Protocol Number: AVXS-101-CL-306

Official Title: Phase 3, Open-Label, Single-Arm, Single-Dose Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type 1 with One or Two SMN2 Copies Delivering AVXS-101 by Intravenous Infusion

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AVXS-101-CL-306 / COAV101A12304

Phase 3, Open-Label, Single-Arm, Single-Dose Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type 1 with One or Two SMN2 Copies Delivering OAV101 by Intravenous Infusion

Statistical Analysis Plan (SAP)

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Approvals

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List of abbreviations

AAV	Adeno-associated virus
AE	Adverse Event
AESI	Adverse Event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AT	Aminotransferase
BiPAP	Bilevel Positive Airway Pressure
BSID	Bayley Scales of Infant and Toddler Development
BUN	Blood urea nitrogen
cDNA	complimentary deoxyribonucleic acid
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CK	Creatine kinase
CK-MB	Creatinine kinase-muscle/brain
cm	Centimeter
COVID	Corona virus disease
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug-induced liver injury
dl	deciliter
DMS	Document Management System
ECG	Electrocardiogram
eCRF	Electronic case report form
ELISA	Enzyme-linked immunosorbent assay
ELISpot	Enzyme-linked ImmunoSpot
FAS	Full Analysis Set
FDA	Food & Drug Administration
g	Gram
GGT	Gamma glutamyl transferase
HEENT	Head, eyes, ears, nose, throat
hSMN	Hereditary sensory motor neuropathy
IA	Interim Analyses
ICH	International Conference on Harmonization
ITT	Intent-to-Treat
IV	intravenous
Kg	kilogram
Lbs	Pounds
LFE	Liver function enzyme
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MGRS	Multicenter Growth Reference Study
mRNA	Messenger ribonucleic acid
PBMC	Peripheral blood mononuclear cell

PCS	Potentially clinically significant
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
QTcB	Corrected Q-T interval using Bazett's formula
QTcF	Corrected Q-T interval using Fridericia's formula
RAP	Reporting & Analysis Process
RBC	Red blood cell
RDW	Red cell distribution width
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard deviation
SFC	Surface
SMA	Spinal muscular atrophy
SMN	Survival motor neuron
SOP	Standard operating procedure
TBL	Total bilirubin
TEAE	Treatment-emergent Adverse Event
TFLs	Tables, Figures, Listings
ULN	Upper limit of normal
USB	Universal serial bus
Vg	Vector genome
VH	Very high
VL	Very low
WBC	White blood cell
WHO	World Health Organization

1 Introduction

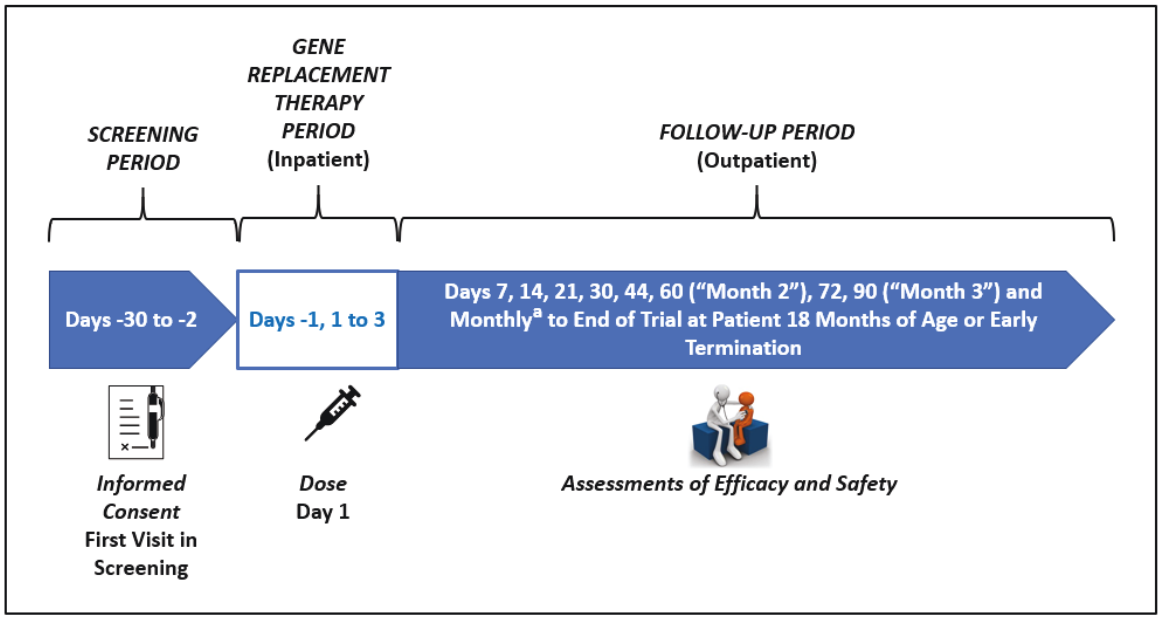
The purpose of this document is to provide further details about the statistical analysis methods, data derivations and data summaries to be employed in the study protocol COAV101A12304 (AVXS-101-CL-306): *Phase 3, Open-Label, Single-Arm, Single-Dose Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type 1 with One or Two SMN2 Copies Delivering OAV101 by Intravenous Infusion.* This statistical analysis plan (SAP) has been based on International Conference on Harmonization (ICH) E3 and E9 guidelines and in reference to protocol version 6.0, dated 11 Nov 2020. The SAP describes the implementation of the statistical analysis for clinical study reporting planned in the protocol. It covers statistical analysis, tabulations and listings of all data including effectiveness and safety data.

1.1 Study design

This is a Phase 3, open-label, single-arm, single-dose trial of OAV101 (gene replacement therapy) in patients with SMA Type 1 with one or 2 copies of SMN2. At least 6 patients < 6 months (< 180 days) of age at the time of gene replacement therapy (Day 1) were planned to be enrolled as part of a combined analysis with Study COAV101A12303. But at the time of this protocol was amended (Protocol version 6.0 amendment 5 dated 11 Nov 2020), the enrollment was closed with 2 active enrolled patients. The combined analysis is no longer to be performed.

The trial includes 3 trial periods: screening, gene replacement therapy, and follow-up (Figure). During the screening period (Days –30 to –2), patients whose parent(s)/legal guardian(s) provide informed consent will undergo screening procedures to determine eligibility for trial enrollment. Patients who meet the entry criteria will enter the in-patient gene replacement therapy period (Day –1 to Day 3). On Day –1, patients will be admitted to the hospital for pre-treatment baseline procedures. On Day 1, patients will receive a one-time intravenous (IV) infusion of the equivalent of OAV101 cohort 2 dose received in the AVXS-101-CL-101 trial over approximately 60 minutes and will undergo in-patient safety monitoring over the next 48 hours. Patients may be discharged 48 hours after gene replacement therapy, based on Investigator judgment. During the outpatient follow-up period (Days 4 to End of Trial at 18 months of age), patients will return at regularly scheduled intervals for efficacy and safety assessments until the patient reaches 18 months of age. Any missed visit should be rescheduled as soon as possible, but within the visit windows shown in the Schedule of Assessments. All visits will be scheduled based on a 30-day month calendar.

Figure 1 - Trial Design



Note: After the End of Trial visit at 18 months of age or at the time of early discontinuation patients will be invited to participate in a long- term follow-up study conducted under a separate protocol.

a All post-treatment visits will be relative to the date on which gene replacement therapy is administered until the patient is 14 months of age, after which all visits will be relative to the patient's date of birth. *Note: Depending on the patient's age at dosing, the duration of participation at the end-of-trial visit can vary from approximately 12 months (baby dosed at approximately 6 months of age) to approximately 18 months (baby dosed near birth "0 months of age").* All visits will be scheduled based on a 30-day month calendar.

After dosing follow-up visits will be conducted according to the Schedule of Assessments. All post-treatment visits will be relative to the date on which gene replacement therapy is administered until the patient is 14 months of age, after which all visits will be relative to the patient's date of birth. For the 14 and 18 months of age visits, the patient will return within 0 to 14 days after the date on which the patient reaches 14 and 18 months of age, respectively. The 18 months of age visit will also serve as the End of Trial visit. After the End of Trial visit, patients will be invited to participate in a long-term follow-up study under a separate protocol. Patients who discontinue prematurely will also be invited to participate in the long-term follow-up study.

In an attempt to dampen the host immune response to the AAV-derived therapy, all patients will receive prophylactic prednisolone.

In the event that unforeseen catastrophic or other serious situations (such as the COVID-19 pandemic) impact the ability to conduct the study on-site, alternative methods of continuing study assessments may be implemented. Alternative visits include phone calls, virtual contacts through teleconsult or videoconference, or visits by site staff/home nursing providers to the

patient's home depending on local regulations, institutional policies, and capabilities of the investigative site. Alternative visits may take place instead of on-site visits until such time that the patient can safely return to the site.

Throughout the study, the scheduling of study visits should adhere to the overall study schedule and visit windows defined in the protocol. For each study visit, all study procedures and assessments should be performed or completed in accordance with the schedule of events. Local institutions or other alternatives may be utilized.

Importantly, in instances in which the final scheduled study visit is not possible to be conducted at the study site, the final scheduled study visit should be performed all or by an alternative visit within the protocol-defined visit window. Critical data that pertain to the primary and secondary endpoints and other information such as adverse events, concomitant medications, use of feeding or ventilatory support, or other safety data that may be obtained remotely should be collected as part of the final study visit and within the protocol-defined visit window.

Procedures such as laboratory and other safety assessments that cannot be performed or obtained as part of a remote visit may be performed separately and preferably within the protocol-defined visit window.

1.2 Study objectives, endpoints and estimands

This trial will assess the efficacy of OAV101 administered IV in terms of functional independent sitting and survival rate in symptomatic SMA Type 1 patients who are homozygous negative for SMN1 exon 7 and have 2 copies of SMN2 without the SMN2 genetic modifier. Only objectives and endpoints in the protocol are listed below.

Table 1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• **EFFICACY:** Determine efficacy by demonstrating achievement of developmental milestone of sitting without support up to 18 months of age as assessed by WHO Motor Developmental Milestones	• Achievement of the ability to sit without support for at least 10 seconds at any visit up to and including the 18 months of age visit. It is defined by the WHO MGRS, confirmed by video recording, [redacted]
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• Determine efficacy based on survival at 14 months of age. Survival is defined by the avoidance of combined endpoint of either (a)	• Survival at 14 months of age amongst symptomatic SMA Type 1 patients who are homozygous negative for SMN1

Objective(s)	Endpoint(s)
death or (b) permanent ventilation which is defined by tracheostomy or by the requirement of ≥ 16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation. Permanent ventilation, so defined, is considered a surrogate for death.	exon 7 and have 2 copies of SMN2 without the SMN2 genetic modifier (see further detail followed the table)
• **SAFETY:** To evaluate the safety and tolerability of OAV101-IV in patients with SMA Type 1	• Incidence of treatment emergent adverse events (TEAEs) and serious TEAEs (SAEs) • Evaluation of changes from baseline in vital signs, and clinical laboratory results
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
[redacted]	[redacted]

Objective(s)	Endpoint(s)
[redacted]	[redacted]

- An "acute reversible illness" is defined as any condition other than SMA that results in increased medical intervention (i.e., increased requirement for respiratory support; use of other concomitant medications as rescue) requirements and is expected to be reversible or improved following definitive intervention (i.e., surgery, antibiotics) or introduction of escalated supportive care, such as hospitalization (i.e., for upper respiratory infection, spontaneous fracture). The specific duration of the condition antecedent intervention shall not be considered in the definition of "acute." The date of "definitive intervention" shall be defined as the date of provision of a procedure (i.e., surgery, etc.) or medication (i.e., antibiotics) intended to cure or substantially improve the condition. For conditions such as viral respiratory infections for which supportive care is provided, the date of "definitive intervention" shall be considered the date of hospitalization or substantial escalation of care.
- "Perioperative" use reflects any alteration of ventilatory use related to a surgical or other medical procedure of any nature for which the patient received medications that could impair or interfere with respiratory function.
- For a patient who develops an acute reversible illness and/or requires perioperative ventilatory support, a recovery period not to exceed 21 days following the date of definitive intervention will be instituted. Following this recovery period, the condition will be considered subacute and the patient will become evaluable with regards to the surrogate survival endpoint (requirement of ventilatory support of ≥ 16 hours/day for 14 or more days).

1.2.1 Primary estimand(s)

Not applicable

1.2.2 Secondary estimand(s)

Not applicable

2 Statistical methods

2.1 Data analysis general information

Novartis Gene Therapies, Inc. will be performing final analysis.

Analyses will be performed using [redacted]

There are no interim analyses. The final analysis will be composed by individual data listings and patient profiles after the final database lock. No data aggregations, summary tables or inferential statistical approaches will be performed.

2.1.1 General definitions

"Day 1" is defined as the day of gene transfer, "Day -1" the day before. Gene transfer is the single-time study treatment as gene therapy infusion. The dose is the total vector genome (vg) delivered, the human SMN cDNA sequence, corresponding to the mature mRNA, cloned into the self-complementary AAV vector plasmid, given in vg per subject weight in kilogram (kg) on Day -1.

For any event, "study day" is defined as the time from Day 1 to the day of the event in days plus 1 day.

"Baseline" refers to a non-missing measurement or evaluation made prior to initiation of gene therapy infusion. If there are multiple measurements prior to the initiation of gene therapy infusion, only the latest measurement will be considered as baseline for analysis purposes. If these multiple measurements occur at the same time or time is not available, then the average of these measurements (for continuous data) or the worst among these measurements (for categorical data) will be considered as the baseline value. This same baseline value will be used for the treatment and post-treatment periods.

"Last contact" refers to the last study visit. If not terminated early, it is the end-of-trial visit at 18 months of age. "Age" will be expressed in months and rounded to one decimal place, where age in months is the time from birth to a date in days, plus 1 day, divided by 30. The final value for each patient is the first non-missing value on or after the participant reaches 18 months of age (540 days) with an upper limit of 570 days. Thus, the earliest visit between 540 and 570 days of age, inclusive, will be used in the "18 months of age" analysis.

Analysis visits are defined per month following a visit windowing approach in two different schedules, one based on study day post dosing and another one based on patient age. For by-visit efficacy endpoints, the time windows describe how efficacy data will be assigned to protocol-specified time points. For a Month K, K>1, the time windows are around Study Day K*30, the nominal time, in a range of -15 to +14 days. Month 1 spans from Study Day 1 to 44. If more than one efficacy observation for a specific assessment is included in a time window, the assessment closer to the nominal time will be used. If there are two efficacy observations

equally distant to the nominal time, the latest one will be used in analyses. Visits at 14 and 18 Months of Age follow an analysis window of 420 to 434 and 540 to 554 days of age, respectively. CHOP-INTEND scores and Bayley Scales will also be presented by analysis visit following an age based visit windowing approach for M months of age in the range of M*30 to (M+1)*30-1 days since birth.

"Bilevel Positive Airway Pressure" (BiPAP) is a form of non-invasive mechanical pressure support ventilation.

"Permanent ventilation" is defined as a requirement of ≥16-hour respiratory assistance per day (includes BiPAP) continuously for ≥14 days in the absence of an acute reversible illness, excluding perioperative ventilation.

A "responder" is a patient who demonstrates achievement of an endpoint at any post-procedure visit up to and including the 18-months-of-age visit.

An "Adverse Event" (AE) is any untoward medical occurrence in a clinical investigation subject, which does not necessarily have a causal relationship with the drug or device under study.

A "treatment-emergent Adverse Event" (TEAE) is any AE whose onset or worsening occurred on or post Day 1.

2.2 Analysis sets

The **Intent-to-Treat** (ITT) population will consist of symptomatic patients with biallelic deletion mutations of SMN1 (exon 7/8 common homozygous deletions) and 2 copies of SMN2 without the known gene modifier mutation (c.859G>C) who receive an IV infusion of OAV101 at less than 180 days of age.

The **ability to thrive** combined study **ITT** population will consist of symptomatic patients with biallelic deletion mutations of SMN1, 2 copies of SMN2 without the genetic modifier (c.859G>C), intact swallowing and receiving no enteral (mechanical) nutrition at baseline, who receive an IV infusion of OAV101 and have at least one post-baseline efficacy evaluation.

The all enrolled population will consist of all patients who receive an IV infusion of OAV101.

The safety analysis population will consist of all patients who receive an IV infusion of OAV101.

2.2.1 Subgroup of interest

None.

2.3 Patient disposition, demographics and other baseline characteristics

Patient disposition will be described for all patients of the all Enrolled population. Demographic data and other baseline characteristics will be reported for the Safety population.

2.3.1 Patient disposition

It will be reported if a patient will still be in the study at 14 and 18 months of age, respectively. Among those who discontinued the study prior to reaching the 18 months-of-age visit, the reasons for discontinuation will be enumerated.

The number of screened patients who screen failed and the reasons for screen failure (inclusion/exclusion criteria, withdrew consent, and/or other) will be reported. A CSR listing of reason for screen failure will be provided for all patients who screen failed.

2.3.2 Demographics and other baseline characteristics

The age of the patient at the time of gene therapy infusion will be described. Patient demographics and other baseline characteristics will be listed using the Safety population.

Demographic data will be determined using the following calculations:

Age at Study day 1 = (Study day 1 visit date - date of birth + 1), expressed in days or

Age at Study day 1 = (Study day 1 visit date - date of birth + 1)/30, expressed in months

Height/Length (in cm) = height (in inches) * 2.54

Weight (in kg) = weight (in lbs) * 0.4536

The following statistics regarding the patient's characteristics at birth will be described including but not limited to, ethnicity, race, gestational age (weeks), birth weight (kg), birth length (cm), and head circumference (cm).

Medical history data will be presented using body systems and conditions/diagnoses as captured on the eCRF. The body systems will be presented in alphabetical order and the conditions/diagnoses will be presented in alphabetical order within each body system.

The presence of significant medical conditions obtained from medical history will described. In particular, the following parameters will be reported regarding symptoms and history of Spinal Muscular Atrophy: age at symptom onset (if applicable), baseline SMA symptoms (if applicable), family history of SMA, and number of siblings affected by SMA.

Patient baseline characteristics, including but not limited to CHOP-INTEND total score, levels of feeding, ventilatory and respiratory support, results from swallowing test, and lab results, will be summarized on the Safety population.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

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

2.4.2 Prior, concomitant and post therapies

Prior and concomitant medications will be described. A prior medication is defined as any medication taken in the two weeks prior to the date of the gene therapy infusion of study drug. A concomitant medication is defined as any medication that started prior to the date of the infusion of study drug and continued to be taken after the infusion of study drug or any medication that started on or after the date of the infusion of study drug. A listing of patients in the safety population taking prior or concomitant medications will be provided by generic drug name based on the WHO Drug Dictionary together with ATC levels.

To reduce the host immune response to the AAV-based therapy, patients will receive prophylactic prednisolone at approximately 2 mg/kg/day on Day -1, Day 1, and Day 2, and then 1 mg/kg/day starting on Day 3 and until at least 30 days post-OAV101 infusion. After 30 days of treatment, the dose of prednisolone can be tapered for patients whose ALT values, AST values, are ≤2 X ULN for ALT and AST in accordance with the following treatment guideline:

- Weeks 5 and 6: 0.5 mg/kg/day
- Weeks 7 and 8: 0.25 mg/kg/day
- Week 9: prednisolone discontinued

The total number of days receiving prednisolone and total cumulative dose of prednisolone administered during the entire study (mg/kg*days) will be computed for each patient.

To compute total cumulative dose, the total dosing period is subdivided into dosing intervals represented by constant dose levels. On the day of a dosage change, the entire day is represented under the new dosing interval at the new dose.

Non-medication Therapies/Procedures will be defined as “Prior” and/or “Concomitant”. Prior Non-medication Therapies/Procedures are defined as therapies or procedures started prior to injection of OAV101. Concomitant Non-medication Therapies/Procedures are defined as therapies or procedures ongoing at time of injection of OAV101 or started after the injection.

A listing of Non-medication Therapies/Procedures will be provided.

2.5 Analysis supporting primary objective(s)

Primary efficacy endpoints will be presented in data listings and patient profiles where patients will be identified as to the analysis set(s) to which they belong.

For completeness, the remainder of the section is only for information purpose.

2.5.1 Primary endpoint(s)

Developmental milestones will be assessed/determined by the qualified Clinical Evaluators at the investigational sites. The assessments will be captured on video from two camera angles.

The videos will then be reviewed and verified by an independent, external reviewer for concordance. Only milestones confirmed by the independent reviewer will be utilized for the primary endpoint.

The primary efficacy endpoint is of symptomatic SMA Type 1 patients who are homozygous negative for SMN1 exon 7 and have 2 copies of SMN2 without the SMN2 genetic modifier that achieve the ability to sit without support for at least 10 seconds at any visit up to and including the 18 months of age visit. It is defined by the World Health Organization Multicentre Growth Reference Trial (WHO MGRS), confirmed by video recording, [redacted]

Primary endpoint data will be listed for the ITT population.

2.5.2 Statistical hypothesis, model, and method of analysis

Not applicable.

2.5.3 Handling of intercurrent events

Not applicable.

2.5.4 Handling of missing values not related to intercurrent event

Not applicable.

2.5.5 Sensitivity analyses

Not applicable.

2.5.6 Supplementary analyses

Not applicable.

2.6 Analysis supporting secondary objectives

Secondary efficacy endpoints will be presented in data listings and patient profiles where patients will be identified as to the analysis set(s) to which they belong. For completeness, the remainder of the section is only for information purpose.

2.6.1 Secondary endpoint(s)

The secondary efficacy endpoint, event-free survival, is defined as avoidance of any one of the following events up to 14 months of age, whichever occurred first:

- Death, *or*
- Tracheostomy, *or*
- Noninvasive Ventilatory support ≥16-hour per day *and* continuously ≥14 days

Usage data for patients using non-invasive ventilatory support will be extracted directly from the device ([redacted]) on an SD card, or USB stick and transferred as an external dataset. Average daily use of non-invasive ventilatory support at baseline, Days 7, 14, 21, 30 and monthly thereafter will be calculated. In the event that data cannot be extracted from an SD card, usage recorded in the electronic case report form may be analyzed. If a patient did not have a device with the capability to record usage data at baseline and was using non-invasive ventilatory support prior to screening, the average daily usage will be based on parent report and documented in the source documentation. As a secondary analysis, the amount of ventilation support will be categorized into None, >0-≤12 hours, >12–<16 hours, ≥16 or permanent ventilation. At each of the above time points, the count and percent of patients in each ventilation support category will be presented.

Secondary endpoint data will be listed for the ITT population.

2.6.2 Statistical hypothesis, model, and method of analysis

Not applicable.

2.6.3 Handling of intercurrent events

Not applicable.

2.6.4 Handling of missing values not related to intercurrent event

Not applicable.

2.6.5 Sensitivity analyses

Not applicable.

2.6.6 Supplementary analyses

Not applicable.

2.7 Safety analyses

Safety will be assessed through the incidence and severity of AEs, vital sign assessments, cardiac assessments, laboratory evaluations (chemistry, hematology, immunology, urinalysis), physical examinations, and use of concomitant medications. Adverse events will be coded in accordance with the most current version of the MedDRA coding dictionary. Safety assessments will be presented in data listings or patient profiles for the safety population. In addition, summary tables will be prepared for treatment-emergent AEs and SAEs together with an overview of AEs.

2.7.1 Adverse events (AEs)

All adverse events will be assessed for their seriousness, relatedness to study treatment, relationship to study discontinuation, and severity according to CTCAE version 4.03 criteria.

Adverse event data will be summarized and presented using primary MedDRA system organ classes (SOCs) and preferred terms (PTs) according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the clinical study report. The system organ classes will be presented in alphabetical order and the preferred terms will be presented in alphabetical order within each system organ class.

The following summaries of adverse events will be generated:

- Treatment-emergent adverse events;
- Serious treatment-emergent adverse events.

For all adverse event summaries, the number of treatment-emergent adverse events, the number and percentage of patients experiencing treatment-emergent adverse events will be tabulated according to SOC and PT. Patients reporting more than one adverse event for a given PT will be counted only once for that term (most severe incident for the severity tables and most related incident for the relationship tables). Patients reporting more than one adverse event within a SOC will be counted only once for that SOC. Patients reporting more than one adverse event will be counted only once in the overall total.

An overview of adverse events will be presented consisting of the number and percentage of patients experiencing at least one event for the following adverse event categories:

- Any adverse event;
- Any serious adverse event;
- Any treatment-emergent adverse event;
- Treatment-emergent adverse events with a "possibly related", "probably related", "definitely related" of being related to OAV101
    - Any AE reported as Possibly, Probably, or Definitely Related will be consolidated into a single category and summarized as “Related” in the tables
    - Any AE reported as Unlikely Related or Unrelated will be consolidated into a single category and summarized as “Not Related” in the tables
- Grade 3 and 4 treatment-emergent adverse events;
- Any serious treatment-emergent adverse events;
- Serious treatment-emergent adverse events “related” to OAV101;
- Treatment-emergent adverse events leading to discontinuation of patient from study;
- Treatment-emergent adverse events leading to death;
- Treatment-emergent adverse events of special interest (cp. Section 2.7.1.1);
- Deaths.

2.7.1.1 Adverse events of special interest / grouping of AEs

The following are considered AEs of special interest (AESIs):

- Hepatotoxicity
- Thrombocytopenia
- Cardiac adverse events
- Sensory abnormalities suggestive of ganglionopathy
- Thrombotic microangiopathy

Primarily defined by using Standard MedDRA queries (SMQ), AESIs are identified as follows:

Hepatotoxicity as hepatic disorders (SMQ), thrombocytopenia as transient thrombocytopenia (CMQ), sensory abnormalities suggestive of ganglionopathy as DRG cell inflammation (CMQ), and cardiac events as ischemic heart disease (SMQ) or cardiomyopathy (SMQ) or cardiac arrhythmias (SMQ) or embolic and thrombotic events (SMQ) or myocardial infarction (SMQ), respectively.

Thrombotic microangiopathy is identified via the following approach:

- Criteria #1: cases with any one of the following PTs: thrombotic microangiopathy OR haemolytic uraemic syndrome OR atypical haemolytic uraemic syndrome (i.e. A).
- Criteria #2: cases with at least one PT from EACH of the following SMQs representing thrombocytopenia, hemolysis and relevant renal events respectively:
  - Haematopoietic thrombocytopenia (SMQ) (i.e. B)
  - Haemolytic disorders (SMQ) (i.e. C)
  - Acute renal failure (SMQ)(i.e. D) OR Renovascular disorders (SMQ) (i.e. E)

2.7.2 Deaths

Deaths will be described by individual data listings and SAE narratives.

2.7.3 Laboratory data

Blood will be collected throughout the study for standard blood chemistry and hematology tests as well as cardiac enzymes. Urine will be collected throughout the study for standard urinalysis exams.

Hematology variables include: hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count, lymphocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils, bands, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), and red cell distribution width (RDW).

Chemistry variables include: albumin, alanine aminotransferase (ALT), alkaline phosphatase, aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, gamma glutamyl

transferase (GGT), glucose, serum total bilirubin, direct bilirubin, total creatine kinase (CK), CK-MB, and electrolytes.

Urinalysis variables include: specific gravity, pH, ketones, glucose, protein, blood, leukocyte esterase, nitrites, bilirubin, red blood cell (RBC) count, white blood cell (WBC) count, yeast, squamous epithelial cells, casts, crystals, bacteria.

During the observation period, laboratory data values will be categorized as low, normal, or high based on normal ranges of the laboratory used in this study. A listing will be provided that presents all of the lab values for the patients including meeting PCS criteria during observation Period. PCS criteria are according to the following tables.

Table 2: Criteria for Potentially Clinically Significant Hematology Values

Test / Units	Age	Normal Range	Very Low (VL)	Very High (VH)
Hemoglobin (g/dL)	0–3 Days	14.5–22.5 g/dl	<10 g/dl	>24.5
	4–14 Days	12.5–21.5	<10 g/dl	>23.5
	15–59 Days	10–18	<10	>20
	60–89 Days	9–14	<9	>16
	90–179 Days	9.5–13.5	<9.5	>15.5
	180–364 Days	10.5–13.5	<10	>15.5
	1 Year - <2 Years	10.5–13.5	<10	>15.5
	≥2 Years - <6 Years	11.5–13.5	<10	>15.5
	≥6 Years - <12 Years	11.5–15.5	<10	>17.5
	≥12 Years - <18 Years	12–16	<10	>18
Platelets Count (GI/L)	0–6 Days	84–478	<75	
	7–364 Days	130–400	<75	
	≥1Year	130–400	<75	
White Blood Cell Count (GI/L)	0–3 Days	9.4–34	<3.0	
	4–14 Days	5–21	<3.0	
	15–59 Days	5–19.5	<3.0	
	60–79 Days	5–18	<3.0	
	180–364 Days	5–17	<3.0	
	≥1 Years - <6 Years	5–17	<3.0	
	≥6 Years - ≤12 Years	4.5–13.5	<3.0	

Test / Units	Age	Normal Range	Very Low (VL)	Very High (VH)
Total Neutrophils (absolute, GI/L)	0–3 Days	5–21	<1.5	
	4–14 Days	1.5–0	<1.5	
	15–59 Days	1–9	<1	
	60–89 Days	1–8.8	<1	
	90–179 Days	1–8.5	<1	
	180–364 Days	1.5–8.5	<1.5	
	≥1 Y	1.8–8	<1.5	
Lymphocytes, Absolute (K/µL)	0–3 Days	2–11.5	<0.8	>11.5
	4–14 Days	2–17	<0.8	>17
	15–59 Days	2.5–16.5	<0.8	>16.5
	60–89 Days	3.3–15	<0.8	>15
	90–179 Days	4–13.5	<0.8	>13.5
	180–364 Days	4–10.5	<0.8	>10.5
	≥1 Y	0.85–4.1	<0.8	>4.1
Eosinophils (%)	0–364 Days	0.5–5		>5%
	≥1 Year	0–5		>5%

Table 3: Criteria for Potentially Clinically Significant Chemistry Values

Test / Units	Age	Normal Range	Very Low (VL)	Very High (VH)
Alkaline Phosphatase	0–6 Days	40–300		>750
	7–364 Days	50–270		>675
	≥1 - <3 Years	50–270		>675
	≥3 - <13 Years	60–415		1037.5
ALT/SGPT	0–6 Days	0–60		>180
	7–364 Days	0–50		>150
	≤1-<3 Years	0–50		>150
	≥3 Years-<13Years	0–48		>144
AST/SGOT	0–364 Days	0–60		>180
	≥1 Year - <3Years	0–60		>180
	≥3Years -64Years	0–42		>126
Total Bilirubin (mg/dL)	0–1 Days	0–6		>9
	2 Days	0–8		>12
	3–5 Days	0–12		>18
	6–90 Days	0–1.3		>1.95
	91–364 Days	0–1.3		>1.95
	≥1 Year	0–1.3		>1.95
Creatinine (mg/dl)	0–2 Days	0.79–1.58		>1.5 X Baseline or >2.37
	3–5 Days	0.46–1.23		>1.5 X Baseline or >1.845
	6–7 Days	0.37–1.05		>1.5 X Baseline or >1.575
	8–30 Days	0.35–0.92		>1.5 X Baseline or >1.38
	31–365 Days	0.27–0.72		>1.5 X Baseline or >1.08
	>1 Year -<4Years	0.3–0.7		>1.5 X Baseline or >1.05
	≥4 Years - <7 Years	0.29–0.68		>1.5 X Baseline or >1.02
	≥7 Years - <10 Years	0.38–0.73		>1.5 X Baseline or >1.095
BUN (Urea Nitrogen) (mg/dl)	0–6 Days	4–15		>22.5
	7–364 Days	5–18		>27
	≥1 Year - <3 Years	5–18		>27
	≥3 Years -<13 Years	8–21		>31.5
	0–6 Days	30–90	<40	>160

Fasting Glucose (mg/dl)	7–90 Days	60–110	<55	>160
	91–364 Days	60–110	<55	>160
	≥1 Year - <13 Years	60–110	<55	>160
Albumin (G/L)	0–6 Days	20–50	<20	
	7–364 Days	30–50	<30	
	≥1Year -<3Years	30–50	<30	
	≥1 - <3 Years	30–50	<30	
	3+ Years	32–50	<30	
GGT	0–6 Days	0–270		>675
	7–364 Days	0–120		>300
	≥1 Year - <3 Years	0–120		>300
	3 Years - 12 Years	0–65		>162.5
Potassium	0–364 Days	3.8–5.5	<3.8	>5.5
	≥1 Year - <3 Years	3.8–5.5	<3.8	>5.5
	≥3 Years - <13 Years	3.5–5.5	<3.5	>5.5
Sodium (mmol/L)	0+ Years	135–146	<135	>155

The Criteria for Potentially Clinically Significant Values will be based upon CTCAE Version 4.03 criteria for Grade 2 or higher adverse event unless otherwise specified.

For hemoglobin and the liver function tests (LFTs) of ALT, AST, alkaline phosphatase, and total bilirubin, patients in each treatment group with a maximum CTCAE Grade of 1, 2, 3, or 4 (see definitions in Table 4) at any post-baseline visit (regardless of the baseline value) through the end of treatment (i.e., Final Treatment Value) will be described. Listings of all ALT, AST, total, indirect and direct bilirubin, and alkaline phosphatase will be created for any patients who had at least a Grade 3 ALT, AST, alkaline phosphatase, or total bilirubin. A listing of hematology results will be provided for patients with hemoglobin abnormalities.

For patients with a Grade 3 or higher total bilirubin elevation, a listing of treatment-emergent adverse events (defined as preferred terms within the "Cholestasis and jaundice of hepatic origin" (broad search) SMQ, excluding preferred terms within the "Investigations" SOC) will be provided.

Table 4: Definitions of CTCAE Grades 1, 2, 3, and 4

Test	Grade 1	Grade 2	Grade 3	Grade 4
ALT/SGPT	>ULN – 3 × ULN	>3–5 × ULN	>5–20 × ULN	>20 × ULN
AST/SGOT	>ULN – 3 × ULN	>3–5 × ULN	>5–20 × ULN	>20 × ULN
Alkaline phosphatase	>ULN – 2.5 × ULN	>2.5–5 × ULN	>5–20 × ULN	>20 × ULN
Total bilirubin	>ULN – 1.5 × ULN	>1.5–3 × ULN	>3–10 × ULN	>10 × ULN
Hemoglobin decreased	<LLN – 8.5 g/dL	<8.5–7.5 g/dL	<7.5–.5 g/dL	<6.5 g/dL

Reference Ranges, [redacted]

In order to assess hepatotoxicity, all elevations in liver transaminases are evaluated using Hy's Law criteria as these help to determine the risk of drug-induced liver injury. All elevations in liver transaminases will be assessed against these criteria. Hy's Law cases have the following three components:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo;
2. Among trial patients showing such aminotransferase (AT) elevations, often with ATs much greater than 3×ULN, one or more patients also shows elevation of serum total bilirubin (TBL) to ≥2×ULN, without initial findings of cholestasis (elevated serum ALP);
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C, pre-existing or acute liver disease, or another drug capable of causing the observed injury [FDA (2009)].

For patients enrolled in this study these criteria are assessed in order to determine both general liver function enzyme changes (LFEs) according to change from baseline and over course of study. In addition, the assessment of changes in ALT or AST relative to TBL allowed assessment if a signal related to DILI occurred in any individual or group of patients.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

Echocardiograms and electrocardiograms will be conducted at screening, Day 2 (ECG), Day 30 and every 3 months beginning with Month 3 through Month 18/ End of Trial (excluding Month 15).

The ECG tracings or ECG machine data will be collected for centralized review and interpretation by a cardiologist. The centralized review data will be used as the primary source for this data- although site-level echocardiogram interpretation will also be captured in the eCRF.

A 12-lead ECG will be conducted at scheduled visits of Screening, Day 2, Day 30 and every 3 months through 18 months of age and assessed by a central reviewer. The central reviewer will identify abnormal ECGs that are potentially clinically significant (PCS), based on central reviewing guidelines provided by the central cardiology vendor. Clinically significant, treatment-emergent findings of ECG, as determined by the central reviewer, will be reported as adverse events. If a site reviewer of the ECG results identifies an abnormality, it will be confirmed by the central reviewer. A listing of all PCS ECGs will be provided.

Table 5. Criteria for Potentially Clinically Significant ECG Values

Test / Measurement	Very Low (VL)	Very High (VH)
Heart rate (bpm)	<5th percentile for age	>95th percentile for age OR Change (increase) from baseline ≥20 bpm
QTcB (msec)	None	≥440 msec OR Change (increase) from baseline ≥30 msec
QTcF (msec)	None	≥440 msec OR Change (increase) from baseline ≥30 msec

Reference: [redacted]

A standard transthoracic echocardiogram will be performed at screening/baseline, Day 2, Day 30, and every 3 months beginning with Month 3, through Month 12, and at the End of Trial when the patient reaches 18 months of age (or early termination). Echocardiograms will be interpreted locally and results from the local interpretation (abnormal/normal, etc.) and captured in the eCRF. Additionally, echocardiogram data will be provided to an external cardiologist for centralized review; this will be considered the primary echocardiogram source data. Clinically significant, treatment-emergent findings will be reported as AEs.

24-hour Holter monitoring will take place at screening, Days -1, 1, 2, 3, 30 and Months 2, 3, 6, 9, 12, and at the End of Trial at 18 months. Holter monitors will be provided to study sites along with a dedicated laptop for uploading the data from the memory cards for centralized review and analysis by a cardiologist within 24 hours of data upload.

2.7.4.2 Vital signs

Blood pressure, respiratory rate, pulse, body temperature, and pulse oximetry will be collected at every visit. Clinically-significant, treatment-emergent findings will be reported as adverse events.

In addition, vital signs results will be flagged as Potentially Clinically Significant (PCS) if they meet the pre-specified criteria outlined in Table 6. The number and percent of patients meeting each PCS criterion will be summarized starting at Day 1 and continuing through Month 18.

The Criteria for Potentially Clinically Significant Vital Sign Findings are presented in Table 6.

Table 6: Criteria for Potentially Clinically Significant Vital Sign Values

Test / Measurement	Very Low (VL)	Very High (VH)
Systolic blood pressure*	<67	>110
Diastolic blood pressure*		>64
Pulse rate**	Below 5th percentile for age	Above 95th percentile for age
Body Weight***	Weight <3rd percentile for age and gender	Weight>97th percentile for age and gender
Temperature	<35°C	>39°C

* Adapted from NHLBI Reference Ranges for age ** Bonafide et al. Pediatrics 2013;131:e1150–e1157

*** Based upon NHANES III Percentiles for age and gender

Pulse oximetry will be measured at specified time points throughout the study through a small infrared light attached to the end of the patient's finger.

2.7.4.3 Physical Examination

Physical examination will include review of the following systems: head, eyes, ears, nose, throat (HEENT), lungs/thorax, cardiovascular, abdomen, musculoskeletal, neurologic, dermatologic, lymphatic, head circumference and genitourinary.

Treatment-emergent abnormal findings on physical examination will be tracked as adverse events. Any post-infusion abnormal physical exam findings will be listed by patient with the corresponding result on the baseline physical examination.

2.7.4.4 Use of Non-Oral Feeding Support

A swallowing test will be performed at baseline and every 6 months through Month 18/End of study to determine if the patient has signs of aspiration. If the test is positive for aspiration, the patient will be recommended to use an alternative method to oral feeding. Once implemented, a non-oral method of feeding support may later be removed. For each placement or removal event, the type of support (type of tube), date of placement, and date of removal will be noted. Actual use of non-oral feeding support will be quantified through the recording of volume, frequency of use, duration, and calories.

2.7.4.5 Immunology

Immunoreactivity to AAV9 and SMN will be measured in antibody titer levels (in 2-fold serial dilutions) as determined by enzyme-linked immunosorbent assays (ELISAs).

Immunoreactivity to AAV9 and hSMN will be monitored by the collection of samples at Screening, Day 7, Day 14, Day 21, and Day 30. Antibody titers >1:50 are considered positive for antibody response while antibody titers ≤1:50 are considered negative.

Immunology variables include: mother's serum binding antibody titer to AAV9, serum binding antibody titer to AAV9, binding antibody titer to SMN.

2.8 Pharmacokinetic endpoints

None.

2.9 PD and PK/PD analyses

Not applicable.

2.10 Patient-reported outcomes

None.

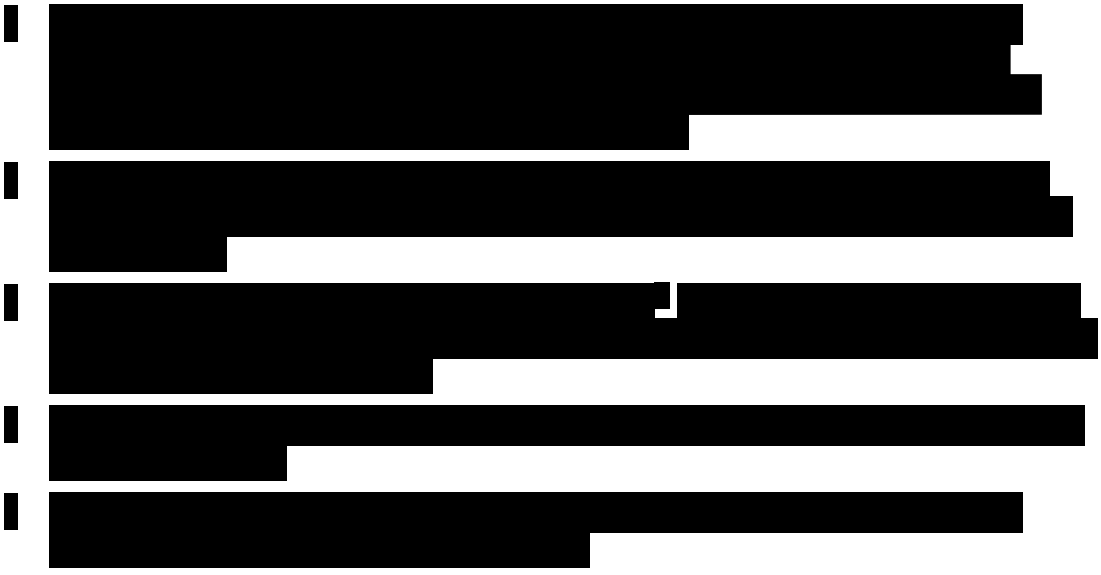
2.11 Biomarkers

Not applicable.

2.12 Other Exploratory analyses

All protocol deviations will be recorded in the clinical database and will be categorized in accord with Novartis Gene Therapies SOPs. Protocol deviations will be described by individual data listings.

Supportive (exploratory) efficacy variables are as follows:



[redacted]

Table 7: Third Percentile Weights for Age and Gender

Age	Gender	Weight (kg)
14 months	Male	8.2
	Female	7.5
18 months	Male	8.9
	Female	8.2

Reference: http://www.who.int/childgrowth/standards/Technical_report.pdf (Table 39 and Table 50).

- Achievement of Developmental Milestones is based on video confirmed central reviewed at any visit during the study.

Exploratory endpoint data will be presented in data listings and patient profiles for the ITT population and, where appropriate, for the Ability to Thrive ITT population.

2.13 Interim analysis

Not applicable.

3 Sample size calculation

The study was originally designed to have sufficient power, when combined with an identically designed study COAV101A12301 (AVXS-101-CL-302), to establish efficacy with regard to the primary and secondary endpoints. Due to the change in data analysis and narrowed scope of COAV101A12304 (OAV101-CL-306), no combined analysis or stand-alone analysis will be conducted.

4 Change to protocol specified analyses

Due to the narrowed scope of COAV101A12304 (AVXS 101 CL 306) and limited subjects enrolled, only individual data listings and patient profiles will be generated, with the exception of three AE summary tables. There are no changes to analyses planned in protocol version 6.0.

5 Appendix

5.1 Imputation rules

Missing values in any of the endpoints will not be imputed when reporting these endpoints by means of individual data listings. For the CHOP-INTEND and BAYLEY instruments, rules

suggested by the producers of these assessments will be followed in calculating scores when individual question/items may be missing. If these rules are not enough for calculating a score, then the endpoint will be considered as having a missing value.

Missing values for safety endpoints will not be imputed.

5.1.1 Study drug

If the date of study drug application will be missing or partial, it will be imputed by the date of the Day 1 visit.

5.1.2 AE date imputation

Missing or incomplete AE start dates will be imputed according to the general Novartis imputation rules:

- If the day is missing then use '01'
- If the day and month is missing use '01JUL'
- If the imputation of a start date causes the start date to be after the non-missing end date, then the start date is set to the same date as the end date.
- If the imputation of a start date causes the start date to be prior to the start of treatment (when the event should be on-treatment), then the start date is set to the same date as the treatment date +1.
- If the imputation of a start date causes the start date to be after the start of treatment (when the event should be before start of treatment), then the start date is set to the treatment date.

AE end dates will not be imputed.

5.1.3 Concomitant medication date imputation

Missing or incomplete start dates of medications will be imputed according to the general Novartis imputation rules:

- If the day is missing then use '01'
- If the day and month is missing use '01JUL'
- If the imputation of a start date causes the start date to be after the non-missing end date, then the start date is set to the same date as the end date.
- If the imputation of a start date causes the start date to be prior to the start of treatment (when the event should be on-treatment), then the start date is set to the same date as the treatment date +1.

Medication end dates will not be imputed.

5.1.3.1 Prior therapies date imputation

Missing or incomplete start dates of prior therapies will be imputed according to the general Novartis imputation rules:

- If the day is missing then use '01'
- If the day and month is missing use '01JUL'
- If the imputation of a start date causes the start date to be after the non-missing end date, then the start date is set to the same date as the end date.
- If the imputation of a start date causes the start date to be after the start of treatment (when the event should be before start of treatment), then the start date is set to the treatment date.

Prior therapies end dates will not be imputed. If the end date is missing, ongoing prior therapies are assumed.

5.1.3.2 Post therapies date or other imputations

Post therapies dates or other data will not be imputed.

5.2 AEs coding/grading

AEs are encoded according to the latest version of MedDRA available at the start of the study. CTCAE grading version 4.0.3 applies.

5.3 Laboratory parameters derivations

Based on CTCAE grading version 4.0.3, PCS criteria will be derived. Also, Hy's law criteria apply.

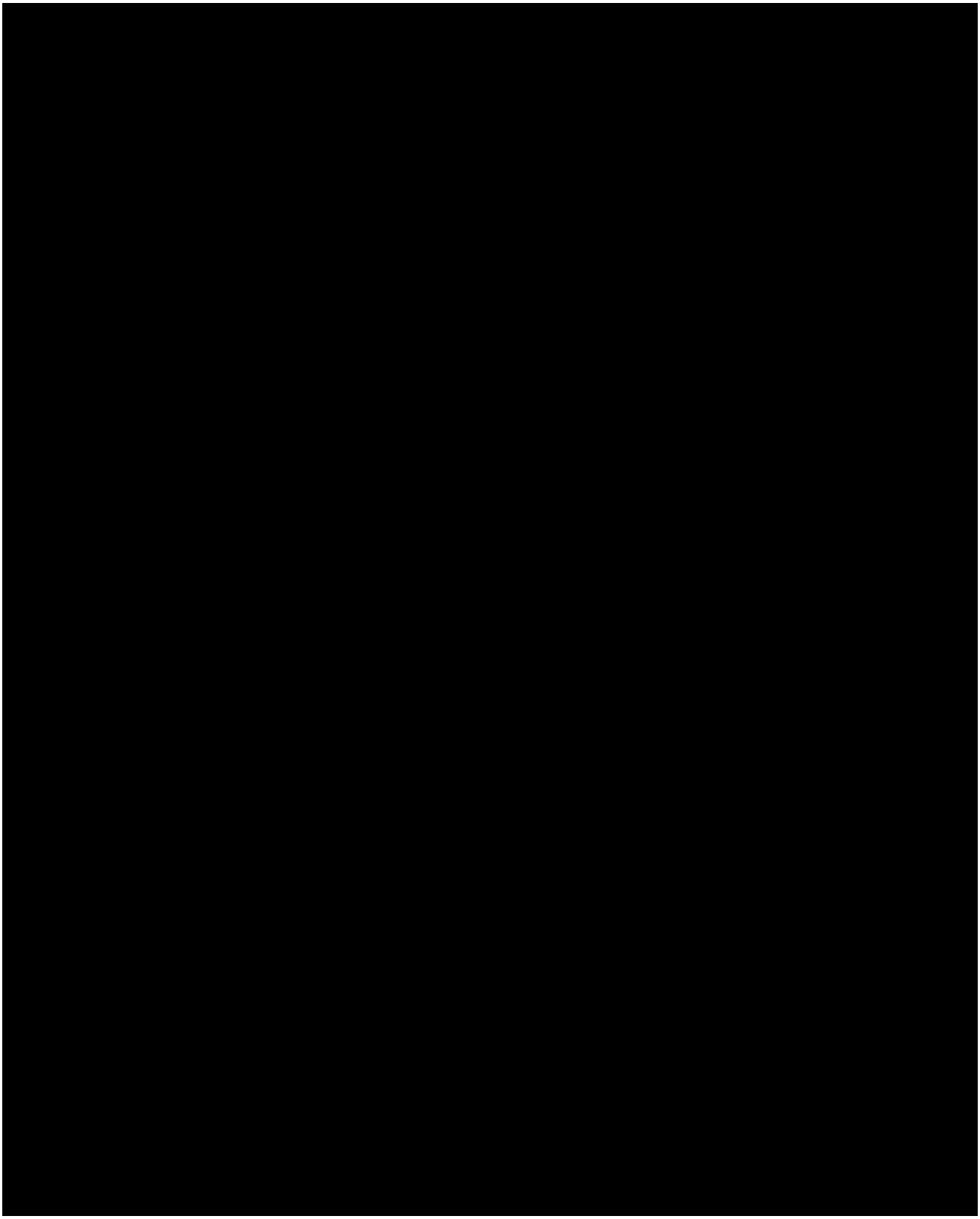
5.4 Performance criteria for Bayley Scales of Infant and Toddler Development (Version 3) Developmental Milestones

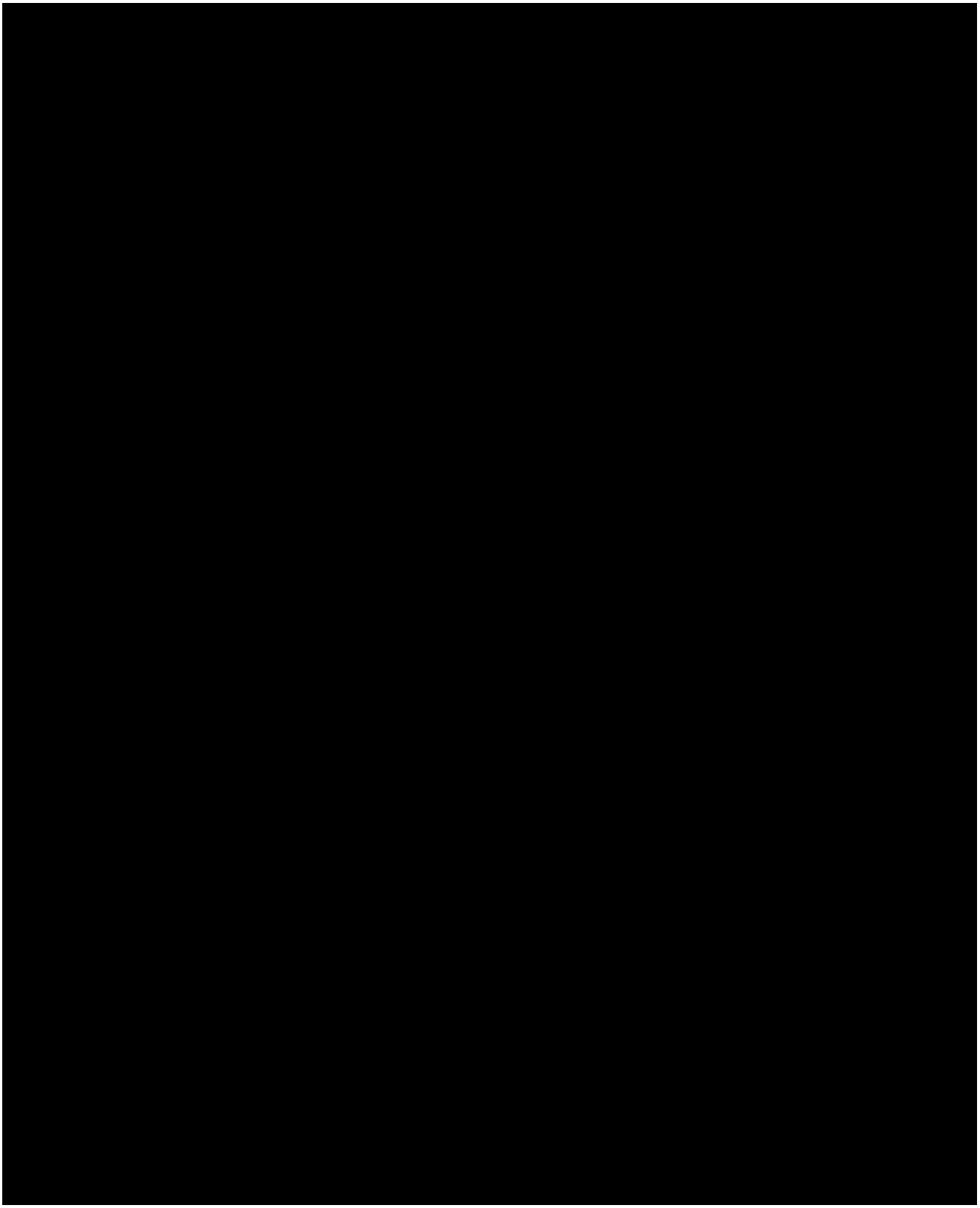
Table 8: BSID Items

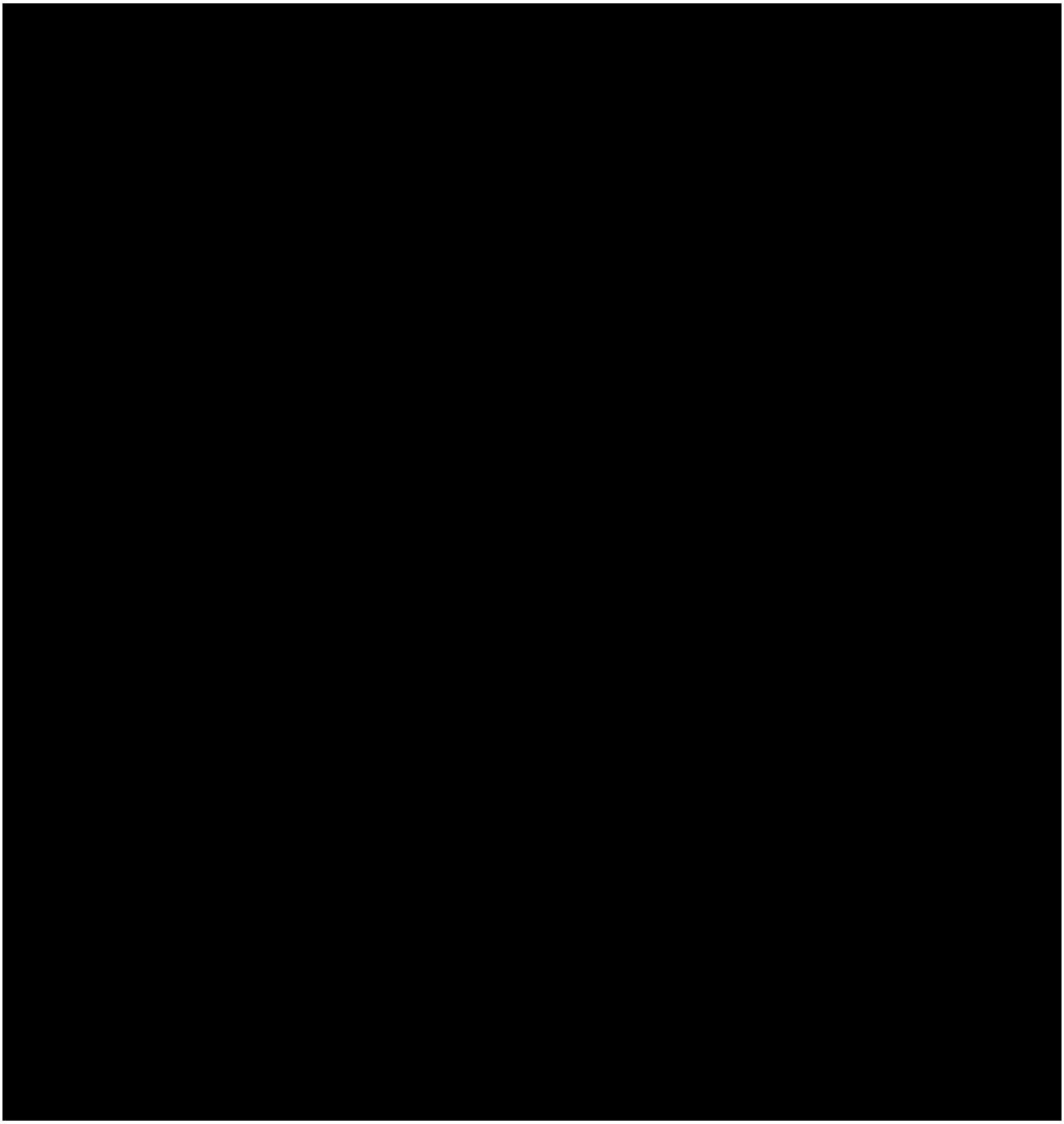
Developmental Milestone	Performance Criteria
Head Control – Gross Motor Subtest Item #4	[redacted]
Rolls from Back to Sides – Gross Motor Subtest Item #20	
Sits Without Support – Gross Motor Subtest Item #26	
Stands with Assistance - Gross Motor Subtest Item #33	
Crawls – Gross Motor Subtest Item #34	
Pulls to Stand – Gross Motor Subtest Item #35	
Walks with Assistance – Gross Motor Subtest Item #37	
Stands Alone – Gross Motor Subtest Item #40	
Walks Alone – Gross Motor Subtest Item #42	

5.5 CHOP-INTEND

[redacted]







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