Protocol Number: AVXS-101-CL-303

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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STATISTICAL ANALYSIS PLAN

Protocol Number and Title: AVXS-101-CL-303

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

Protocol Version and Date: Version 4.0 / 04 Oct 2018

Author(s): [redacted]
Sr. Biostatistician

SAP Version: 5.0

SAP Version Date: 10 Dec 2019

Notice of Confidential and Proprietary Information

Revision History

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1.0	02-Aug-2017	[redacted]	Initial Release Version
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3.0	14-Jun-2018	[redacted]	Update SAP to reflect necessary revisions identified during TLF programming
4.0	20-Feb-2019	[redacted]	Updated to reflect protocol amendment
5.0	10-Dec-2019	[redacted]	Final version

I confirm that I have reviewed this document and agree with the content.

APPROVALS

[redacted]
Sr. Biostatistician, AveXis, Inc

Date (dd-Mmm-yyyy)

[redacted]
Chief Medical Officer, AveXis, Inc

Date (dd-Mmm-yyyy)

[redacted]
Sr. Director, Regulatory Affairs, AveXis, Inc

Date (dd-Mmm-yyyy)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. GLOSSARY OF ABBREVIATIONS AND DEFINITIONS

1.1. Glossary of Abbreviations

Abbreviation	Description
AE	Adverse Event
ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical
ANOVA	Analysis of Variance
AAV9	Adeno-associated virus serotype 9
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BDRM	Blinded Data Review Meeting
BLQ	Below Levels of Quantification
BMI	Body Mass Index
CI	Confidence Interval
CK-MB	Creatine kinase isoenzyme
CMAP	Compound Motor Action Potential
CRF/eCRF	Case Report Form/ electronic Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CSR	Clinical Study Report
CV	Coefficient of Variation
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
ECG/EKG	Electrocardiogram/Electrocardiogram
ELISAs	Enzyme-Linked Immunosorbent Assays
ELISpot	Enzyme-Linked ImmunoSpot
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice

Abbreviation	Description
GPP	Good Pharmacoepidemiology Practice
HEENT	Head, eyes, ears, nose, throat
HLT	High Level Term
ICH	International Conference on Harmonization
ITT	Intent-To-Treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
MAR	Missing at random
Max	Maximum
MCAR	Missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
N/A	Not Applicable
NA	Not Applicable
NCI	National Cancer Institute
NTF	Note-To-File
OR	Observational Research
PASS	Post Authorization Safety Study
PAES	Post Authorization Efficacy Study
PBMC	Peripheral Blood Mononuclear Cells
PCS	Potentially Clinically Significant
PD	Pharmacodynamic
PDS	Pharmacodynamic Set
PK	Pharmacokinetic
PKS	Pharmacokinetic Set
PNCR	Pediatric Neuromuscular Clinical Research Network

Abbreviation	Description
PT	Preferred Term
QC	Quality Control
QTc	Corrected QT Interval
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Standard Error
SFC	Spot forming cells
SI	Standard International System of Units
SMN	Survival Motor Neuron
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
SOP	Standard Operating Procedure
SS	Safety Set
TEAE	Treatment Emergent Adverse Event
TLF	Table, Listing and Figure
WHO	World Health Organization

1.2. Glossary of Definitions

Abbreviations list pertains to the SAP only.

Abbreviation	Description
AE	Adverse Event: Any untoward medical occurrence in a clinical investigation subject which does not necessarily have a causal relationship with the drug or device under study.
Age	For a given event, age will be expressed in days or months and rounded to one decimal place for months. A month is standardized to a period of 30 days.

Abbreviation	Description
	Age at Event = (Date of Event – Date of Birth + 1)/ 30 (displayed as months). Age at Baseline = (Date of Gene Therapy Infusion – Date of Birth + 1)/ 30 (displayed as months).
Baseline	Baseline, e.g., in terms of baseline laboratory values, vital signs, or physical exam results, refers to a 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 in most cases will be considered as baseline for analysis purposes or defined specifically.
BiPAP	Bilevel Positive Airway Pressure, a form of non-invasive mechanical pressure support ventilation.
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, a 16-item motor function assessment validated for use in infants with spinal muscular atrophy.
CMAP	Compound Muscle Action Potential, the total electrophysiological output in a muscle or muscle group recorded by surface electrodes following supramaximal stimulation of the innervating nerve.
Day 1	The day of the gene therapy treatment
Dose	Total vector genome delivered (in $^{vg}/_{\text{patient weight on Day } -1(\text{kg})}$).
MedDRA	Medical Dictionary for Regulatory Activities is a medical terminology used to classify adverse event information associated with the use of biopharmaceuticals and other medical products.
CTCAE	Common Terminology Criteria for Adverse Events version 4.03. The CTCAE is descriptive terminology, involving a severity scale, which is used for AE reporting in particular for unique patient populations. It is a subset of MedDRA terminology.
Permanent Ventilation	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.
PNCR	Pediatric Neuromuscular Clinical Research Network
Study Day	For any event of interest, Study Day = calendar date of event – calendar date of gene transfer +1. Day 1 is the Study Day of the gene transfer and any events occurring on the same calendar day as the gene transfer.
TEAE	Treatment-emergent Adverse Event = any adverse event whose onset (or worsening of an existing AE) occurred on or post day of gene therapy infusion.

Abbreviation	Description
Vector genome	The human SMN cDNA sequence, corresponding to the mature mRNA, cloned into the self-complementary AAV vector plasmid.

2. PURPOSE

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 15699-AVXS-101-CL-303: *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*. This statistical analysis plan (SAP) has been based on International Conference on Harmonization (ICH) E3 and E9 guidelines and in reference to protocol version 1.0: dated 29 March 2017 and Annotated Case Report Form (aCRF): dated 17 August 2017. The statistical analysis plan covers statistical analysis, tabulations and listings of all data including effectiveness and safety data. Analyses will be performed using SAS® Version 9.4 (SAS Institute, Inc., Cary, NC) or later under the Windows (Server 2008 R2) operating system.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified.

2.1. Responsibilities

AveXis, Inc. is responsible for ownership and approval of the SAP.

[redacted] is responsible for deriving the data set according to CDISC standards and create data set specifications based on the SAP. [redacted] will perform the statistical analyses and are responsible for the production and quality control of all tables, listings and figures.

2.2. Timing of Analysis

The primary analysis will occur at such time that the last intent-to-treat (ITT) patient has reached 18 months of age; database lock will occur after all enrolled patients have completed the 18 months of age visit or have discontinued study early.

2.2.1. DSMB Quarterly Data Reviews

The DSMB's primary responsibilities will be to:

- safeguard the interests of study patients and assess the safety of the study treatment(s) and study procedures in a confidential manner
- assess the data quality, completeness and timeliness and provide recommendations about stopping or continuing the studies or otherwise modifying the studies
- contribute to enhancing the integrity of the studies, by formulating recommendations relating to the patient recruitment, selection and patient management during the studies
- further enhance the ability to evaluate the cumulative safety data by making recommendations regarding the format of the statistical summaries in the open and closed reports
- attend to safety and risk: benefit considerations in tandem with study designs, planned objectives, and patient care in accordance with ICH, FDA, EMA, Declaration of

Helsinki, and Operational Guidelines for Establishment and Function of Data Safety Monitoring Boards/Data Monitoring Committees

- consider factors external to the studies when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the studies
- review the conduct of the studies including protocol violations

The DSMB will serve in an advisory role to the AveXis Study Team. AveXis representatives will be responsible for promptly reviewing the DSMB recommendations, determining whether any changes to the studies are required (including protocol amendments), and initiating any changes to the studies.

2.2.2. DSMB Reporting and Meetings

Reports describing the status of the study will be prepared by AveXis and sent to each DSMB member prior to each meeting for review and preparation. DSMB meetings will occur on quarterly basis, aligning with the AveXis quarterly data cut reviews (as AVXS summary report completed in following month).

Reports include the following:

- A brief narrative of the study status, including the target enrollment, current and projected time to completing enrollment. Any significant events and/or difficulties should be briefly described in this narrative.
- A brief narrative for each participant describing gender, age, race and ethnicity and other relevant demographic characteristics. The narrative for each participant should briefly describe his/her study status (i.e., dose level, visit number, adverse event information).
- A timeline outlining the study progress relative to visit number for each participant, as well as time points for each SAE/Dose Limiting Toxicity. A total for Adverse Events (AEs) for each participant should be included.
- A summary of AEs by grade levels
- A listing of AE details grouped by participant
- A listing of SAE details grouped by participant
- A listing of deaths
- A summary of clinically significant laboratory test results
- Other key information related to safety/conduct of the study

2.2.3. Stopping/Discontinuation Rules

An independent Data Safety Monitoring Board (DSMB) has been selected for the study. Safety data will be monitored on a continual basis throughout the trial in accordance with ICH/GCP and institutional requirements, including Sponsor Safety Management Plan (SMP). The DSMB could recommend early termination of the trial for reasons of safety. Study enrollment could be halted by the Sponsor when any patient experienced a Grade 3 or higher adverse event toxicity that is possibly, probably, or definitely related to the study drug. This

includes any patient death, important clinical laboratory finding, or any severe local complication in the injected area related to administration of the study agent.

The DSMB charter and all materials developed for the DSMB to review and all documented recommendations will be maintained according to confidentiality requirements.

3. STUDY OBJECTIVES

3.1. Primary Objective(s)

The co-primary objectives of this gene therapy clinical trial are to determine the efficacy of AVXS-101 by demonstrating achievement of developmental milestone of functional independent sitting for at least 30 seconds at the 18 months of age study visit and to determine the efficacy of AVXS-101 based on survival at 14 months of age. Survival is defined by the avoidance of combined endpoint of either (a) death or (b) permanent ventilation, which is defined by tracheostomy or by the requirement of ≥16 hours of respiratory assistance per day (via noninvasive 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.

3.2. Secondary Objective(s)

The secondary objective is the determination of efficacy of AVXS-101 based upon all available data at the time when all patients have reached 18 months of age. The co-secondary efficacy endpoints are:

- The proportion of patients maintaining the ability to thrive, defined as the ability to tolerate thin liquids (as demonstrated through a formal swallowing test) and to maintain weight (>third percentile based on World Health Organization [WHO] Child Growth Standards [1] for age and gender) without need of gastrostomy or other mechanical or non-oral nutritional support at 18 months of age.
- The proportion of patients who are independent of ventilatory support, defined as requiring no daily ventilator support/usage at 18 months of age, excluding acute reversible illness and perioperative ventilation, as defined above through assessment of actual usage data captured from the device (Phillips Trilogy).

[redacted]

3.4. Safety Objectives

The safety objectives are to:

- Evaluate the safety of AVXS-101 in patients with SMA Type 1
- Determine the safety of AVXS-101 based on the development of unacceptable toxicity defined as the occurrence of any Common Terminology Criteria for Adverse Events (CTCAE) [CTCAE_04] Grade 3 or higher, unanticipated, treatment-related toxicity.

3.5. Study Design

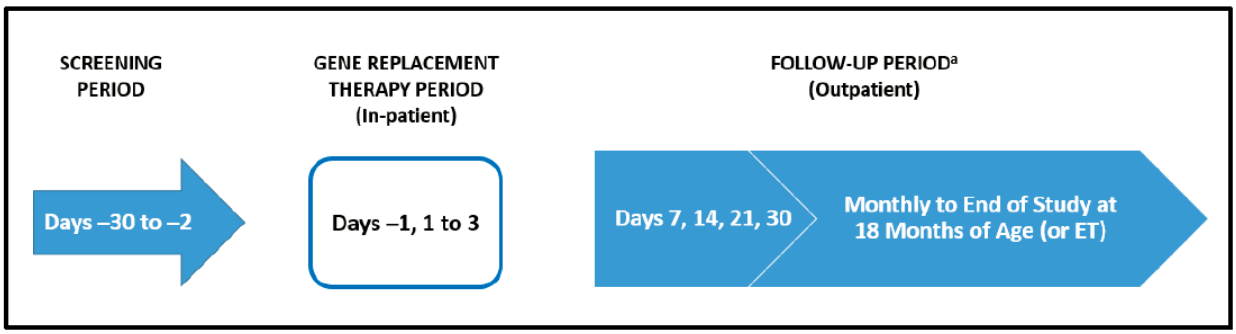
This is a pivotal Phase 3, open-label, single-arm, single-dose, study assessing the efficacy and safety of AVXS-101 (gene replacement therapy) in up to twenty (20) patients with spinal muscular atrophy (SMA) Type 1 who meet enrollment criteria, may be either symptomatic or pre-symptomatic and are genetically defined by no functional survival motor neuron 1 gene (*SMN1)* with 1 or 2 copies of survival motor neuron 2 gene (*SMN2*) and who are < 6 months (< 180 days) of age **at the time** of gene replacement therapy (Day 1). Enrolling up to twenty (20) patients under the broader enrollment criteria is projected to enable enrollment of at least fifteen (15) patients that meet the Intent-to-Treat Population (ITT) criteria. The ITT

population is identified as symptomatic patients with bi-allelic *SMN1* deletions and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C) and will comprise the primary population for evaluation of the primary and secondary endpoints. Study power is based upon efficacy analysis of the ITT population. Furthermore, the first three patients enrolled must meet criteria for the Intent-To-Treat Population to enable a comparison of CHOP-INTEND scores at one-month following gene replacement therapy to enable a comparison of patient response between AVXS-101-CL-303 patients and Cohort 2 patient results from the Phase 1 trial (AVXS-101-CL-101). Patients with 1 copy of *SMN2*, pre-symptomatic patients and patients with the *SMN2* gene modifier mutation (c.859G>C) and other permutations outside of those specified in the ITT population will be evaluated separately as part of additional subgroup analyses. Details of all analyses will be contained within this Statistical Analysis Plan.

This is a Phase 3, open-label, single-arm, single-dose study of AVXS101 (gene replacement therapy) in patients with SMA Type 1 with 1 or 2 copies of *SMN2*. The study includes 3 study periods: screening, gene replacement therapy, and follow-up (Figure 1). During the screening period (Days -30 to -2), patients undergo screening procedures to determine eligibility for study enrollment. Those 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 IV infusion of the equivalent of AVXS-101 1.1×10^{14} vg/kg over approximately 30–60 minutes, dependent upon total volume required per patient weight, 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 (Day 4 to End of Study 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 7 days and still within the required visit window.

All post-treatment visits will be relative to the date on which gene replacement therapy is administered, except for the 14 and 18 months of age visits, which 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 Study visit. After the End of Study visit, eligible patients may roll over into the long-term follow-up study.

Figure 1: Study Design Schematic



Note: After the End of Study visit at 18 months of age, eligible patients may directly roll over into the long-term follow-up study.
ET = early termination
a All post-treatment visits will be relative to the date on which gene replacement therapy is administered, except for the 14 and 18 months of age visits, which will be relative to the patient's date of birth.

A schedule of study assessments is provided in Table 1. Efficacy will be assessed by primary, secondary, [redacted] endpoints (see Section 4.1, Efficacy Endpoints: (see Section 8 for Details) and [redacted]. Safety will be assessed through monitoring AEs, concomitant medication usage, physical examinations, vital sign assessments, cardiac assessments, and laboratory evaluations (see Section 4.3, Safety Endpoint through Section 4.8, Other Endpoints).

3.5.1. Schedule of Assessments

Table 1: Schedule of Assessments

Study Period	Screening	Gene Replacement Therapy (In-patient)				Follow-up (Outpatient)					
Visit #	1	2				3	4	5	6	7+	End of Study[a]
# of Days in Study	–30 to –2	-1	1[b]	2	3	7	14	21	30	Monthly[c]	18 Months of Age (or ET)
Window						± 2 days				± 7 days (0–14 days at 14 Months of Age)	0–14 days
Informed Consent	X										
Prednisolone Pre-Dosing		X[q]	X	X	X	X	X	X	X[q]		
AVXS-101 Infusion			X								
Bayley Scales/WHO Developmental Milestones[d] (with video)[e]	X								X[f]	X[f]	X
CHOP-INTEND[g] (with video)[e]	X	X[s]				X	X	X	X	X	X
CMAP	X									X[j]	X
Demographic/Medical History	X										
Physical Exam	X		X	X	X	X	X	X	X	X	X
Vital Signs[h]/Weight & Length	X	X	X[i]	X	X	X	X	X	X	X	X
12-Lead ECG	X	X	X	X						X[j,t]	X
12-Lead Holter Monitoring[k]		X	X	X	X					X[j,t]	X
Echocardiogram	X									X[j,t]	X
Pulmonary Examination	X	X		X	X	X	X	X	X	X	X
Swallowing Test	X									X[j]	X
Photograph of Infusion Site			X	X	X	X	X	X	X		

Study Period	Screening	Gene Replacement Therapy (In-patient)				Follow-up (Outpatient)					
Visit #	**1**	**2**				**3**	**4**	**5**	**6**	**7+**	**End of Study[a]**
# of Days in Study	**–30 to –2**	**-1**	**1[b]**	**2**	**3**	**7**	**14**	**21**	**30**	**Monthly[c]**	**18 Months of Age (or ET)**
Window						**± 2 days**				**± 7 days (0–14 days at 14 Months of Age)**	**0–14 days**
Hematology/Chemistry/ Urinalysis	X	X[o]		X		X	X	X	X	X	X
CK-MB	X					X			X	X[r]	X
Virus Serology	X										
Capillary Blood Gas		X		X							
ELISA anti-AAV9/SMN Ab	X					X	X	X	X[l]		
Immunology Testing (ELISpot)						X			X[l]		
AAV9 Ab Screen in Mother	X										
Blood for Diagnostic Confirmation Testing	X										
Saliva, Urine, and Stool Samples (for viral shedding)[p]	X			X[m]	X[m]	X	X	X	X		
Adverse Events[n]	X	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant Medications	Collected from 2 weeks before gene replacement therapy until End of Study visit										

Note: Missed visits should be rescheduled as soon as possible, but within 7 days.
Ab = antibody; CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP = compound motor action potential; ECG = electrocardiogram; ELISA = enzyme-linked immunosorbent assay; ELISpot = Enzyme-linked ImmunoSpot; ET = early termination; WHO = World Health Organization
a The End of Study visit must occur within 0 to 14 days after the date on which the patient reaches 18 months of age (or ET).
b Day 1 assessments will be performed prior to the start of gene replacement therapy infusion.
c The 14 months of age visit must occur within 0 to 14 days after the date on which the patient reaches 14 months of age.
d Developmental milestones will be assessed as defined by Bayley Scale of Infant and Toddler Development, version 3 (independent sitting will be assessed also by WHO Multicentre Growth Reference Study).
e Videos may be submitted for review by a central reader.
f The full Bayley test will be administered every 6 months, starting at Month 6, whereas the Bayley fine and gross motor subtests will be administered at each monthly visit.
g Patients who achieve 3 consecutive CHOP-INTEND scores ≥58 will not continue CHOP-INTEND assessments.
h Vital signs include blood pressure, respiratory rate, pulse, axillary temperature, and pulse oximetry
i Vital signs will be continuously monitored throughout the infusion of gene replacement therapy and recorded every 15 minutes for the first 4 hours after the start of infusion, then every hour until 24 hours after the start of infusion. Axillary temperature will be recorded pre- and post-infusion.
j Completed every 6 months, starting at Month 6.
k Serial ECG data will be pulled in triplicate from the Holter monitor at the following time points: pre-dose (within 24h), 2h, 4h, 6h, 8h, 12h, 24h, 36h, and 48h post-dose.
l Additional sampling may be performed at subsequent time points if ELISpot value(s) continue to be elevated, based on further discussion with the Principal Investigator and Medical Monitor.
m Collected at 24 and 48 hours post-dose.
n Serious adverse events are collected from signing of the informed consent through the last study visit. All adverse events that occur from the start of gene replacement therapy through the last study visit are collected.

o Laboratory samples collected on Day 1 to be processed locally, prior to dosing.
p Sites participating in the viral shedding sub-study will collect 24-hour full volume samples for urine and feces at 24 and 48 hours. All other sites will collect singular urine and feces samples within 24 hours and 48 hours of dosing.
q Prednisolone to be given 24 hours prior to scheduled AVXS-101 dosing, and continued as per protocol Section 9.2.1.
r CK-MB will be collected at Day 60, Month 6, 9, 12, 15, and 18
s If a Day -1 CHOP-INTEND assessment is not completed, a CHOP-INTEND assessment should be completed on Day 1 prior to dose administration.
t for patients enrolled in the study prior to amendment 3 and irrespective of study schedule, after signing an updated informed consent form, an echocardiogram, 24-hour Holter monitoring, and 12-lead ECG will be performed at the next scheduled visit and then in accordance with the Schedule of assessments Compound Motor Action Potential Manual

3.6. Patient Selection

The current version of the protocol (v3.0) allows for up to 20 patients, who are 6 months of age or younger at time of gene replacement therapy infusion (Day 1) diagnosed with SMA Type 1 who meet enrollment criteria, which may be either symptomatic or pre-symptomatic and are genetically defined by no functional survival motor neuron 1 gene (*SMN1)* as well as 1 or 2 copies of survival motor neuron 2 gene (*SMN2*). Enrolling up to twenty (20) patients under the broader enrollment criteria is projected to enable enrollment of at least fifteen (15) patients that meet the Intent-to-Treat Population (ITT) criteria. The ITT population is identified as symptomatic patients with bi-allelic *SMN1* deletions and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C) who meet all other study enrollment criteria. In addition, the first three patients enrolled must meet the criteria for the Intent-to-Treat Population to enable a comparison of CHOP-INTEND scores at one-month following gene replacement therapy to enable a comparison of patient response between AVXS-101-CL-303 patients and Cohort 2 patient results from the Phase 1 trial (AVXS-101-CL-101). Patients with 1 copy of *SMN2*, pre-symptomatic patients and patients with the *SMN2* gene modifier mutation (c.859G>C) and other permutations outside of those specified in the ITT population will be evaluated separately as part of additional subgroup analyses. Details of all analyses will be contained within this Statistical Analysis Plan.

3.6.1. Inclusion Criteria

See protocol for details.

3.6.2. Exclusion Criteria

See protocol for details.

3.7. Determination of Sample Size

This study will enroll up to twenty (20) patients with spinal muscular atrophy (SMA) Type 1 who meet enrollment criteria, may be either symptomatic or pre-symptomatic and are genetically defined by no functional survival motor neuron 1 gene (*SMN1)* with 1 or 2 copies of survival motor neuron 2 gene (*SMN2*) and who are < 6 months (< 180 days) of age **at the time** of gene replacement therapy (Day 1). Enrolling up to twenty (20) patients under the broader enrollment criteria is projected to enable enrollment of at least fifteen (15) patients that meet the Intent-to-Treat Population (ITT) criteria. The ITT population is identified as symptomatic patients with bi-allelic *SMN1* deletions and 2 copies of *SMN2* without the

SMN2 gene modifier mutation (c.859G>C) and will comprise the primary population for evaluation of the primary and secondary endpoints. Study power is based upon efficacy analysis of the ITT population. Furthermore, the first three patients enrolled must meet criteria for the Intent-To-Treat Population to enable a comparison of CHOP-INTEND scores at one-month following gene replacement therapy to enable a comparison of patient response between AVXS-101-CL-303 patients and Cohort 2 patient results from the Phase 1 trial (AVXS-101-CL-101). Patients with 1 copy of *SMN2*, pre-symptomatic patients and patients with the *SMN2* gene modifier mutation (c.859G>C) and other permutations outside of those specified in the ITT population will be evaluated separately as part of additional subgroup analyses.

The two co-primary efficacy endpoints will be assessed in sequence: The endpoint of functional independent sitting will be assessed first and, only if this assessment meets statistical significance will the endpoint of survival be assessed.

The first co-primary efficacy endpoint hypothesis is:

$$\mathbf{H_0}: p_{AVXS-101} = 0.1\%$$

versus the alternative

$$\mathbf{H_a}: p_{AVXS-101} > 0.1\%,$$

where p is the proportion of functional independent sitting for at least 30 seconds at the 18 - month of age study visit.

It is assumed that the true response rate for the primary endpoint is actually zero (or as low as 0.1%) in the population of historical control; the first co-primary efficacy endpoint hypothesis is that the AVXS-101 treated patients achieve a response rate greater than 0.1%. Based upon preliminary results from the ongoing Phase 1 clinical study AVXS-101-CL-101, at least 40% of treated symptomatic patients with bi-allelic deletions of *SMN1* and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C) are expected to achieve the co-primary efficacy endpoint of functional independent sitting for at least 30 seconds at 18 months of age. With the assumption for the true response rate of AVXS-101 for the primary endpoint being in the range of 30% - 40%, a sample size of 15 patients that meet ITT criteria will be enrolled and assuming approximately 30% of patients are excluded from analysis, would yield an ITT population that would provide power of >90% to detect a significant difference with α=0.025 using a 1-sided exact test for a binomial proportion.

The second co-primary efficacy endpoint hypothesis:

$$\mathbf{H_0}: p_{AVXS-101} = p_{HISTORICAL-FINKEL}$$

versus the alternative

$$\mathbf{H_a}: p_{AVXS-101} \neq p_{HISTORICAL-FINKEL},$$

where p is the proportion patients of surviving at 14 months of age.

Based upon preliminary results from the ongoing Phase 1 clinical study AVXS-101-CL-101, at least 80% of treated symptomatic patients with bi-allelic *SMN1* deletions and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C) are expected to achieve the co-primary efficacy endpoint of survival through 14 months of age. It is anticipated that 75% of patients in the PNCR [5] population would not survive beyond 13.6 months of age, and that these control patients will represent a 25% survival rate based upon the natural history of the disease. With this efficacy, an enrolled sample size of 15 patients that meet ITT criteria (assuming 30% of patients are excluded from the analysis) would provide power of >80% to detect a significant difference with $\alpha = 0.05$ using a two sample 2-sided Fisher's exact test, comparing to patient-level data drawn from a published natural history observational study dataset with patients who meet the eligibility criteria for this study (bi-allelic *SMN1* deletions, 2 copies of *SMN2*, age of onset ≤6 months of age). The natural history observational study dataset was collected by PNCR network from the study performed at three large, tertiary care centers in the United States (Harvard University, Columbia University, Children's Hospital of Philadelphia; PNCR).

3.8. Treatment Assignment and Blinding

This is an open-label study. All enrolled patients will receive AVXS-101.

3.9. Administration of Study Medication

Refer to Section 3.5 of the SAP.

3.10. Study Procedures and Flowchart

Refer to Section 3.5 of the SAP.

3.11. Statistical Hypotheses

3.11.1. Primary Efficacy Hypothesis

Primary and secondary efficacy analyses will be based on the ITT population, which consists of those symptomatic patients with bi-allelic deletion mutations of *SMN1* and 2 copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C). These analyses are to test the superiority of AVXS-101 versus the results from natural observation study (PNCR).

The first co-primary efficacy hypothesis to be tested is:

$\mathbf{H_0}: p_{AVXS-101} = 0.1\%$

versus the alternative

$\mathbf{H_a}: p_{AVXS-101} > 0.1\%,$

where p is the proportion of functional independent sitting for at least 30 seconds at the 18-month of age study visit.

The second co-primary efficacy hypothesis to be tested is:

$$\mathbf{H_0}: p_{AVXS-101} = p_{HISTORICAL-FINKEL}$$

versus the alternative

$$\mathbf{H_a}: p_{AVXS-101} \neq p_{HISTORICAL-FINKEL},$$

where p is the proportion surviving event-free to 14 months.

Testing for the first co-primary endpoint, functional independent sitting will first be performed using a 1-sided exact binomial test. Only if the null hypothesis of equality in proportion of functional independent sitting is rejected at p <0.025, will the co-primary endpoint survival improvement be tested using a 2-sided Fisher's exact test on the ITT population, comparing to match patients from the natural observational study (PNCR). This hierarchy approach strongly prevents the Type I error rate from inflation.

3.11.2. Secondary Efficacy Hypotheses

The hypothesis for both co-secondary efficacy endpoints to be tested is:

$$\mathbf{H_0}: p_{AVXS-101} = 0.1\%$$

versus the alternative

$$\mathbf{H_a}: p_{AVXS-101} > 0.1\%,$$

where p is the proportion of patients maintaining the ability to thrive/are independent of ventilatory support.

One-sided exact binomial tests will be executed for secondary efficacy analyses on the ITT population. The same test hierarchy approach will apply to secondary efficacy analyses, which is the co-secondary endpoint of ability to thrive will be tested first. Only if the null hypothesis of ability to thrive is rejected at p<0.025, will the co-secondary endpoint of independent of ventilatory support will be similarly tested. Pre-specification of the order of testing within this hierarchical framework eliminates type 1 error inflation due to multiplicity.

4. ENDPOINTS

4.1. Efficacy Endpoints: (see Section 8 for Details)

4.1.1. Primary Efficacy Endpoints

One co-primary efficacy endpoint is achievement of functional independent sitting. The other co-primary efficacy endpoint is survival, defined as avoidance of either (a) death or (b) permanent ventilation. Permanent ventilation is defined by tracheostomy or 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.

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. Milestones determined by the qualified Clinical Evaluators at the investigational sites will be presented in listings.

4.1.2. Secondary Efficacy Endpoints

One co-secondary outcome will include the proportion of patients who did not require parenteral nutrition prior to therapy who maintain the ability to thrive, defined by all of the following:

- ability to tolerate thin liquids as demonstrated through a formal swallowing test
- no requirement of nutrition through mechanical support (i.e., feeding tube)
- maintenance of weight (>third percentile for age and gender) at 18 months of age.

The other co-secondary secondary outcome will include the proportion of patients who are independent of ventilatory support, defined as requiring no daily ventilator support/usage at 18 months of age, in the absence of acute reversible illness and excluding perioperative ventilation.

[redacted]

[redacted]

4.2.1. CHOP-INTEND Score

There are 16 items in CHOP-INTEND assessment (Section 21.2). A rating of Brazelton behavioral states (Section 21.3) was recorded for each item. As suggested by manual [9], the optimal state for testing is state 4 ("alert, with bright look") and 5 ("eyes open"). If a subject cannot be tested for an item due to an adverse behavioral state, it should be scored as "CNT" (cannot test) and NOT a zero. In item 1 to 11, 13 and 16, both left and right sides need to be evaluated, and the maximum score should be selected for the best score of the item. If both sides are scored "CNT", the item should be scored as "CNT". If only one side scored "CNT", the other side score should be used for the best score of the item. If any of these 16 items scored "Cannot test" or "CNT", the total score should be set missing.

4.3. Safety Endpoint

The primary safety endpoint is the development of unacceptable toxicity, defined as the occurrence of any one Grade III or higher, unanticipated, treatment-related toxicity that presents with clinical symptoms and requires medical treatment.

4.4. Pharmacokinetic Endpoints

Not applicable for this SAP.

4.5. Pharmacodynamic Endpoints

Not applicable for this SAP.

4.6. Additional Safety Endpoints

Additional safety analyses include:

4.6.1. Adverse Events

Other than Grade III or higher adverse events used to define unacceptable toxicity in the primary endpoint, 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.

4.6.2. Vital Signs

Length, weight, blood pressure, respiratory rate, pulse, axillary temperature, and pulse oximetry will be collected at every visit. For detailed schedule of events table, see Table 1.

4.6.3. 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, and genitourinary.

4.6.4. Laboratory Evaluations

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.

4.6.5. Use of Non-oral Feeding Support

A swallowing test will be performed at baseline and every 6 months 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 implanted, 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.

4.6.6. Pulse Oximetry

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

4.6.7. Cardiovascular Safety Evaluations

A 12-lead electrocardiograms will be conducted on the schedule of assessment (Table 1). The ECG tracings or ECG machine data will be collected for centralized review and interpretation by a cardiologist.

Additionally, a Holter monitor will be placed 24 hours prior to dose administration through 48 hours after dose administration. On Day -1 to Day 3, serial ECG data will be pulled in triplicate from the Holter monitor at the following time points:

- Pre-dose (within 24 hours prior to gene replacement therapy)
- 2 hours
- 4 hours
- 6 hours
- 8 hours
- 12 hours
- 24 hours
- 36 hours
- 48 hours

Twenty-four hour Holter monitoring will also be performed at the 3, 6, 9, and 12 month visits and every 6 months thereafter.

4.6.8. 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). T-cell response to AAV9 and SMN will be measured in number of spot forming cells per million peripheral blood mononuclear cells (PBMCs) as determined by Enzyme-Linked ImmunoSpot (ELISpot) assays.

4.6.9. Concomitant Medications

Prior and concomitant medications will be captured in the eCRF from two weeks prior to study dosing through the last study visit and coded using the WHO Drug dictionary, version March 2016 C Final 2.

4.6.10. Non-invasive Ventilatory Support

Patients will be assessed by a pulmonologist at the time points specified in the Schedule of Assessments and may be fitted with a non-invasive positive pressure ventilator (e.g., Bilevel Positive Airway Pressure (BiPAP)) at the discretion of the pulmonologist and/or investigator. Non-invasive ventilatory support equipment may be provided by AveXis, Inc. through a third-party vendor (as necessary).

Each patient will be assessed by investigator whether permanent ventilation criteria has been met. If the patient meets the permanent ventilation criteria, the daily hours of ventilation support (including Trilogy) usage will be reported through [redacted] Also, if trilogy BiPap machine is used with SD card, the daily real hours of usage data will be sent to AveXis.

4.7. Health-economics Endpoints

Not applicable for this SAP.

4.8. Other Endpoints

Additional analyses of the two co-primary and other additional endpoints utilizing a natural history cohort as a comparison may be incorporated, as appropriate.

5. ANALYSIS POPULATION

Safety will be assessed based on all patients who underwent gene therapy at day 1. The primary population for the primary and secondary efficacy analyses will be the ITT population. Patients with 1 copy of *SMN2*, pre-symptomatic patients and patients with the *SMN2* gene modifier mutation (c.859G>C) and other permutations outside of those specified in the ITT population will be evaluated separately as part of additional subgroup analyses.

5.1. Safety Population

All patients who underwent gene therapy infusion will be included. All safety analysis will be based on safety population, unless specified otherwise.

5.2. Intent-to-Treat (ITT) Population

The ITT population will consist of symptomatic patients with bi-allelic deletion 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 AVXS-101 at less than 180 days of age. The first three patients enrolled must meet the criteria for the Intent-to-Treat Population.

5.3. Efficacy Completers Population

The efficacy completers analysis population will consist of:

- All treated patients who reach 14 months of age for the survival endpoint or 18 months of age for the endpoint of achievement of functional independent sitting, OR
- All treated patients who meet discontinuation criteria, discontinue the study due to an AE, or experience death

5.4. All Enrolled Population

The all enrolled population will consist of all patients who receive an IV infusion of AVXS-101. Analyses of endpoints in this population are considered descriptive.

5.5. PNCR Control Population

The PNCR Natural History dataset (Finkel, 2014) is drawn from a large natural history study performed on a large cohort of 337 patients with any form of spinal muscular atrophy followed at 3 large, internationally recognized tertiary medical centers with significant expertise in the management of SMA (Harvard University/Boston Children's Hospital, Columbia University and the University of Pennsylvania/Children's Hospital of Philadelphia). Previously identified patients followed in PNCR site clinics and newly diagnosed patients were enrolled. All eligible patients were offered participation in the PNCR study. Study visits were scheduled at baseline and at 2, 4, 6, 9, and 12 months and every 6 months thereafter. The SMA standard of care guidelines published in 2007 were used as a basis for providing uniform care among the study sites. For purposes of this study, sitting (for SMA Type 2) was defined as being able to sit independently for >10 seconds;

children who were unable at any point to achieve this milestone were classified as SMA Type 1.

A natural history control population is drawn from the PNCR Natural History Dataset (Finkel, 2014) consisting of all patients with age of onset ≤6 months, bi-allelic deletion of *SMN1* (exon 7/8 common homozygous deletion) and 2 copies of *SMN2* for whom enrollment data (retrospective and prospective) is available to determine survival based on the defined criteria. The *SMN2* modifier mutation (c.859G>C) described by Prior and colleagues (Prior, Thomas W., et. al. "A positive modifier of spinal muscular atrophy in the *SMN2* gene." *The American Journal of Human Genetics* 85.3 (2009): 408-413.) was not assessed in the PNCR study cohort. Based on these criteria, 23 patients from the PNCR dataset are included in the control population. Among them, 17 patients reached the combined endpoint of death or the need for a minimum of 16 hours/day of noninvasive ventilation support for a minimum of 14 continuous days by 13.6 month of age. The survival rate at 13.6 months of age is approximately 25% (17/23), of which the control cohort will be used as comparator with ITT population for survival analysis.

5.6. Pharmacokinetic Set

Not applicable for this SAP.

5.7. Pharmacodynamic Set

Not applicable for this SAP.

5.8. Protocol Deviations

All deviations will be recorded in the [redacted] database and will be categorized in accord with AveXis SOPs. As this is a single dose study, protocol deviations will be described; however, there will be no separate statistical analysis.

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. General Methods

All hypothesis testing will be conducted at one-sided with significance level α=0.025 or two-sided, at significance level α=0.05, as appropriate. Categorical measures, such as percent surviving event-free, will be summarized using count and percentages.

Continuous data, such as CHOP-INTEND scores, will be summarized using count, mean, median, standard deviation (SD), minimum, and maximum. For continuous data specified to be analyzed using parametric procedures, non-parametric procedures will be used if assumptions of parametric tests are not met.

Summary tables, listings, and figures, and statistical analyses will be done using SAS version 9.3 or higher.

Efficacy analyses will be conducted on the ITT and the Efficacy Completers population, as indicated. Additional efficacy analyses for other subgroups of patients may also be conducted, as appropriate. The analysis based on the ITT population will be considered as the primary analysis. Safety analyses will be conducted on the Safety Analysis population only.

6.2. Key Definitions

6.2.1. Definition of Baseline

The baseline value refers to the last non-missing measurement collected before gene therapy infusion of study drug. On Study Day 1, all assessments should be performed prior to administering the gene therapy infusion of study drug per protocol. The baseline value is therefore determined by the last non-missing measurement collected on or before the first day of study drug administration. If multiple measurements are recorded on the same day, the last measurement recorded prior to the gene therapy infusion will be used as the baseline value. 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. For some special measures, the baseline value will be defined explicitly in the corresponding section.

The baseline values will be the first non-missing values collected for the control patients from the PNCR dataset.

6.2.2. Definition of Study Days (Days Relative to the Gene Therapy Infusion)

Study Days are calculated for each time point in the treatment period relative to the gene therapy infusion of study drug. Study Days are negative values when the time point of interest is prior to the study drug infusion day. Study Days are positive values when the time point of interest is after the first study drug dose day. Study Day 1 is the day of the infusion of the gene therapy study drug.

6.2.3. Definition of Final Treatment Value

For the purposes of the co-primary endpoint of survival (see Section 8.1.2), the first non-missing value after the participant reaches 14 months of age. There is no upper bound for the "14 months" age visit; that is, no visit is too late to represent the "14 months of age" analysis. The earliest visit on or after 420 days of age will be used in the "14 months of age" analysis.

For all other endpoints, including the co-primary endpoint of functional independent sitting (see Section 8.1.1), the co-secondary endpoints of "maintain ability to thrive" (see Section 8.2.1), "independence of ventilatory support" (see Section 8.2.2), and [redacted] the final treatment 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.

6.2.4. Derived and Transformed Data

6.2.4.1. Primary Efficacy Variables

The co-primary efficacy endpoint is functional independent sitting at the 18 months of age visit.

Functional independent sitting: this is assessed by video evaluation by an expert reviewer of videos taken either at scheduled visits (see

Table 4 and

Table 5) or provided by parent/legal guardian, if patient meets the criterion:

- Child sits alone without support for at least 30 seconds. This will be collected from external dataset.

The other co-primary 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 (Triology 100, Triology 200) on an SD card, and transferred as an external dataset. Average daily use of non-invasive ventilatory support by visits (if available) will be calculated. If a patient did not have a Trilogy device 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. The count and percent of patients in each ventilation support category at each visit (if available) will be displayed.

6.2.4.2. Supportive (Secondary [redacted] Efficacy Variables

Supportive (secondary) efficacy variables are as follows:

- Proportion of patients who did not require parenteral nutrition prior to therapy who maintain the ability to thrive, defined by the ability to tolerate thin liquids as demonstrated through a formal swallowing test, do not receive nutrition through mechanical support (i.e., feeding tube), and maintain weight (>third percentile for age and gender) at 18 months of age.
- Proportion of patients who are independent of ventilatory support, defined as requiring no daily ventilator support/usage at 18 months of age, in the absence of acute reversible illness and excluding perioperative ventilation.

[redacted]

6.2.4.3. First observed date of video confirmed milestone

Home recorded milestone video will be brought by parents at the official clinical visit, which will be assessed by investigator at the site. If the investigator confirms the milestone, the recording will be captured in [redacted] and the video will be uploaded for central review. If the central reviewer confirms tt the milestone, the first observed date will be the date captured in [redacted] If the central reviewer is not able to confirm the milestone, the attempt will be made

to confirm the milestone in the next clinical visit. If confirmed in the next clinical visit, the reported first observed date of the confirmed milestone will be the end date of that clinical visit. This alternative process is due to clinical operation difficult.

6.2.4.4. Safety Variables

The safety endpoint is defined as the patient meeting the following criteria:

- Unanticipated toxicity event of Grade ≥3 (as per CTCAE)
- Adverse events of special interest (see Section 10.3.2.4)
- 'Possibly Related' or 'Probably Related' or 'Definitely Related' to study treatment
- Requires medical treatment or presents with symptoms

This will be collected at all scheduled visits (see Table 1) from patient's CRF. Adverse Event collection methods for the observational natural history cohort were not consistent with rigorous Adverse Event collection methods demonstrated in the context of an interventional clinical research study; therefore, only descriptive statistics will be presented.

6.3. Handling Missing Data

All patients in the ITT analysis set will be included in the primary efficacy analysis for a given endpoint provided there are non-missing baseline values. If a patient misses a regularly scheduled visit, every attempt will be made to reschedule a visit within that visit window to obtain evaluations or tests.

For co-primary and co-secondary endpoints, missing values will be imputed as non-responsive.

Additional sensitivity analyses will be performed if there is at least 1 missing value. They include:

- An analysis based on completer population, from which the missing value(s) will be excluded.
- An estimate based on missing values imputed as follows:
    - Set the value to nonresponsive, if a patient discontinues the study due to an AE or experiences death for missing data occurring after these events.
    - Set the value based on the last available response, if otherwise.
- An estimate based on multiple imputation may be carried out using last available response, assuming Missing at Random (MAR).

If an endpoint value is a composite "response-type" (such as maintain ability to thrive) at any visit which is missing due to missing values in any of the components, while the patient is still enrolled (this is expected to happen very infrequently), it may still be possible to determine the response status using those component variables that are not missing. In this case, no imputation method is needed. However, if the response status cannot be determined in the presence of missing components, the method of last observation carried forward (LOCF) or non-responsive will be specified explicitly when applied to any of the missing

components. From that mix of actual and carried-forward values, the value of the "response-type" endpoint at 18 months of age will be determined. This type of LOCF method will be known as "LOCF mixed components," since it is based on calculating the composite value based on a mixture of values at a visit and values carried forward from previous visits.

[redacted]

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, and this missing value may be addressed as specified in the two paragraphs above or left as missing if acceptable.

Missing values in any of the endpoints will not be imputed when summarizing these endpoints using descriptive statistics.

In addition, missing values for safety endpoints will not be imputed.

Table 2: Rules of Date Imputation: Pre-Dose Data

Partial Missing Start or Stop Date	Imputed Start Date	Imputed Stop Date
Missing month and day, but the year is present	January 1 of that year or dose date if the year is the same as the year of dose date	December 31 of that year
Missing day, but year and month are present	First day of that month or dose date if the year and month are the same as the year and month of dose date	Last day of that month
Missing month, but year and day are present	Missing month imputed as January	Missing month imputed as December

Table 3: Rules of Date Imputation: Post-Dose Data

Partial Missing Start or Stop Date	Imputed Start Date	Imputed Stop Date
Missing month and day, but the year is present	Date of dose	December 31 of that year

Partial Missing Start or Stop Date	Imputed Start Date	Imputed Stop Date
Missing day, but year and month are present	First day of that month or dose date if the year and month are the same as the year and month of dose date	Last day of that month
Missing month, but year and day are present	Date of dose	Missing month imputed as December

6.4. Visit Windows

For efficacy analysis, the time windows specified in

Table 4 describe how efficacy data will be assigned to protocol-specified time points, as displayed in the Schedule of Assessments in SAP Section 3.5.1. All time points and corresponding time windows are defined based on Dosing Date.

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. Any efficacy assessments occurring outside the analysis windows will be considered an assessment of an unscheduled visit.

Table 4: Analysis Time Windows of Bayley Scales, CHOP-INTEND, Development Milestones and Pulmonary Exam*

Scheduled Visit	Nominal Days (Study Day)	Acceptable Analysis Window in Study Days (Min Day – Max Day)
Baseline	-	<1
Month 1	30	1 to 44
Month 2	60	45 to 74
Month 3	90	75 to 104
Month 4	120	105 to 134
Month 5	150	135 to 164
Month 6	180	165 to 194
Month 7	210	195 to 224
Month 8	240	225 to 254
Month 9	270	255 to 284
Month 10	300	285 to 314
Month 11	330	315 to 344
Month 12	360	345 to 374
Month 13	390	376 to 404

Scheduled Visit	Nominal Days (Study Day)	Acceptable Analysis Window in Study Days (Min Day – Max Day)
Month 14	420	405 to 434
Month 15	450	435 to 464
Month 16	480	465 to 494
Month 17	510	495 to 539
Month 18	540	540 to 570
Final Treatment Visit and 14 Months of Age Analysis Window		0 to ≤14 days after patient reaches 14 months of age (420-434 days of age) visit window; 0 to ≤14 days after patient reaches 18 months of age (540 days of age) visit window

*Depending on age at time of dosing, patients will complete varying number of visits. The patient must complete a visit within 2 weeks after reaching 14 months of age; subsequent visits will be scheduled from that visit date. The patient must also complete the final study visit within 2 weeks after reaching 18 months of age.

Due to the difficulty in clinical operation, some landmark visits criteria, like 14 or 18 months of age visits, may not be attained in the protocol defined visit windows. As long as a formal landmark visit cannot be scheduled and the next planned visit is made, for example age of 15 months visit, or survival status is confirmed, for example still survived after age of 18 months, data collected at the unscheduled visit may still be able to map to the landmark visit and included in the corresponding landmark analysis. And protocol deviation will be filed accordingly.

Safety data, such as laboratory results, vital signs, ECGs, and physical exams will be assessed by date and study day. For change from baseline analyses the value associated with the scheduled visit will be used. For summaries of shifts from baseline and potentially significant values all values will be considered for these analyses. Baseline for safety measures will be defined as the latest value before Day 1.

The efficacy data of this study will be compared to the data from the PNCR network. The analysis visit of PNCR will be based on the Visit Month defined in the PNCR dataset.

Table 5: Analysis Time Windows for Dataset from PNCR Network

Scheduled Visit	PNCR
Baseline	<= Enrollment Date
Month 2	Visit Month 2
Month 4	Visit Month 4
Month 6	Visit Month 6
Month 9	Visit Month 9
Month 12	Visit Month 12
Month 18	Visit Month 18

6.5. Data Cutoff Rule and Date

Analyses will be done when all patients have completed the final treatment visit.

6.6. Pooling of Centers

This is a multiple-center single dose treatment study. Given that the expected enrollment at any individual site is expected to be fewer than 3 patients, patients from all sites will be pooled together into a combined site in the analyses for the primary and secondary effectiveness endpoints. A site effect will be not examined because there will be too few patients within each center to provide an informative estimate of this effect.

•

6.7. Subgroups

Two subgroups based on age at dosing (study day 1) will be assessed in the selected analysis (developmental milestones and statistical modeling parts):

- Patients with age at dosing (study day 1) <= 4 months (120 days)
- Patients with age at dosing (study day 1) > 4 months (120 days).

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1. Patient Disposition and Withdrawals

The number and percent of patients who are still in the study when all patients reach 14 and 18 months-of-age will be tabulated.

Among those who discontinued the study prior to reaching the 18 months-of-age visit, the distribution of reasons for discontinuation will be enumerated.

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

Reasons for dose interruption will be presented in a listings if any.

This analysis will be conducted on the Safety Analysis Set.

7.2. Demographic Data

The age of the patient at the time of gene therapy infusion will be summarized. The distribution of patients by sex, ethnicity (Hispanic/Latino vs. Non-Hispanic/non-Latino), and race will be presented. Patient demographics will be summarized using the Safety Analysis Set.

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

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 summarized: gestational age (weeks), birth weight (kg), birth length (cm), and head circumference (cm).

The presence of significant medical conditions obtained from medical history will summarized. In particular, the following parameters will be summarized 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 will be summarized on the Safety Analysis Set.

7.3. Medical History and Concomitant Diseases

Medical history data will be summarized and 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 number and percentage of patients with a particular

condition/diagnosis will be summarized by overall. Patients reporting more than one condition/diagnosis within a body system will be counted only once for that body system.

7.4. Prior and Concomitant Medications

Prior and concomitant medications will be summarized by overall. A prior medication is defined as any medication taken 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. The number and percentage of patients taking prior or concomitant medications will be summarized by generic drug name based on the WHO Drug Dictionary.

7.4.1. Specific Medication Subgroups

In an attempt to reduce the host immune response to the AAV-based therapy, patients will receive prophylactic prednisolone (approximately 1 mg/kg/day) 24 hours prior to the gene transfer and continuing for approximately 30 days. After 30 days of treatment, the dose of prednisolone can be tapered for patients whose ALT values, AST values, and T-cell response are below the threshold of ≤2 X ULN for ALT and AST, and <100 SFC/10^6 PBMCs 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) will be computed for each patient. Doses captured as volume (e.g., 5 mL QD) will be converted to mg/kg utilizing the patient's screening weight and known prednisolone solution concentration (25 mg/5 mL or 5 mg/mL).

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.

For example, consider a patient who receives 1.0 mg/kg of prednisolone for Day 1 to Day 20, then on Day 20, dose is elevated to 2.0 mg/kg until Day 30, at which point it is tapered to 1.5 mg/kg. On Day 35, the dose is lowered to 1.0 mg/kg and continues until Day 40 when it is lowered further to 0.5 mg/kg until all prednisolone dosing stops on Day 45. For this patient,

Total Cumulative Dose= (1.0 mg/kg x 19 days) +
(2.0 mg/kg x 10 days) +
(1.5 mg/kg x 5 days) +
(1.0 mg/kg x 5 days) +
(0.5 mg/kg x 6 days) = 54.5 mg/kg

Exposure will be summarized for the Safety Analysis Set.

7.4.2. Other Therapies

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 AVXS-101. Concomitant Non-medication Therapies/Procedures are defined as therapies or procedures ongoing at time of injection of AVXS-101 or started after the injection.

Non-medication Therapies/Procedures will not be summarized. A listing will be provided.

8. EFFICACY

8.1. Primary Efficacy Endpoints and Analysis

8.1.1. Co-Primary Efficacy Endpoint: Functional Independent Sitting at 18 months of age

An independent expert reviewer will evaluate recorded videos of CHOP-INTEND or Bayley Scales assessments conducted at clinic visits. The reviewer will judge whether the video reveals evidence of the milestone achievement of functional independent sitting [redacted].

During the Screening visit, the physical therapist will complete an assessment of baseline milestone achievement, including functional independent sitting; this assessment must address all milestones/items noted in Appendix 21.1 that are at or below the child's expected function for age. Items that are below the child's expected function for age that are not successfully achieved during the baseline evaluation should be repeated at subsequent visits until successfully performed.

The milestones of sitting independently (Bayley Scales gross motor subtests item 22 and 26) will be assessed at every subsequent visit regardless of starting point on the scale. These milestones will also be assessed at the 18 months of age visit, regardless of previous attainment, as the Bayley Scales do not necessarily require the child to repeat previously attained milestones.

The number and percent of patients whom, through video evidence, exhibit the milestone achievement of independent sitting for at least 30 seconds at 18 months of age study visit will be summarized for the ITT population. Potential missing values will be imputed per Section 6.3. A one-sided Exact Binomial Test will be used to test the null hypothesis of p=0.1% at significance level of 0.025. Furthermore, the corresponding 97.5% confidence intervals will be estimated by the exact method for binomial proportions.

In case for the presence of missing value, sensitivity analyses outlined in Section 6.3 will be carried out to evaluate the appropriateness of assumptions for the missing data.

Additionally, for patients who achieve the functional independent sitting at 18 months of age visit, the age at which the subjects first achieved independent sitting for 30 seconds will be summarized.

8.1.2. Co-Primary Efficacy Endpoint: Avoidance of Death or Surrogate for Death (Permanent Ventilation)

The co-primary efficacy endpoint is defined by avoidance of the combined endpoint of either (a) death or (b) permanent ventilation, defined as requirement of tracheostomy or ≥16 hours of respiratory assistance per day (includes non-invasive ventilatory support) continuously for ≥14 days in the absence of an acute reversible illness, excluding perioperative ventilation. Permanent ventilation, so defined, is considered a surrogate for death.

Non-invasive ventilatory support usage data will be extracted directly from each patient's device; the data will be downloaded from the device's SD card through software provided by the

manufacturer and transferred as an external dataset. Each patient will also be assessed by investigator whether permanent ventilation criteria has been met, which is the primary endpoint. If the permanent ventilation criteria are met, the event (surrogate for death) will be reported in [redacted] system for primary efficacy analysis.

An "acute reversible illness" is defined as any condition other than spinal muscular atrophy that results in increased medical intervention (i.e., increased requirement for external ventilator support; use of other concomitant meds 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 ventilator use related to a surgical or other medical procedure of any nature for which the participant received medications that could impair or interfere with respiratory function.

For a participant who develops an acute reversible illness and/or requires perioperative ventilator 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 sub-acute and the participant will become evaluable with regards to the surrogate survival endpoint (Requirement of ventilator support of ≥16 hours/day for greater than 14 days).

Example: Using this approach it would mean that on day 1, patient A receives definitive intervention for an acute reversible illness resulting in ventilator support for ≥16 hours/day. Days 1-21 will be provided to permit recovery from the acute reversible illness. On Day 22, the participant is no longer considered to have an acute illness. Should the participant continue to require ≥16 hours/day of ventilator support from day 22 to day 36, he or she shall be considered to meet the surrogate endpoint.

Statistical approach: The proportion surviving event-free to 14 months of age will be computed in the ITT population. Patients who terminate the study prior to reaching 14 months of age for any reason will be considered treatment failures (event).

As a comparator, in a natural history study of SMA Type 1 patients, Finkel et al (2014) estimated that only 25% of SMA Type 1 patients with 2 copies of *SMN2* would survive event-free to 13.6 months of age.

The observed proportion surviving in the current study will be compared to the natural history data (5) of the matching cohort using a two-sample Fisher's exact test, along with the corresponding 95% confidence intervals.

If status at 14 months of age is coded using variable SURVIVE as 1 if patient survived to 14 months of age without requiring permanent ventilation, and 2 otherwise, then the SAS code to generate the endpoint analysis is:

```
proc format;
    value survive
    1= 'Yes'
    2= 'No'
    ;
    Value grp
    1='AVXS'
    2='PNCR'
;
run;
proc freq data=x order=data;
    table grp*survive / measures riskdiff;
    exact fisher / alpha=0.05;
run;
```

Time to death or permanent ventilation through 14 months of age is an additional sensitivity analysis. In case if there is at least 1 patient who is event-free, but discontinue study prior to his/her 14 month birthday, a sensitivity analysis, based on the approach for time to event, will be carried out. In this analysis, time to event will be censored at 14 months of age or at the date of discontinuation. The survival rate at 14 months of age will be estimated by Kaplan-Meier method, and survival curves for AVXS treated patients and the PNCR cohort will be compared using log-rank test at significance level of 0.05.

Additionally, the proportion of patients who experience each of the following events by 14 months of age will be summarized:

- Death
- Permanent ventilation

8.2. Secondary Efficacy Endpoint(s) and Analyses

8.2.1. Co-secondary Efficacy endpoint: Maintain ability to thrive

At baseline, a patient will be defined as not requiring parenteral nutrition if the child, 1) does not use parenteral nutrition of any kind (i.e., gastrostomy, nasogastric tube, nasojejunal tube, etc.); and 2) demonstrates intact swallowing on baseline assessment such that the child does not receive a recommendation for implementation of parenteral nutrition prior to receipt of AVXS-101.

The proportion of patients who at baseline do not require parenteral nutrition (as defined) who maintain the ability to thrive at the time of the child's study visit when he or she reaches 18 months of age will be summarized by subgroup and overall in the ITT population.

The ability to thrive is defined by meeting all of the following criteria:

- the ability to tolerate thin liquids as demonstrated through a formal swallowing test
- does not receive nutrition through mechanical support (i.e., feeding tube)
- maintains weight (>third percentile for age and gender as defined by WHO guidelines) at 18 months of age.

A patient who is not required mechanical support to receive nutrition at the date of 18 months of age visit is considered to meet the feeding criterion.

A one-sided Exact Binomial Test will be used to test the null hypothesis of p=0.1% at significance level of 0.025. Furthermore, the corresponding one-sided 97.5% confidence interval will be estimated by the exact method.

In case for the presence of missing value, sensitivity analyses outlined in Section 6.3 will be carried out to evaluate the appropriateness of the assumption for missing data.

Additionally, the proportion of patients meeting each of the criteria will be summarized.

8.2.2. Co-secondary Efficacy endpoint: Independence of ventilatory support

The proportion of patients who are independent of ventilatory support will be summarized overall. Independence of ventilatory support is defined as requiring no daily invasive or non-invasive ventilator support/usage at 18 months of age, in the absence of acute reversible illness and excluding perioperative ventilation. Ancillary devices used in pulmonary care such as a cough assist device shall not be considered ventilatory support. For a child who experiences an acute reversible illness or requires perioperative ventilation at the time that he or she reaches 18 months of age, ventilatory independence will be defined as not requiring ventilatory support over the 2-week interval prior to the development of the acute reversible illness or perioperative use.

Non-invasive ventilatory support usage data will be extracted directly from each patient's device; the data will be downloaded from the device's SD card through software provided by the manufacturer and transferred as an external dataset. Each patient will be assessed whether the permanent ventilation criteria is met. Those patients who met the criteria will be reported in a listing.

Due to the way of collecting ventilatory data, missing values will not be imputed. For example, a patient is never reported ventilatory support either in [redacted] or through SD card. The patient will be regarded as independence of ventilatory support. A one-sided Exact Binomial Test will be used to test the null hypothesis of p=0.1% at significance level of 0.025. Furthermore, the corresponding one-sided 97.5% confidence interval will be estimated by the exact method.

In case for the presence of missing value, sensitivity analyses outlined in Section 6.3 will be carried out to evaluate the appropriateness of the assumption for missing data.

These analyses will be performed on the ITT population.

[redacted]

[redacted]

[redacted]

[redacted]

8.4. Multiplicity

The primary and secondary efficacy hypotheses are to be tested in a hierarchy approach that specifies the order in which they are to be evaluated. This strategy requires that only when first co-primary endpoint meets significance will the second co-primary endpoint be tested;

only when the first co-secondary endpoint meets significance will the second co-secondary endpoint be tested; only if both primary endpoints meet significance will the secondary endpoint be tested. The order of testing will be: first, functional independent sitting (first co-primary endpoint); second, event-free survival (second co-primary endpoint); third, maintenance of ability to thrive (first co-secondary endpoint); fourth, independence from ventilator support (second co-secondary endpoint). Such pre-specification of the order of testing within hierarchical framework strongly prevents type 1 error inflation due to multiplicity.

9. ANALYSIS OF PHARMACOKINETICS

Not applicable to this SAP.

10. SAFETY

10.1. Extent of Exposure

The actual, weight-adjusted dose, in vg/kg, of AVXS-101 administered during the infusion will be summarized, as well as the site of infusion, duration of infusion, whether the entire volume was delivered, and whether the infusion was interrupted.

10.2. Treatment Compliance

Weight-adjusted dose of AVXS-101 administered and dosing compliance will be summarized.

The treatment compliance of each patient at Baseline will calculated as:

Percentage of compliance (%) = 100% * total volume administered / planned dose

The treatment compliance will be summarized by actual product received.

10.3. Adverse Events / Adverse Drug Reactions

10.3.1. Treatment-Emergent Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are defined as any event that begins or worsens in severity after initiation of study drug through the last study visit. If an incomplete onset date was collected for an adverse event, the event will be assumed to be treatment-emergent, unless there is other evidence that confirms that the event was not treatment-emergent (e.g., the event end date was prior to the study drug start date).

10.3.2. Tabulations of Treatment-Emergent Adverse Events

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.

Adverse events will be presented using Safety Set.

10.3.2.1. Adverse Event Overview

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

- Any treatment-emergent adverse event;

- Treatment-emergent adverse events with a "possibly related", "probably related", "definitely related" of being related to AVXS-101
  - 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;
- Serious treatment-emergent adverse events;
- Treatment-emergent adverse events leading to discontinuation of patient from study;
- Treatment-emergent adverse events leading to death;
- Deaths.

For each adverse event presented in the overview by overall.

For the final analysis tables (i.e., after database lock of the study), just the two relatedness categories (“Related”, “Not Related”) will be presented.

For an interim run of this table (i.e., using an interim data cut), it is possible that there will be AEs with unknown relationship present. If this situation occurs, the table will present a third row (“Unknown”) in addition to “Related” and “Not Related” and the AEs with unknown relationship will be summarized in the “Unknown” row. If there are no AEs with unknown relationship in the interim cut of data, the “Unknown” row in the table will not be included.

Data listings, patient narratives, etc. will present the relationship to study treatment as collected on the CRF.

10.3.2.2. Adverse Event by SOC and PT

The following summaries of adverse events will be generated:

- Treatment-emergent adverse events;
- Treatment-emergent adverse events occurring in two (2) or more patients;
- Treatment-emergent adverse events categorized as "related" to AVXS-101;
- Serious treatment-emergent adverse events;
- Grade 4 treatment-emergent adverse events;
- Grade 3 or 4 (see definition below) treatment-emergent adverse events;
- Treatment-emergent adverse events leading to discontinuation of patient from study;
- Treatment-emergent adverse events leading to death;
- Treatment-emergent adverse events leading to concomitant medication use (events with other action taken of "concomitant medication prescribed").

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.

A listing by treatment group of treatment-emergent adverse events grouped by body system and preferred term with patient numbers will be created.

10.3.2.3. Adverse Event by PT

The number of treatment-emergent adverse events and the number and percentage of patients experiencing treatment-emergent adverse events will be tabulated according to preferred term and sorted by overall frequency. Similar summaries will be provided for Grade 3 and 4 treatment-emergent adverse events and treatment-emergent adverse events with a "possibly related" to AVXS-101 categorization.

10.3.2.4. Adverse Events of Special Interest

The following specific treatment-emergent adverse events of special interest, which may be searched using Standardized MedDRA queries, will be summarized:

- Hepatotoxicity, identified via the following SMQs:
  - Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ)
  - Hepatic disorders (SMQ)
- Thrombocytopenia, identified via the following SMQs/HLT:
  - Hematopoietic thrombocytopenia (SMQ)
  - Haemorrhages (SMQ)
  - All TEAEs which code into the “Platelet disorders NEC” HLT
- Cardiac events, identified via the following SMQs:
  - Ischemic heart disease (SMQ)
  - Cardiomyopathy (SMQ)
  - Cardiac arrhythmias (SMQ)
  - Embolic and thrombotic events (SMQ)
  - Myocardial infarction (SMQ)
- Ganglionitis, with potential cases identified by reviewing all TEAEs which code to the “Nervous System Disorders” SOC

For each AE of interest category, the number and percentage of patients experiencing at least one TEAE in the search for the event of interest will be presented overall. AEs of interest will be summarized by SOC and PT overall.

10.3.2.5. Related Adverse Events by Maximum Grade

Treatment-emergent adverse events and treatment-emergent adverse events with a "possibly related", "probably related", or "definitely related" of being related to AVXS-101 will be summarized by maximum grade of each preferred term. If a patient has an adverse event with unknown grade, then the patient will be counted in the grade category of "unknown," even if the patient has another occurrence of the same event with a grade present.

10.3.2.6. Adverse Events by Maximum Severity Grade Level

Treatment-emergent adverse events will be summarized by maximum CTCAE grade level of each preferred term. Each preferred term will be assigned to a grade level based on severity and seriousness, adapted from CTCAE Version 4.03 for grading severity of adverse events.

All serious adverse events will be categorized according to Grade definition.

If a patient has a non-serious adverse event with unknown grade, then the patient will be counted in the severity grade level category of "unknown," even if the patient has another occurrence of the same event with a grade present.

10.3.2.7. Adverse Events by Maximum Relationship

Treatment-emergent adverse events also will be summarized by maximum relationship of each preferred term to study drug (AVXS-101), as assessed by the investigator. If a patient has an adverse event with unknown relationship, then the patient will be counted in the relationship category of "unknown," even if the patient has another occurrence of the same event with a relationship present. The only exception is if the patient has another occurrence of the same adverse event with a relationship assessment of "possibly related" or higher. In this case, the patient will be counted under the "related" category.

10.4. Laboratory Evaluations

10.4.1. Analysis of Laboratory Data

Safety laboratory data and genetic diagnosis laboratory data generated by local lab and by Q2, the designated central laboratory, will be used in all analyses. Immunoassay data generated by CTL will be used in all analyses.

Viral shedding data generated by PPD may not be summarized in the clinical study report; however, a separate analysis report will be completed.

10.4.2. Variables and Criteria Defining Abnormality

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/SGPT), alkaline phosphatase, aspartate aminotransferase (AST/SGOT), 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.

Immunology variables include: mother's serum binding antibody titer to AAV9, serum binding antibody titer to AAV9, binding antibody titer to SMN, T-cell response to AAV9 and SMN.

The Criteria for PCS Laboratory Findings are maintained outside of this SAP.

10.4.3. Statistical Methods

Clinical laboratory test will be summarized at each visit during the treatment period. The baseline value will be the last measurement on or before the day of the infusion of study drug. This same baseline value will be used for all changes from baseline tables in the treatment period and post-treatment period. Natural history control data is not available for this evaluation.

Mean changes from baseline to End of Study/Early Termination will be summarized for each protocol-specified laboratory parameter with the baseline mean, visit mean, change from baseline mean, standard deviation, minimum, maximum, and median.

During the treatment period, laboratory data values will be categorized as low, normal, or high based on normal ranges of the laboratory used in this study. Shift tables from baseline to minimum value, maximum value, and final values during the treatment period will be created. The shift tables will cross tabulate the frequency of patients with baseline values below/within/above the normal range versus minimum/maximum/final values below/within/above the normal range.

The number and percentage of patients with post-baseline values during the treatment period meeting the specified criteria for Potentially Clinically Significant (PCS) laboratory values will be summarized. A post-baseline value must be more extreme than the baseline value to be considered a PCS finding. A listing will be provided that presents all of the lab values for the patients meeting PCS criteria during treatment Period.

For hemoglobin and the liver function tests (LFTs) of ALT, AST, alkaline phosphatase, and total bilirubin, the number and percentage of patients in each treatment group with a maximum CTCAE Grade of 1, 2, 3, or 4 (as defined by the central laboratory and based on CTCAE v4.03) at any post-baseline visit (regardless of the baseline value) through the end of treatment (i.e., Final Treatment Value) will be summarized. All LFT tables will include summary rows for the number and percentage of patients with at least Grade 2 and at least Grade 3 laboratory abnormalities. The hemoglobin table will include a summary row for the number and percentage of patients with at least a Grade 2 laboratory abnormality. 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.

The number and percentage of patients meeting the following criteria will be summarized overall.

- ALT ≥ 3x ULN with bilirubin < 2x ULN
- AST ≥ 3x ULN with bilirubin < 2x ULN
- ALT ≥ 5x ULN with bilirubin < 2x ULN
- AST ≥ 5x ULN with bilirubin < 2x ULN
- ALT ≥ 10x ULN with bilirubin < 2x ULN
- AST ≥ 10x ULN with bilirubin < 2x ULN
- ALT ≥ 20x ULN with bilirubin < 2x ULN
- AST ≥ 20x ULN with bilirubin < 2x ULN
- ALT ≥ 3x ULN with bilirubin ≥ 2x ULN
- AST ≥ 3x ULN with bilirubin ≥ 2x ULN
- ALT ≥ 5x ULN with bilirubin ≥ 2x ULN
- AST ≥ 5x ULN with bilirubin ≥ 2x ULN
- ALT ≥ 10x ULN with bilirubin ≥ 2x ULN
- AST ≥ 10x ULN with bilirubin ≥ 2x ULN
- ALT and AST ≥ 3x ULN with bilirubin < 2x ULN
- ALT and AST ≥ 5x ULN with bilirubin < 2x ULN
- ALT and AST ≥ 10x ULN with bilirubin < 2x ULN
- ALT and AST ≥ 3x ULN with bilirubin ≥ 2x ULN
- ALT and AST ≥ 5x ULN with bilirubin ≥ 2x ULN
- ALT and AST ≥ 10x ULN with bilirubin ≥ 2x ULN
- ALT and AST ≥ 20x ULN with bilirubin ≥ 2x ULN

A patient or event will be counted if the post-baseline laboratory values meet the above criteria regardless of the baseline laboratory value (i.e., the post-baseline laboratory value does not need to be worse than the baseline laboratory value). For patients meeting any elevation criterion, a corresponding listing of all ALT, AST, alkaline phosphatase, and total, direct, and indirect bilirubin values will be provided.

10.4.4. Drug-Induced Liver Injury

Drug-induced liver injury (DILI) has been the most frequent single cause of safety-related drug marketing withdrawals and as such with this pediatric population (SMA patients) and unique intervention (gene therapy), Sponsor took care to assess hepatic test results as drugs can cause liver injuries by many different mechanisms. Severe DILI cases rarely have been seen in drug development programs of significantly hepatotoxic drugs that do cause such injury. Evidence of hepatocellular injury is thus a necessary, but not sufficient, signal of the potential to cause severe DILI (note, however, that the drugs causing hepatic injury through mitochondrial toxicity may not cause early hepatotoxicity).

It is possible that although a drug may not cause severe liver injury, it could still result in laboratory evidence of mild, transient hepatic injury, with leakage of liver enzymes and the appearance in serum of elevations in aminotransferase activities to levels of 3, 5, and sometimes greater than 5 times the upper limits of normal (ULN). The liver enzyme data was evaluated according to these criteria and according to Hy's Law.

A finding of ALT elevation, usually substantial, seen concurrently with bilirubin >2xULN, identifies a drug likely to cause severe DILI (fatal or requiring transplant) at a rate roughly 1/10 the rate of Hy's Law cases. It is critical to rule out other causes of injury (e.g., other drugs or viral hepatitis) and to rule out an obstructive basis for the elevated bilirubin, so that alkaline phosphatase (ALP) should not be substantially elevated. In all cases to date, the small number of Hy's Law cases has arisen on a background of an increased incidence of more modest signs of hepatocellular injury (e.g., greater incidence of 3xULN elevations in AT than seen in a control group).

Briefly, Hy's Law cases have the following three components:

- 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 (nonhepatotoxic) control drug or placebo.
- Among trial patients showing such AT elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP).
- No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

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.

10.5. Vital Signs

Vital signs (pulse, respiration, temperature, diastolic blood pressure, body weight, systolic blood pressure, pulse oximetry) will be examined at each visit. Clinically-significant, treatment-emergent findings will be reported as adverse events.

A summary of changes from first recorded value in vital signs will be described at each visit on the safety set. In addition, vital signs results will be flagged as Potentially Clinically Significant (PCS) if they meet the pre-specified criteria. The number and percent of patients meeting each PCS criterion will be summarized starting at Day 1 and continuing through the end of study.

10.6. ECG

Serial ECG data will be pulled in triplicate from a Holter monitor at the following time points and will be provided in an external dataset:

- Pre-dose (within 24 hours prior to gene replacement therapy)
- 2 hours
- 4 hours
- 6 hours
- 8 hours
- 12 hours
- 24 hours
- 36 hours
- 48 hours

A 12-lead ECG will be conducted at scheduled visits of Screening, Day 1, Day 2, and every 6 months through 18 months of age, and assessed by a central reviewer. The baseline value will be the average of all measures within 6 hours of prior to dosing. Mean changes from baseline, standard deviation, minimum, maximum, and median to End of Study/Early Termination visit will be summarized for HR, PR, QR, QRS, QTcF.

The central reviewer will identify abnormal ECGs that are PCS, the definitions for which are maintained outside of this document.

A listing of all PCS ECGs will be provided. Summaries of ECG data will be presented overall.

10.7. 12-Lead Holter Monitor

A Holter monitor will continuously record the patient's 12-lead ECG for a total of 72 hours from Day –1 (24 hours prior to the start of gene replacement therapy infusion) through 48 hours after the start of infusion. On Days -1 to Day 3, serial ECG data will be pulled in triplicate from the Holter monitor at time points of 'pre-dose', '2 hour', '4 hour', '6 hour', '8 hour', '12 hour', '24 hour', '36 hour' and '48 hour' post-dose and assessed by a central reviewer. The triplicate of each parameter for HR, PR, QRS, QTcF, as measured by the central reviewer, at each time point will be averaged for summaries. The summaries of Holter monitor data will be done by the actual treatment received overall.

Twenty-four-hour Holter monitoring will also be performed at the 3, 6, 9, and 12-month visits and every 6 months thereafter.

The central reviewer will identify abnormal ECGs that are PCS based on central reviewing guidelines provided by BMS. The number and percent of patients meeting each PCS criterion will be summarized starting at '2 hour' and continuing through '48 hour'.

10.8. Physical Examination

Treatment-emergent abnormal findings on physical exam 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 exam. Descriptive statistics only are planned for this data.

Shift tables summarizing the shift of physical examination results ('Normal', 'Abnormal Not Clinically Significant', 'Abnormal Clinically Significant') for examination items from baseline to post-baseline visits will be presented. A table summarizing observed and change from baseline values for head circumference will be produced.

A listing of physical examination findings (normal or abnormal) will be provided.

10.9. Pulmonary Exam

Patients will be assessed by a pulmonologist at the time points specified in the Schedule of Assessments on of the pulmonologist and/or investigator. Non-invasive ventilatory support equipment will be provided by AveXis, Inc. through a third-party vendor.

Pulmonary exam results will be presented in a listing.

10.10. Echocardiogram

Echocardiograms will be conducted at the time points specified in the Schedule of Assessments. Echocardiograms will be interpreted locally and results from the local interpretation (abnormal/normal, etc.) will be captured in the eCRF. Clinically significant, treatment-emergent findings (as determined locally) may be reported as AEs. A listing of echocardiogram results (abnormal/normal, etc.) and findings (left ventricle function, patent foramen ovale, or other) will be provided for all screening and post-baseline visits.

Additionally, echocardiogram data will be provided to an external cardiologist for centralized review. For any future analyses, the centrally reviewed data will be considered the primary echocardiogram source data.

10.11. Ventilatory support

The number of hours per day of non-invasive positive pressure ventilator in the intervals between each post-baseline visit will be summarized overall using descriptive statistics.

10.12. Other Safety

10.12.1. Additional Safety Endpoint: Immunologic Response

Immunoreactivity to AAV9 and SMN will be monitored by the collection of samples at Screening, Day 7, Day 14, Day 21, and Day 30. Antibody titer levels are measured through

ELISA immunoassay. Antibody titers >1:50 are considered positive for antibody response while antibody titers ≤1:50 are considered negative. The number and percent of patients responding Positive or Negative for antibody response at each time point will be summarized. Furthermore, the distribution of patients by titer level will be summarized.

Secondly, T-cell response to AAV9 and SMN will be measured by the collection of samples at Day 7 and 30 and determined through the quantification of number of Spot Forming Cells (SFC) per million Peripheral Blood Mononuclear Cells (10^6PBMC). SFC values >100 are considered positive. T-cell response to AAV9 will be measured separately in 2 peptide pools. T-cell response to SMN will be measured in a single peptide pool.

The number of SFC/10^6 PBMC will be summarized at each sample time point. For each post-infusion time point, the number and percent of patients responding positively for T-cell response will be summarized.

10.12.2. Vector Shedding

Saliva, urine, and stool samples will be collected for vector shedding in accordance with the Schedule of Study Assessments, which includes 24 hours (Day 2) and 48 hours (Day 3) post-dose. Patients at all sites ≥ 48 months who are no longer in diapers will provide full volume urine and full volume feces samples at Day 7, Day 14, and Day 30 for at least one void and one defecation. A subset of patients at sites opting to participate in the vector shedding sub-study will have 24-hour total volume urine and fecal samples collected through 24 hour-post dose and 48 hours-post dosing.

Descriptive statistics of mean, standard deviation, minimum, maximum, and median on volume of saliva, urine and feces at each scheduled visit will be summarized. A listing of vector shedding will be provided.

11. HEALTH ECONOMICS

Not applicable for this SAP.

12. INTERIM ANALYSES

Not applicable for this SAP.

13. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

The co-primary efficacy endpoint defined as the proportion of patients that achieve functional independent sitting for at least 30 seconds at the 18 months of age study visit included the assumption for the true response rate of AVXS-101 being in the range of 30% - 40%, with a sample size of 15 patients (assuming 30% of patients do not qualify for the ITT population or are otherwise excluded from the analysis) which would provide power of > 90% to detect a significant difference with $\alpha = 0.05$ using a 1-sided exact test for a binomial proportion. **However, for this analysis a 1-sided exact test for a binomial proportion will be used with $\alpha = 0.025$. The co-secondary endpoints will also be analyzed in this fashion.**

The efficacy completers population definition in the 15 Oct 2017 version of the protocol reflects:

- All treated patients who reach 14 months of age, OR
- All treated patients who meet discontinuation criteria, discontinue the study due to an AE or death

However, for this analysis the efficacy completers analysis population will consist of:

- All treated patients who reach 14 months of age for the survival endpoint **or 18 months of age for the endpoint of achievement of functional independent sitting**, OR
- All treated patients who meet discontinuation criteria, discontinue the study due to an AE, or experience death
    - All treated patients who reach 14 months of age, OR
    - All treated patients who meet discontinuation criteria, discontinue the study due to an AE or death

However, for this analysis the efficacy completers analysis population will consist of:

- All treated patients who reach 14 months of age for the survival endpoint **or 18 months of age for the endpoint of achievement of functional independent sitting**, OR
- All treated patients who meet discontinuation criteria, discontinue the study due to an AE, or experience death

[redacted]

14. REFERENCE LIST

1 Wijnhoven TM, de Onis M, Onyango AW, et al. Assessment of gross motor development in the WHO Multicentre Growth Reference Study. *Food Nutr Bull.* 2004;25(1 Suppl): S37-45.

2 Glanzman AM, McDermott MP, Montes J, et al. Validation of the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND). Pediatr Phys Ther. 2011;23(4):322-326.

3 Glanzman AM, Mazzone E, Main M, et al. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND): test development and reliability. Neuromusc Disord. 2010;20(3):155-161.

4 Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 4.3, DCTD, NCI, NIH, DHHS (http://ctep.cancer.gov), Publish Date: May 28, 2009.

5 Finkel RS, McDermott MP, Kaufmann P, Darras BT, Chung WK, Sproule DM, Kang PB, Foley AR, Yang ML, Martens WB, Oskoui M, Glanzman AM, Flickinger J, Montes J Dunaway S, O'Hagen J, Quigley J, Riley S, Benton M, Ryan PA, Montgomery M, Marra J, Gooch C, De Vivo DC. Observational study of spinal muscular atrophy type I and implications for clinical trials. Neurology. 2014 Aug 26;83(9):810-7.

6 Reference Ranges, Kathleen Nicol, Department of Pathology and Laboratory Medicine of Nationwide Children's Hospital, Columbus, Ohio, 1-11.

7 Bonafide CP, Brady PW, Keren R, Conway PH, Marsolo K, Daymont C. Development of Heart and Respiratory Rate Percentile Curves for Hospitalized Children. Pediatrics. 2013 April; 131(4): e1150–e1157.

15. PROGRAMMING CONSIDERATIONS

See TLF documentation for details.

16. QUALITY CONTROL

Refer to Quality Control Plan for SAS programs.

17. INDEX OF TABLES AND LISTINGS

Refer to TFLs.

18. INDEX OF FIGURES

19. INDEX OF LISTINGS

Index to be added once the TLF shells are generated.

20. MOCK-UPS

Refer to TLF Mock-ups.

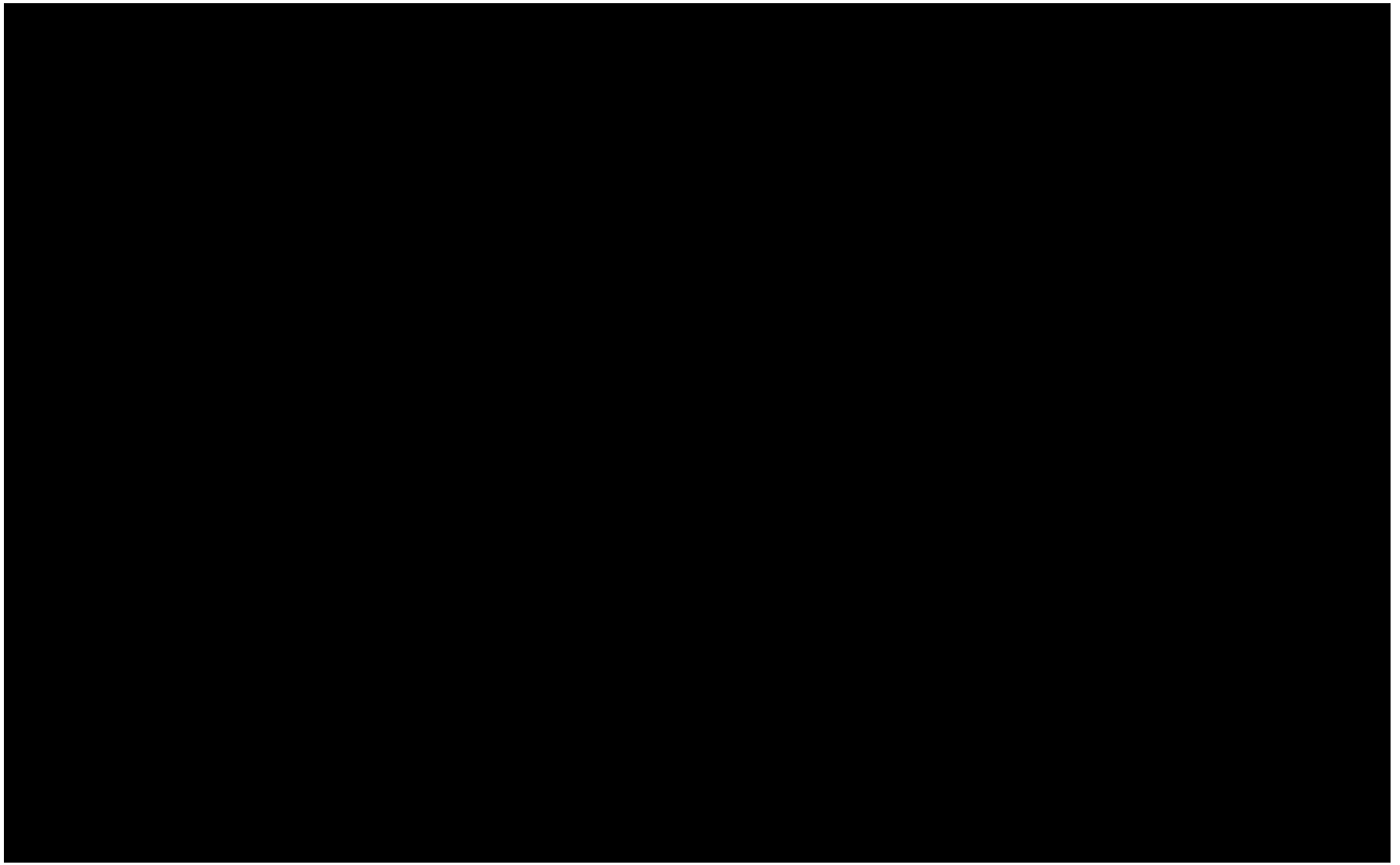
21. APPENDICES

21.1. Performance Criteria for Bayley Scales of Infant and Toddler Development (Version 3) Developmental Milestones

Developmental Milestone	[redacted]
Head Control – Gross Motor Subtest Item #4	
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	

21.2. CHOP-INTEND

CHILDREN'S HOSPITAL *of* PHILADELPHIA INFANT TEST OF NEUROMUSCULAR DISORDERS



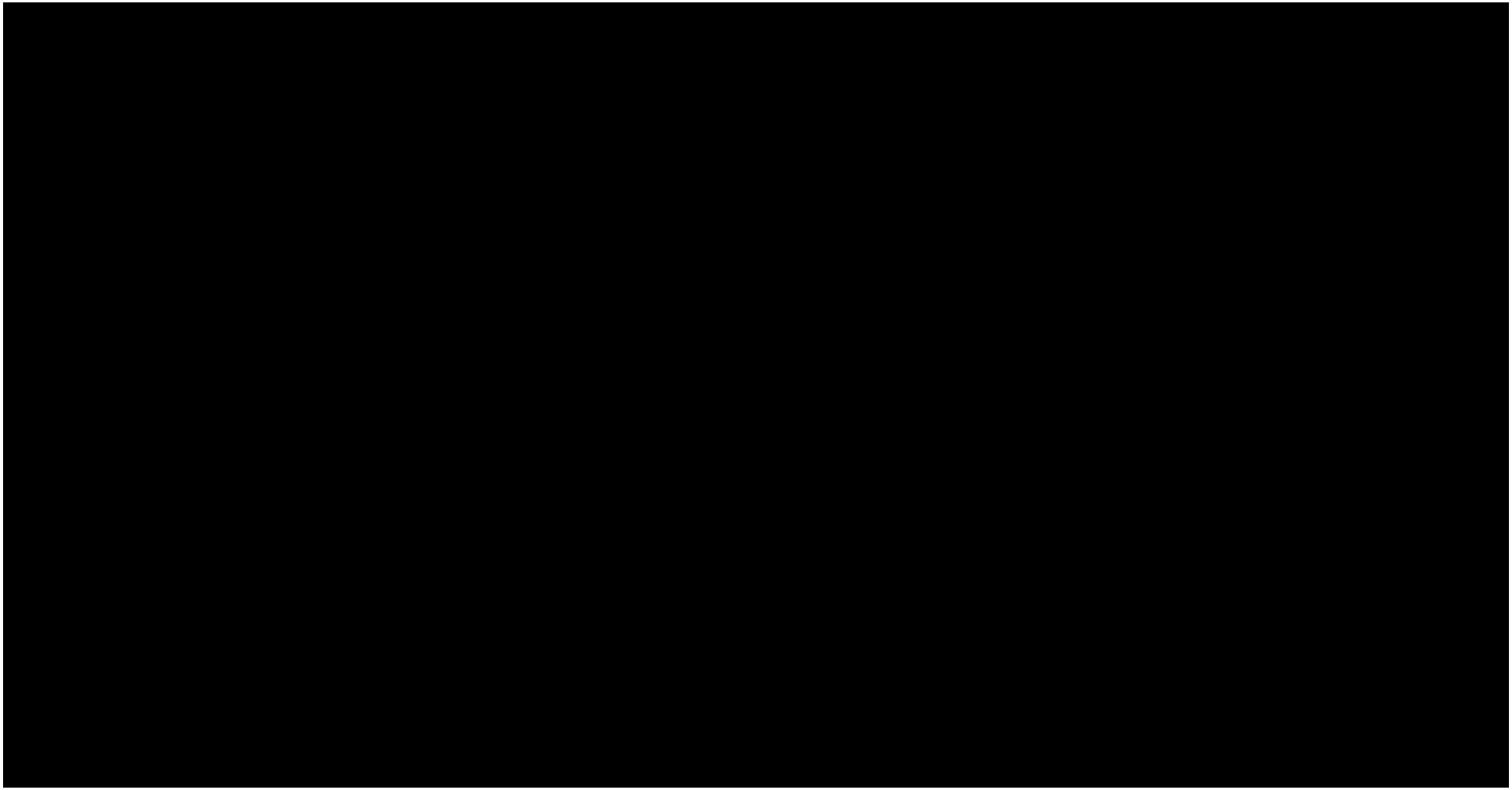
Time of evaluation: (AM/PM) Hours off BiPAP at testing: (h)						
Item	**Position**	**Test Procedure**	**Graded Response**		**Score**	
Rolling: elicited from legs*	away from the Side tested	bringing pelvis vertical maintain traction and ***pause in this position***. **2.** If infant rolls to side apply traction at a 45º diagonal to body and pause to allow infant to attempt to de-rotate body	Rolls through side lying into prone without lateral head righting, clears weight-bearing arm to complete roll	3	To L	State:
			Pelvis, trunk and arm lift from support surface, head turns and rolls onto side, arm comes thru to front of body	2		
			Pelvis and trunk lift from support surface and head turns to side. Arm remains behind trunk	1		
			Pelvis lifted passively off support surface.	0		
7 Rolling: elicited from arms*	Supine (arms at side) Keep side tested up roll away from the Side tested	**1.** Hold infant at the elbow move toward opposite shoulder maintain traction on limb and ***pause with the shoulders vertical*** allow infant to de-rotate **2.** if the pelvis achieves vertical continue to provide traction	Rolls to prone with lateral head righting	4	To R To L	Best side: State:
			Rolls into prone without lateral head righting; must clear weight-bearing arm completely to finish roll	3		
			Rolls onto side, leg comes thru and adducts, bringing the pelvis vertical	2		
			Head turns to side and shoulder and trunk lift from surface	1		
			Head turns to side; body remains limp or shoulder lifts passively	0		
8	Side-lying with upper arm at 30º of	Prompt reach for a toy presented at arm's length	Clears hand from surface with antigravity arm movement	4	L	Best side:

Time of evaluation: (AM/PM) Hours off BiPAP at testing: (h)						
Item	**Position**	**Test Procedure**	**Graded Response**		**Score**	
Shoulder and elbow flexion and horizontal abduction	shoulder extension and elbow flexion and supported on body (restrain lower arm if needed)	at shoulder level (may provide stimulation and ***observe spontaneous movement***)	Able to flex shoulder to 45 degrees, without antigravity arm movement	3	R	State:
			Flexes elbow after arm comes off body	2		
			Able to get arm off body	1		
			No attempt	0		
9 Shoulder flexion & Elbow flexion	Sitting in lap or on mat with head and trunk support (20º recline)	Present stimulus at midline and at shoulder level at arm's length (may provide stimulation and ***observe spontaneous movement***)	Abducts or flexes shoulder to 60 degrees	4	L	Best side:
			Abducts or flexes shoulder to 30 degrees	3		
			Any shoulder flexion or abduction	2		
			Flexes elbow only	1	R	State:
			No attempt to lift arm	0		
10 Knee extension	Sitting in lap or over edge of mat with head and trunk support (20º recline) thigh horizontal to ground	Tickle plantar surface of foot or gently pinch toe	Extends knee to >45 degrees	4	L	Best side:
			Extends knee 15 to 45 degrees	2		
			Any visible knee extension	1		
			No visible knee extension	0	R	State:
11	Hold infant against your body with legs	Stroke the foot or pinch the toe	Hip flexion or knee flexion >30º	4	L	Best side:
			Any hip flexion or knee flexion	3		

Time of evaluation: (AM/PM) Hours off BiPAP at testing: (h)						
Item	**Position**	**Test Procedure**	**Graded Response**		**Score**	
Hip flexion and foot dorsiflexion	free, facing outward. Support at the abdomen with the child's head resting between your arm and thorax		Ankle dorsiflexion only	2	R	State:
			No active hip, knee or ankle motion	1		
			Hip flexion or knee flexion >30º	0		
12 Head control*	Sitting with support at the shoulders and trunk erect	Place the infant in ring sit with head erect and assistance given at the shoulders (front and back) (***may delay scoring a grade of 1 and 4 until end of test***).	Attains head upright from flexion and turns head side to side	4	L R	Best side: State:
			Maintains head upright for >15 sec (for bobbing head control score a 2)	3		
			Maintains head in midline for >5 sec. with the head tipped in up to 30º of forward flexion or extension	2		
			Actively lifts or rotates head twice from flexion within 15 seconds (do not credit if movement is in time with breathing)	1		
			No response, head hangs	0		
13 Elbow flexion Score with item 14	Supine	**Traction response:** pull to sit extend arms at 45-degree angle, to point of nearly lifting head off surface	Flexes elbow	4	L R	Best side: State:
			Visible biceps contraction without elbow flexion	2		
			No visible contraction	0		
14	Supine		Lifts head off bed	4		Score:

Time of evaluation: (AM/PM) Hours off BiPAP at testing: (h)						
Item	**Position**	**Test Procedure**	**Graded Response**		**Score**	
Neck Flexion Score with item 13		Traction response: hold in neutral proximal to wrist and shoulder at 45º, *to point of nearly lifting head off surface*	Visible muscle contraction of SCM	2		State:
			No muscle contraction	0		
15 Head/Neck Extension (Landau)	Ventral suspension: Prone, held in one hand upper abdomen	Stoke along spine from neck to sacrum. The coronal axis of the head when parallel to the bed surface = 0 degrees (horizontal)	Extends head ***to*** horizontal plane or above	4		Score:
			Extends head partially, but not to horizontal	2		
			No head extension	0		State:
16 Spinal Incurvation (Galant)	Ventral suspension: Prone, held in one hand upper abdomen	Stroke Right then Left throacolumbar paraspinals or tickle abdomen or foot or tilt in infants with For infant over 10 kg knees and head may touch	Twists pelvis towards stimulus off axis	4	L	Best side:
			Visible paraspinal muscle contraction	2		
			No response	0	R	State:
Total score, best score on each side for each item (maximum 64 points):						
Comments:						

* Adapted from the Test of Infant Motor Performance, Campbell, SK; et al. 2001.



21.3. Rating of Brazelton behavioral states

21.5. Summary of Changes

The section below highlights content changes represented in version 5.0 of the SAP.

Global updates made throughout the entire document and not specified in the list of section-specific changes below:

Minor wording and formatting updates have been made throughout the SAP in order to correct typographical errors and to align wording across sections. These changes did not change the intent of the analysis.

Section 4.2.1 was added to describe the method of calculating CHOP-INTEND score.

Section 6.7 was updated to redefine the subgroup based on age at dosing. Also, only milestones and statistical modeling related TFLs will be presented subgroup information.

Section 8.1.1 was updated to report one-sided 97.5% confidence interval.

Section 8.2.1 was updated to report one-sided 97.5% confidence interval.

Section 8.3.1 was updated to only summarize the portion of patients who achieved ability to hold head erect without support and remove the statistical test due to lack of history data.

Section 8.3.2-8.3.10 was updated to report one-sided 97.5% confidence interval.

Section 8.3.11-8.3.12 was updated to specify the statistical modeling with age subgroup as covariate.

Section 8.3.13 was updated to report one-sided 97.5% confidence interval.

Section 10.2 was updated to describe treatment compliance which based on information directly from [redacted]

Section 10.3.2.1 was updated Adverse Event results for relatedness which will be collapsed into RELATED and NOT RELATED for presentation in summary tables. The original related rating will remain in the database and listings.

Section 10.3.2.4 was updated list of adverse events of special interest based on Standardized MedDRA queries.

Section 10.4.2 was updated to use SI units for laboratory parameters only.

Section 10.4 text was added to clarify that the listing of PCS laboratory values would include all the results for only the parameter(s) meeting PCS criteria; to clarify how elevated LFTs would be summarized.

Section 10.7 added 12-Lead Holter Monitor due to protocol amendment.

Section 10.12.2 added vector shedding listing.

Section 21.3 add the table of rating of Brazelton behavioral states for explaining CHOP-INTEND calculation method.