tibia to the inferior edge of the medial malleolus.
- The measurement should be conducted with the child in a seated position facing the observer with the left ankle or calf resting on the right knee so that the medial aspect of the tibia faces upwards. Measurements are recorded in centimeters (cm).
- The calculation should be checked by a different healthcare professional.

Use the following equation for both males and females to estimate height in males and females who are ≥ 2 to ≤ 12 years of age (Stevenson Equation).

- Height = (3.26 × TL) + 30.8
- TL=Tibial length

Use the following equations for males and females to estimate height in males and females who are > 12 years of age (Gauld Equation).

- Males: Height = (2.758 × TL) + (1.717 × A) + 21.818
- Females: Height = (2.771 × TL) + (1.457 × A) + 37.748
- TL = Tibial length (cm)
- A = age in years to one decimal place (e.g 5.3 years)

8.4.6.2 Body weight

Weight measurement for all trial participants should be performed as follows:

- Remove shoes and heavy clothes. Weights taken with shoes on will be considered invalid. A thin set of clothes or examination gown is permitted.
- Disposable undergarments (e.g., diapers) should be dry.
- All medical appliances must be removed (e.g., ankle foot orthosis; thoraco-lumbar-sacral orthosis)
- Use appropriately calibrated digital scale
- Values are recorded in kilograms (kg) to two decimal places (e.g., 15.25 kg).
- Participants who cannot stand alone on the scale will be weighed with the assistance of an adult. In order to obtain the patient weight, the adult weight is subtracted from the total weight of the patient+adult.

8.4.6.3 BMI

BMI is a person's weight in kilograms divided by the square of height in meters. BMI must be calculated using height derived as explained in Section 8.4.6.1, and the calculation should be checked by a different healthcare professional.

Use the following equation:

- $BMI = W / H^2$
- W = weight in kilograms (kg) to two decimal places (e.g. 15.25 kg)
- H = height in meters (m) to two decimal places (e.g. 0.92 m)

8.4.7 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 4.6, 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 may be collected remotely (e.g., web portal, telephone interviews) depending on local regulations, technical capabilities, and following any applicable training in the required process.

Clinician Reported Outcomes (ClinRO)

The impact of OAV101 on ClinROs will be assessed by the following measures in order to understand clinically meaningful aspects of motor improvements.

- Hammersmith Functional Motor Scale Expanded (2019 version) (Section 8.3.1.1)
- Revised Upper Limb Module (16-Dec-2014) (Section 8.3.1.2)
- [redacted]
- [redacted]
- [redacted]

Data will be captured through the use of an electronic clinical outcome assessment (eCOA) device, as provided to sites by selected third-party vendor.

Observer Reported Outcomes (ObsRO)

The impact of OAV101 on caregiver experience will be assessed by the following measure.

- ACEND instrument Section 8.3.3.6)

The participant's caregiver is to be provided with the electronic version of the ACEND instrument to be completed at the scheduled visit, in accordance with the Assessment Schedule (Table 8-1). Data is to be captured through the third-party vendor provided hand-held electronic

device, with web back-up. The caregiver should be given sufficient space and time to complete the ACEND instrument independently, and should be completed in the language most familiar to the caregiver. The caregiver should be made aware that provided responses are not reviewed by the investigator/study personnel. Attempts should be made to obtain responses from the same participant's caregiver throughout the duration of the study. A caregiver's refusal to complete all or any part of the ACEND instrument should be documented in the study data capture system and should not be captured as a protocol deviation. Handling of protocol deviations can be modified if needed per study protocol.

[redacted]

- C-SSRS (see Section 8.4.4.1)
- [redacted]

[redacted]

[redacted]

[redacted]

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation from study treatment

Since this is a single dose trial of gene therapy, discontinuation of study treatment is not possible since the vector transduces patient cells resides as episomal concatemers in the host cell nucleus. 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 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 Visit should be completed (refer to Section 8). 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

9.1.2 Discontinuation from study

Discontinuation from study is when the participant permanently stops any protocol-required assessments or follow-up, for any reason.

Discontinuation could also occur if, in the judgement of the investigator, an SMA-disease modifying drug such as nusinersen or risdiplam is recommended for the benefit of the participant or has otherwise been taken.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table (refer to Section 8). Participants who discontinue or withdraw will be offered to enroll in a long-term follow-up study (up to 15 years) to monitor long-term safety and efficacy.

9.1.3 Lost to follow-up

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

9.2 Withdrawal of informed consent/Opposition to use data/biological samples

Withdrawal of consent/opposition to use of data and/or biological samples occurs in countries where the legal justification to collect and process the data is consent and when a participant:

- Explicitly requests to stop use of their data
  and
- No longer wishes to receive study treatment prior to OAV101 administration
  and
- Does not want any further visits or assessments (including further study-related contacts)

This request should be per local regulations (e.g. in writing) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the participant, collect follow-up data (e.g. to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definition of these terms.

In this situation, the Investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/exercise data privacy rights and record this information. The investigator shall clearly document if the participant has withdrawn his/her consent for the use of data in addition to a study discontinuation.

No further assessments must 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.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/exercise data/privacy rights should be made as detailed in the assessment table (refer to Section 8).

Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

9.3 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their last study 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.

9.4 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 applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development
- 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 participant who discontinued from study treatment: 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. The Principal Investigator or designee will contact the study participant and/or the caregiver and provide instructions for returning to the Independent Treatment Site, or the Local Study Site, as appropriate. Every effort will be made to complete all end of study visit assessments for all treated study participants in the case of early study termination by the sponsor.

10 Safety monitoring, reporting and committees

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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

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

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

The occurrence of AEs must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

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

Adverse events will be assessed as follows:

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 ongoing)
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 with study treatment
6. Its outcome (i.e., recovery status or whether it was fatal)

All adverse events must be treated appropriately.

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 through the end of study visit. If prednisolone (or equivalent) treatment is required after the end of study visit (Week 52), AE monitoring will continue for 30 days after the last dose of prednisolone.

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 known adverse drug reactions for the investigational drug can be found in the Investigator's Brochure.

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

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

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Appendix 1, Section 16.1.

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

- Hepatotoxicity
- Transient thrombocytopenia
- Thrombotic microangiopathy
- Cardiac adverse events
- Dorsal root ganglia toxicity
- New malignancies

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 ICH-E2A Guidelines 1994).

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

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2A Guidelines 1994).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and throughout the 52-week duration post study treatment must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each site.

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

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode

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

If the SAE is not listed in the Reference Safety Information in the Investigator's Brochure (IB) and is reported or assessed to be related to the study treatment, a Novartis Chief Medical Office and Patient Safety (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 European Union (EU) Clinical Trial Regulation 536/2014 (if submitted under EU CTR) or Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Information about all SAEs is collected and recorded on the eSAE with paper backup Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

Any SAEs experienced after last follow-up visits should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

10.1.4 Pregnancy reporting

If a female participant becomes pregnant, the pregnancy consent form should be presented to the participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Risks to the fetus of recombinant AAV gene therapy to the fetus are unknown.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship of OAV101 to any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

If a female partner of a male participant who took study treatment in this study becomes pregnant, pregnancy outcomes should be collected. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

NOTE: Payment for all aspects of obstetrical care, child or related care will be the participant's responsibility.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA definition).

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to safety only if associated with a SAE. For more information on AE and SAE definition and reporting requirements, please see the respective sections.

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 Appendix 2, Section 16.2 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every hepatotoxicity event defined in Section 16.2 should be followed up by the Investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-1 and Table 16-2.

If elevated, repeat liver chemistry tests (i.e., ALT, AST, total bilrubin (TBL), prothrombin time/international (PT/INR), ALP, and GGT) will be performed within 48-72 hours to confirm elevation. These liver chemistry repeats will be performed at a local laboratory to monitor the safety of the participant. Any local liver chemistry tests should have results recorded on the appropriate CRF.

If the initial elevation is confirmed, the follow-up requirements include (refer to Table 16-1 and Table 16-2):

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

- Pediatric gastroenterology or hepatology consultations, if appropriate

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

[redacted]

10.2.3 Post-mortem data collection

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

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

Final autopsy report will be stored in the electronic trial master file (eTMF).

10.3 Committees

10.3.1 Data Monitoring Committee

This study will include a data monitoring committee 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

Code of Federal Regulations (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 personnel (or designated Clinical Research Organization (CRO)) 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 World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

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

11.3 Site monitoring

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

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

The Investigator must give to 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.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novartis. No records may be transferred to another location or party without written notification to Novartis.

12 Data analysis and statistical methods

12.1 Analysis sets

The full analysis set (FAS) is comprised of all participants who are enrolled in this study and received OAV101 through IT administration. The safety analysis set (SAF) is defined as the same as the FAS, therefore all the efficacy and safety analyses will be conducted using FAS.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by strata and overall for the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. 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 and preferred term by strata and overall for the FAS.

12.3 Treatments

The FAS 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 details pertaining to the administration of study treatment will be summarized by means of descriptive statistics using the FAS.

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

12.4 Analysis supporting primary objectives

The primary objective of the study is described in Table 2-1. Efficacy analyses will use the FAS.

A final analysis will be performed after all participants have completed Week 52 or discontinued prior to Week 52.

12.4.1 Definition of primary endpoint(s)

The primary endpoint includes the number and percentage of participants reporting AEs, related AEs, SAEs, and AESIs.

12.4.2 Statistical model, hypothesis, and method of analysis

The number and percentage of participants reporting AEs, related AEs, SAEs and AESIs will be summarized by strata and overall in the safety analysis set. Summaries will also be provided by MedDRA system organ class and preferred terms.

No hypothesis testing will be performed.

12.4.3 Handling of intercurrent events of primary estimand

All intercurrent events including receiving prohibited concomitant medications will be handled by treatment policy strategy, namely, all AEs, related AEs, SAEs (including death) and AESIs observed while/after receiving prohibited concomitant medications will be reported.

12.4.4 Handling of missing values not related to intercurrent event

Not applicable.

12.4.5 Sensitivity analyses

Given the descriptive nature of the summary of primary safety endpoints, no sensitivity analyses will be performed.

12.4.6 Supplementary analysis

No supplementary analysis will be performed.

12.5 Analysis supporting secondary objectives

The secondary objective of the study is described in Table 2-1 . Efficacy analyses will use the FAS.

A final analysis will be performed after all participants have completed Week 52 or discontinued prior to Week 52.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

The secondary endpoints include change from baseline to Week 52 visit in the HFMSE total score, change from baseline to Week 52 visit in the RULM total score and change from baseline to Week 52 visit in the ACEND instrument total score.

Change from baseline to Week 52 visit in the HFMSE total score, the RULM total score and the ACEND instrument total score will be summarized descriptively by strata and overall for the FAS.

No hypothesis testing will be performed.

[redacted]

[redacted]

Number and percentage of participants with suicidal ideation, suicidal behavior, or self-injurious behavior as assessed by the C-SSRS

[redacted]

12.7 Interim analyses

Not applicable.

12.8 Sample size calculation

[redacted]

[redacted]

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

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT). In addition, after study completion (defined as last participant last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial

results website and all required Health Authority websites (e.g., Clinicaltrials.gov, EudraCT etc.).

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

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

Summary results of primary and secondary endpoints will be disclosed based upon global Last Participant Last Visit (LPLV) date, since multinational studies are locked and reported based upon the global LPLV.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures 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.

13.5 Participant Engagement

The following participant engagement initiatives are included in this study and will be provided, as available, for distribution to study participants at the timepoints indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis.

- Thank you letter
- Plain language trial summary - after CSR publication

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

References are available upon request

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16 Appendices

16.1 Appendix 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).

The full list of clinically relevant laboratory abnormalities will be included in the CSR and detailed summary methods will be specified in the Statistical Analysis Plan.

Vital signs

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

The full list of clinically relevant vital signs will be included in the CSR and detailed summary methods will be specified in the Statistical Analysis Plan.

16.2 Appendix 2: Liver laboratory triggers & follow-up monitoring requirements

16.2.1 Liver laboratory triggers

Liver laboratory triggers which require follow-up monitoring include:

- ALT > 3 × ULN
- TBL > 1.5 × ULN (in the absence of known Gilbert's syndrome)
- Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated (direct) fraction] without notable increase in ALP to > 2 × ULN)

16.2.2 Follow-up requirements for liver laboratory triggers ALT and AST, with and without TBL

Table 16-1 Follow-up requirements for liver laboratory triggers – ALT and AST, with and without TBL

ALT	TBL	Liver Symptoms	Actions and Follow-up Monitoring
ALT > 3 x ULN	• Normal • For participants with Gilbert's syndrome: No change in baseline TBL	None	• Review compliance with immunomodulatory therapy (Section 6.2) • Measure ALT, AST, TBL, fractionated bilirubin (direct and indirect), INR, and GLDH within 48- 72 hours. • Follow-up for symptoms.
ALT > 5 x ULN	• Normal • For participants with Gilbert's syndrome: No change in baseline TBL	With or without symptoms	• Review compliance with immunomodulatory therapy (Section 6.2.2) • Measure ALT, AST, TBL, fractionated bilirubin (direct and indirect), INR, albumin, creatine kinase (CK), and GLDH within 48 - 72 hours of test results.
ALT or AST > 3 x ULN	• TBL > 2 x ULN (or INR > 1.5) • For participants with Gilbert's syndrome: Doubling of direct bilirubin	With or without symptoms	

ALT	TBL	Liver Symptoms	Actions and Follow-up Monitoring
ALT > 3 x ULN	● Normal or elevated	Severe fatigue, nausea, vomiting, and/or right upper quadrant pain	● Follow-up for symptoms. ● Initiate close monitoring (hospitalization when appropriate) and workup for competing etiologies[a] ● Exclude underlying liver disease ● Obtain detailed history of concomitant medications (e.g acetaminophen) ● Consult pediatric gastroenterologist[b]

[a] Work-up for competing etiologies may include (but not limited to) viral hepatitis panel (IgM anti-hepatitis A virus (HAV); hepatitis B virus surface antigen (HBsAg), IgM and total anti-hepatitis B core (HBc), hepatitis B virus (HBV) DNA, hepatitis C virus (HCV) ribonucleic acid (RNA), anti-HCV, Immunoglobulin M (IgM) & immunoglobulin G (IgG), hepatitis E virus (HEV) RNA, anti-HEV IgM and IgG), viral panel (CMV IgM and IgG, Epstein Barr virus (EBV) IgM and IgG, herpes simplex virus (HSV) IgG and Type 1 and 2 DNA), autoimmune hepatitis (anti-nuclear antibodies titer and pattern, anti-smooth muscle antibody)

[b]Consider appropriate imaging and liver biopsy in consultation with a pediatric gastroenterologist

16.2.3 Follow-up requirements for liver laboratory triggers - isolated hyperbilirubinemia

Table 16-2 Follow-up requirements for liver laboratory triggers - isolated hyperbilirubinemia

Criteria Total Bilirubin (isolated)	Actions required	Follow-up monitoring
>1.5 – 3.0 x ULN	● Repeat LFTs within 72 hours of test results	● Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline
> 3 - 10 x ULN (in the absence of known Gilbert's syndrome)	● Repeat LFT within 72 hours of test results ● Hospitalize if clinically appropriate ● Establish causality ● Record the AE and contributing factors (e.g. concomitant medications, medical history, laboratory results) in the appropriate CRF	● Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline (ALT, AST, TBL, albumin, 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. concomitant medications, medical history, laboratory results) in the appropriate CRF	● ALT, AST, TBL, Alb, PT/INR, until resolution (frequency at Investigator discretion)

LFT(s) = liver function tests based on Investigator's discretion; investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, pediatric gastroenterologist's or

Criteria Total Bilirubin (isolated)	Actions required	Follow-up monitoring
hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.		

16.2.4 Prednisolone dosing

Prednisolone dosing

- [redacted]
- [redacted] (as specified in Section 16.2.1), refer to follow-up requirements specified in Table 16-1 and Table 16-2.
- Live vaccines are prohibited while receiving corticosteroids. Participants are advised to complete all age-appropriate inoculations with live vaccines prior to enrolling in the study if possible.
- [redacted]

16.3 Appendix 3: Specific Renal Alert Criteria and Actions and Event Follow-up

Not applicable