Protocol Number: AVXS-101-CL-102

Official Title: Phase I, Open-Label, Dose Comparison Study of AVXS-101 for Sitting but Non-ambulatory Patients with Spinal Muscular Atrophy

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STATISTICAL ANALYSIS PLAN

Protocol Number and Title:	AVXS-101-CL-102 Phase I, Open-Label, Dose Comparison Study of AVXS-101 for Sitting but Non-ambulatory Patients with Spinal Muscular Atrophy
Protocol Version and Date:	Amendment 7 / Protocol Version 8 / 17 June 2019
Author(s):	[redacted] Biostatistician, Contractor for AveXis Inc.
SAP Version:	6.0, Amendment 5
SAP Version Date:	22November2021

Final

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REVISION HISTORY

Version #	Date (dd-Mmm-yyyy)	Document Owner	Revision Summary
0.1	26-Sep-2016	[redacted]	Initial Release Version
0.2	4-Oct-2016		Review comments on version 0.1 incorporated.
0.3	24-Oct-2016		Review comments from AveXis on version 0.2 incorporated
1.0	15-Nov-2016		Review comments from AveXis on version 0.3 incorporated. SAP finalized and signed
2.0	24-Aug-2017		Update to Amendment 1 due to Protocol Amendment 3
3.0	12-Dec-2017		Update SAP to Protocol Amendment 4
4.0	14-Jun-2018		Update SAP to reflect necessary revisions identified during TLF programming
4.1	11-Feb-2019		Update SAP to Protocol Amendments 5 and 6
4.2	03-Mar-2019		Review comments from AveXis on version 4.1 incorporated.
4.3	03-Sept-2019		Update SAP to Protocol Amendment 7
4.4	12-Sept-2019		Added additional analyses requested by study physician.
4.5	23-Sept-2019		Review comments on version 4.4 incorporated.
4.6	28-Oct-2019		Updated based on dry-run review comments
4.7	06-Nov-2019		Updated to refer to the final list of adverse events of special interest
5.0	08-Nov-2019		SAP finalized and signed.
6.0	22-Nov-2021		Updated to address data handling for COVID-19 disruptions Updated throughout to address early close-out of the study Updated to comments based on final dry-run

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

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AAV / AAV9	Adeno Associated Virus 9
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
Bayley-III	Bayley Scale of Infant and Toddler Development-Third Edition
BiPAP	Bilevel Positive Airway Pressure
BMI	Body Mass index
CE	Clinical Evaluator
CI	Confidence Interval
CDISC	Clinical Data Interchange Standards Consortium
CRF/eCRF	Case Report Form / electronic Case Report Form
dL	Deciliter
DILI	Drug-induced Liver Injury
DSMB	Data Safety Monitoring Board
ECAS	Efficacy Completer Analysis Set
ECG	Electrocardiogram
FAS	Full Analysis Set
GGT	Gamma Glutamyl Transferase
GLM	General Linear Model
HFMSE	Hammersmith Functional Motor Scale-Expanded
HLT	High Level Term
ICD-10	International Statistical Classification of Diseases and Related Health Problems
IFN-γ	Interferon Gamma
IRB	Institutional Review Board
ITT	Intent-to-treat
LFE	Liver Function Enzyme
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
MMRM	Mixed-Model Repeat Measure
PCS	Potentially Clinically Significant
PNCR	Pediatric Neuromuscular Clinical Research
PT	Preferred Term
SAE	Serious Adverse Event

Abbreviation	Description
SAP	Statistical Analysis Plan
SMA	Spinal Muscular Atrophy
SMN	Survival Motor Neuron
SMN1	Survival Motor Neuron 1 gene
SMN2	Survival Motor Neuron 2 gene
SOC	System Organ Class
SOP	Standard Operating Procedure
SS	Safety Analysis Set
TBL	Total Bilirubin
TEAE	Treatment Emergent Adverse Event
TLF	Table, Listing and Figure
ULN	Upper Limit Normal

1.1. Key Definitions

Term	Definition
AE	Adverse Event (AE): Any untoward medical occurrence in a clinical investigation patient 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 months and rounded to one decimal place. A month is standardized to a period of 30 days. Age at event = (date of event – date of birth +1) / 30. Age at Baseline will be defined/displayed in months. Age at Baseline = (first dose date – date of birth +1)/30.
Baseline	Baseline, unless otherwise specified in the Statistical Analysis Plan (SAP) sections, refers to the last measurement or evaluation made prior to the injection of AVXS-101.
First Dose Date	The first dose date, study day 1, will be the date of administration of the first dose of study drug after enrollment.
MedDRA	Medical Dictionary for Regulatory Activities (MedDRA) is a medical terminology used to classify adverse event information associated with the use of biopharmaceuticals and other medical products.
Study Day	First dose of study medication will be administered on study day 1. There is no study day 0. If the event happened on or after the first dose date, study day is defined as event date – first dose date + 1. If the event happened prior to the first dose date, study day is defined as event date – first dose date.

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives. The SAP was drafted with respect to the AVXS-101-CL-102 protocol version 8.0, incorporating amendment 7, dated 17 June 2019 entitled, *Phase I, Open-Label, Dose Comparison Study of AVXS-101 for Sitting but Non-ambulatory Patients with Spinal Muscular Atrophy*.

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.(AveXis) is responsible for ownership and approval of the SAP.

A Contract Research Organization (CRO) selected by AveXis will derive the data set according to Clinical Data Interchange Standards Consortium (CDISC) standards and create data set specifications based on the SAP. The CRO will perform the statistical analyses and is responsible for the production and quality control of all tables, figures and listings.

2.2. Timings of Analyses

2.2.1. Primary Safety and Efficacy Analysis

Patients from Cohort 1 and Cohort 2 will be followed for a total of 12 months post-dose; patients from Cohort 3 will be followed for a total of 15 months post-dose. The primary analyses for efficacy will be assessed when all patients have completed 12 months of follow-up study visits following AVXS-101 administration, and the primary analyses for safety will be assessed when the last patient of Cohort 3 reaches 15 months post-dose (and database lock will take place after the last patient reaches 15 months post-dose).

On 18-November-2021, AveXis made the decision to terminate the study early. As a result, Cohort 3 did not enroll the full number of planned patients. Per the protocol, a total of 24 patients were planned to be enrolled into Cohort 3: 12 patients aged > 6 months and < 24 months and 12 patients aged ≥ 24 and < 60 months. When the decision was made to terminate the study early, a total of 4 patients aged > 6 months and < 24 months had been enrolled and treated in Cohort 3. Because of the early study termination, the majority of analyses pre-specified in the protocol to be conducted on patients in Cohort 3 are no longer applicable. Unless otherwise specified, the data collected for patients in Cohort 3 will be summarized using descriptive statistics and summarized in data listings.

2.2.2. Additional Safety and Efficacy Analysis

An additional analysis of efficacy and safety data was conducted once the last Cohort 2 patient completed the 12 month visit.

3. STUDY OBJECTIVES

3.1. Primary Objectives

3.1.1. Safety

The primary safety objective is to assess the safety and tolerability of intrathecal administration of AVXS-101 by the incidence and severity of adverse events (AEs) while determining the optimal dose of AVXS-101 that demonstrates acceptable safety with maximum preliminary efficacy administered by intrathecal injection.

3.1.2. Efficacy

Patients ≥ 6 months and < 24 months at time of dosing:

The primary efficacy objective is to determine the proportion of patients ≥ 6 months and < 24 months at time of dosing achieving the ability to stand alone (Bayley© Scales of Infant and Toddler Development-Third Edition [Bayley-III] – Gross Motor Subtest #40).

Patients ≥ 24 months and < 60 months of age at time of dosing:

The primary efficacy objective is to determine the change from baseline in Hammersmith Functional Motor Scale-Expanded (HFMSE) for patients ≥ 24 and < 60 months of age at time of dosing.

3.2. Secondary Objective(s)

3.2.1. Efficacy

Patients ≥ 6 months and < 24 months at time of dosing:

The secondary efficacy objective is to determine the proportion of patients that achieve the ability to walk alone (Bayley-III Gross Motor Subtest #43).

Patients ≥ 24 months and < 60 months of age at time of dosing:

The secondary efficacy objective is to determine the proportion of patients that achieve ability to walk alone (Bayley-III - Gross Motor Subtest #43).

[redacted]

3.4. Statistical Hypothesis

3.4.1. Hypothesis of Categorical Primary Endpoint and Secondary Endpoints

The comparisons of primary endpoints and secondary endpoints in proportions between AVXS-101 (Cohort 2, Dose B) and the historical data of the Pediatric Neuromuscular Clinical Research (PNCR) network will be summarized by differences in response rates with 95% confidence intervals (CIs). Data for Cohort 1 (Dose A) and for Cohort 3 (Dose C) will be summarized descriptively and will not be compared to the historical data of the PNCR network. Two-sided tests will be performed to test the null hypothesis at a significance level of 5%:

$$H0: P(\text{AVXS-101}) = P(\text{PNCR})$$
$$Ha: P(\text{AVXS-101}) \neq P(\text{PNCR})$$

where P is defined below as:

Primary Endpoint:

- The proportion of patients ≥ 6 months and < 24 months at time of dosing that achieve the ability to stand alone (Bayley-III – Gross Motor Subtest item #40) at any post-baseline visit up to 12 months.

Secondary Endpoints:

- The proportion of patients ≥ 6 months and < 24 months at time of dosing that achieve the ability to walk alone (Bayley-III - Gross Motor Subtest #43) at any post-baseline visit up to 12 months.
- The proportion of patients ≥ 24 months and < 60 months at time of dosing that achieve the ability to walk alone (Bayley-III - Gross Motor Subtest #43) at any post-baseline visit up to 12 months.

3.4.2. Hypothesis of Continuous Primary Endpoint

For the primary endpoint with a continuous variable, a two-sided test at a significance level of 5% will be performed to test the following null hypothesis:

$$H0: \mu(\text{AVXS-101}) = \mu(\text{PNCR})$$
$$Ha: \mu(\text{AVXS-101}) \neq \mu(\text{PNCR}),$$

Where μ is the mean change from baseline in the measures as follows:

- Change from baseline in HFMSE at the 12 month study visit for patients ≥ 24 months and < 60 months of age at time of dosing.

The comparison of this continuous endpoint between AVXS-101 (Dose B) and the historical data of PNCR network will be summarized by differences in change from baseline at the 12-month study visit with 95% CIs.

3.5. Study Design

The AVXS-101-CL-102 study is a Phase I, open-label, single-dose administration study of infants and children with a genetic diagnosis consistent with spinal muscular atrophy (SMA), bi-allelic deletion of survival motor neuron 1 gene (*SMN1*) and 3 copies of survival motor neuron 2

gene (*SMN2*) without the genetic modifier who are able to sit but cannot stand or walk at the time of study entry. Patients will receive AVXS-101 of up to three potential therapeutic doses as described below. Patients will be stratified in two groups, those ≥ 6 months and < 24 months of age at time of dosing and those ≥ 24 months and < 60 months of age at time of dosing. At least fifteen (15) patients ≥ 6 months and < 24 months will be enrolled and twelve (12) patients ≥ 24 and < 60 months will be enrolled.

The first cohort (Cohort 1) will enroll three (3) patients ≥ 6 months and < 24 months of age who will receive administration of 6.0×10^{13} vg of AVXS-101 (Dose A). There will be at least a four (4)-week interval between dosing of each patient within the cohort. The investigators will confer with the Data Safety Monitoring Board (DSMB) on all Grade III or higher AEs within 48 hours of awareness that are possibly, probably, or definitely related to the study agent before continuing enrollment. Safety data will be reviewed by the DSMB during quarterly meetings; following enrollment of the three patients and based upon the available safety data a decision will be made whether to: a) stop due to toxicity, or b) proceed to Cohort 2 using Dose B.

Should the determination be made to advance to Dose B, three (3) patients < 60 months of age will be enrolled to receive administration of 1.2×10^{14} vg of AVXS-101 (Dose B). Again, there will be at least a 4-week interval between dosing of the three patients within the cohort. Based on the available safety data from the three Cohort 2 patients and all of the Cohort 1 patients, the DSMB may decide and document during quarterly meetings that further 4-week intervals between patients dosing is unnecessary. AveXis, Inc. will take this recommendation into consideration and will make the final determination whether to persist with 4-week intervals between patients dosing going forward; the decision will be communicated to sites and Institutional Review Boards (IRBs) in a formal sponsor letter. The investigators will confer with the DSMB on all Grade III or higher AEs within 48 hours that are possibly, probably, or definitely related to the study agent before continuing enrollment. Safety data will be reviewed by the DSMB during quarterly meetings; following enrollment of the first six (6) patients and based upon available safety data, a decision will be made whether to a) stop due to toxicity, or b) continue to enroll an additional 21 patients until twelve (12) patients ≥ 6 months and < 24 months and twelve (12) patients ≥ 24 months and < 60 months have received Dose B.

Based on an ongoing assessment of safety and efficacy data from patients treated with the 1.2×10^{14} vg dose, an option for testing of a third dose (Dose C) will be considered. A meeting of the DSMB will be called to obtain agreement on the safety of escalating to a higher dose prior to proceeding. If, based on all available data, this is judged to be necessary, three (3) patients < 60 months of age will receive 2.4×10^{14} vg of AVXS-101 (Dose C). If agreement is obtained from the DSMB, there will again be a four-week interval between dosing of the first three patients receiving Dose C, as in Cohorts 1 and 2. Safety data will be reviewed by the DSMB during quarterly meetings; following enrollment of the first three (3) Dose C patients and based upon available safety data, a decision will be made whether to: a) stop due to toxicity, or b) continue to enroll an additional 21 patients until there are a total of twelve (12) patients > 6 months and < 24 months and twelve (12) patients ≥ 24 and <60 months that have received Dose C.

All patients enrolled in Cohort 1 (Dose A) and Cohort 2 (Dose B) will be followed for a total of 12 months. Patients enrolled in Cohort 3 (Dose C) will be followed for a total of 15 months. The primary analyses for efficacy will be assessed when all patients in each age group reach 12 months post-dose and the primary analyses for safety will be assessed when the last patient of

Cohort 3 reaches 15 months post-dose (and database lock will be performed at the time point at which the last patient reaches 15 months post-dose). An additional analysis of efficacy and safety data was conducted when the last Cohort 2 patient completed the 12 month visit.

Safety will be assessed through monitoring AE reports and concomitant medication usage, and by conducting physical examinations, vital sign assessments, cardiovascular evaluations, laboratory evaluations, and pulmonary examinations. Patients will be observed at the hospital for 48 hours post intrathecal injection. Patients will return for follow up visits on Days 7, 14, 21, and 30. Patients will return monthly thereafter, following the Day 30 visit, according to the Schedule of Assessments. Patients in Cohort 3 who were enrolled into the study after Protocol Version 8 (Amendment 7) went into effect will return for follow up visits on Days 44 and 72 for laboratory assessments (liver function tests only).

Upon study completion, study patients will be asked to enroll in a vital long-term follow-up study examining the lasting safety of AVXS-101 up to 15 years. Long term evaluations will be conducted under a separate protocol.

3.6. Patient Selection

Patients with a genetic diagnosis consistent with SMA, bi-allelic deletion of *SMN1* and 3 copies of *SMN2* without the genetic modifier who demonstrate the ability to sit unassisted for 10 or more seconds but cannot stand or walk at the time of study entry will be enrolled in this clinical study. Patients will be of any racial, ethnic, or gender background. Enrollment will be staggered with at least four (4) weeks between patient injections for all patients in Cohort 1 and at least the first three patients in Cohort 2 and Cohort 3.

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 is designed to assess the impact of AVXS-101 on non-ambulatory young children with SMA who have 3 copies of *SMN2*, with efficacy outcomes specifically assessing improvement in motor function from that expected in the natural history of non-ambulatory children with SMA. Data will be compared with patient-level data drawn from a widely (peer-reviewed) published natural history dataset collected by the PNCR network.

Although patients with SMA Type 2 and 3 are easily differentiated in a retrospective manner by best clinical function, given the genetic and (early) clinical overlap between the two phenotypes it is sometimes difficult at the time of diagnosis to predict the ultimate clinical course for an individual patient at the time of initial diagnosis. The published literature from a large natural history study (Kaufman 2012) suggests that a significant majority of the patients eligible for this study will, in fact, have SMA Type 2. However, it is also expected based upon this literature that a small percentage of children eligible for this study (3 copies of *SMN2*, age of symptom onset less than 12 months, sitting but not standing or walking independently) will, in fact, be children

who would ultimately walk independently as part of the normal course of their disease (and therefore would be ultimately re-classified as SMA Type 3). The study design, statistical considerations, and study size are based upon this presumption.

Patients will be stratified into 2 groups based upon age at dosing. Between Dose A and Dose B, fifteen patients will be enrolled aged ≥ 6 months and < 24 months at dosing, and 12 patients will be enrolled who are aged 24 months to < 60 months at the time of dosing. Up to an additional 24 patients may be enrolled and receive a higher dose (Dose C) if deemed appropriate and necessary by AveXis, Inc and recommended by the DSMB.

The primary efficacy endpoint for the group of patients ≥ 6 months and < 24 months of age at time of dosing will be the proportion of patients who achieve the ability to stand alone up to the 12-month study visit. Twenty-four (24) children aged ≥ 6 months and < 24 months will be enrolled, with twelve (12) children receiving Dose B and twelve children receiving Dose C. The proportion of patients developing the ability to stand alone will be compared with a cohort of eligibility-matched patients from the PNCR natural history study of SMA; this comparison will be conducted for Dose B only. Based upon a review of eligibility-matched patients from the PNCR, fourteen percent (14%) of patients who meet the study criteria for patients ≥ 6 months and < 24 months of age achieved the ability to stand alone, and ten percent (10%) achieved the ability to walk alone. It is expected that 85% of treated patients ≥ 6 months and < 24 months of age will achieve the ability to stand alone and 60% will achieve the ability to walk alone. With this efficacy, a sample size of 12 patients would provide power of > 90% to detect a significant difference compared with the matched control cohort with $\alpha = 0.05$ using a two sample 2-sided Fisher exact test.

The primary efficacy endpoint will be the change in HFMSE in treated patients who are ≥ 24 months and < 60 months of age at time of dosing. Twenty-four (24) children aged ≥ 24 months and < 60 months will be enrolled, with twelve (12) children receiving Dose B and twelve (12) children receiving Dose C. Change in HFMSE score at 12 months will be compared with a cohort of eligibility-matched patients from the PNCR natural history study of SMA; this comparison will be conducted for Dose B only. Based upon a review of eligibility-matched patients from the PNCR dataset, a mean change of -1.33 points (standard deviation = 4.32 points) in the HFMS is seen at 12 months from baseline among patients aged 2-5 years at first evaluation with 3 copies of *SMN2*. However, the primary endpoint for this cohort is HFMSE, not HFMS. As such, the comparison to PNCR will utilize HFMSE. Among patients in this PNCR cohort, a mean change of -1.13 points (standard deviation=4.90) was seen in HFMSE, in line with other publications describing disease progression in SMA type 2 and 3 patients. It is expected to observe a mean increase of 8 points from baseline on the HFMSE in AVXS-101 treated patients with equivalent variance. Based upon these assumptions, twelve patients aged ≥ 24 and <60 months at enrollment will have > 90% power to detect a significant difference with $\alpha = 0.05$ when compared to patient-level data available from the PNCR dataset using a two-sample Analysis of Variance (ANOVA).

3.8. Treatment Assignment and Blinding

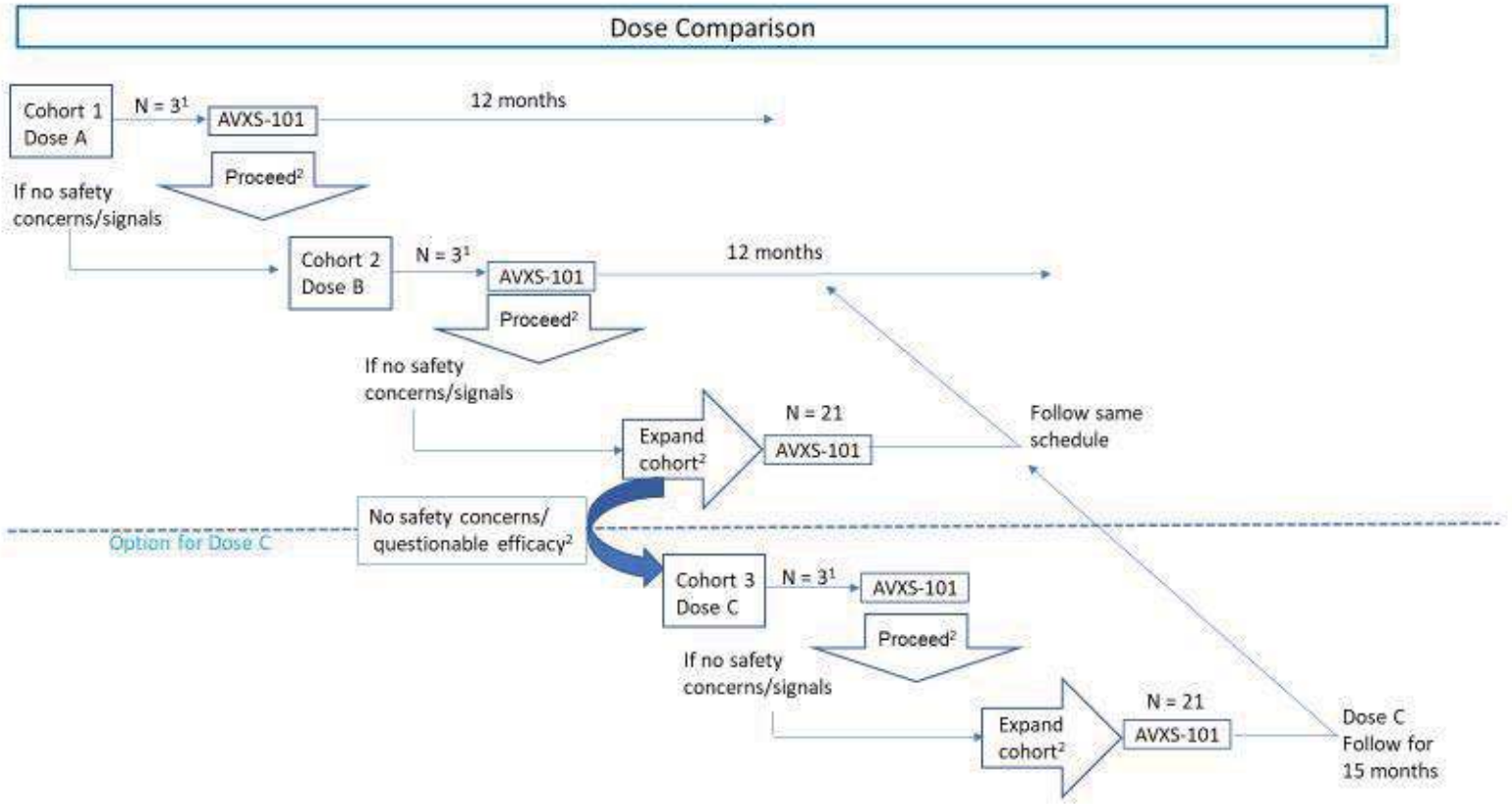
The clinical study is a Phase I, open-label, single-dose administration study. The treatment assignment will be conducted as specified in Section 3.5 of the SAP. No blinding will be conducted.

3.9. Administration of Study Medication

Refer to Section 3.5 of the SAP.

3.10. Study Flowchart and Schedule of Assessments

Figure 1: Study Design



[1] Four (4) week dosing between first three patients within each cohort to allow safety monitoring
[2] Provided no dose related toxicities and DSMB determines acceptable to escalate/expand during quarterly meeting

Refer to Appendix 22.3 for the schedule of assessments.

4. ENDPOINTS

4.1. Primary Efficacy Endpoints

Primary efficacy endpoints are assessed independently for each age group and for each dose separately. As detailed in Section 3.4.1 of this SAP, Dose A and Dose C will each be summarized descriptively and will not be compared to the historical data of the PNCR network. Assessment of developmental milestones will be determined by the clinical evaluator (CE) at the investigative sites. The primary source for developmental milestone data will be based on documented video evidence captured by site CE or patient families that is reviewed and concurred by an independent central reviewer.

- Patients ≥ 6 months and < 24 months at time of dosing:

  The primary efficacy endpoint is the proportion of treated patients who achieve the ability to stand alone (Bayley-III – Gross Motor Subtest item # 40) at any post-treatment visit up to the 12-month study visit.

- Patients ≥ 24 months and < 60 months at time of dosing:

  The primary efficacy endpoint is the change from baseline in HFMSE in treated patients at the 12-month study visit.

4.2. Secondary Efficacy Endpoints

The secondary endpoints for both patient age groups (aged ≥ 6 months and < 24 months at dosing, aged ≥ 24 and < 60 months at dosing) are the proportion of patients achieving the ability to walk alone (Bayley-III Gross Motor Subtest # 43) at any post-treatment visit up to the 12-month study visit. Assessment of developmental milestones will be determined by CEs at the investigative sites. The primary source for developmental milestone data will be based on documented video evidence captured by site CEs or patient families that is reviewed and concurred by an independent central reviewer.

4.4. Primary Safety Endpoints

The primary safety endpoints are as follows:

- Any AE
- Any serious AE
- Any AE related to study product
- Any AE with CTCAE Grade ≥ Grade 3

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. AEs spontaneously reported by the patient or family and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. However, abnormal values that constitute a Serious Adverse Event (SAE) or lead to discontinuation of administration of study product must be reported and recorded as an AE. Information about AEs will be collected from the time of intrathecal injection until the end of the study. SAE information will be collected from signing of consent form until the last study visit.

4.5. Secondary Safety Endpoint

The secondary safety endpoint is defined as average number of hours per day of 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).

4.6. Pharmacokinetic Endpoints

Not applicable to this SAP.

4.7. Pharmacodynamic Endpoints

Not applicable to this SAP.

4.8. Additional Safety Endpoints

4.8.1.1. Laboratory Tests

Blood samples will be collected and measured for the parameters of hematology, coagulation, chemistry and other relevant tests such as capillary blood gas, and serum antibodies and T-cell response to adeno associated virus 9 (AAV9) and survival motor neuron (SMN). Urine samples will be collected for urinalysis parameters. Saliva, urine, and stool will be collected for viral shedding sample analysis. Only descriptive statistics are planned for this data.

4.8.1.2. Vital Signs and Body Weight and Length

Vital signs will include blood pressure, respiratory rate, pulse, heart rate, pulse oximetry and axillary temperature. Body weight and length and/or height will also be collected. Only descriptive statistics are planned for this data.

4.8.1.3. Physical Exam

Physical exam will be performed including head, eyes, ears, nose and throat, lungs/thorax, cardiovascular, abdomen, musculoskeletal, dermatologic, lymphatic, neurologic and genitourinary.

Head circumference will be measured with each physical exam. Measurements will be taken 3 times, and the largest measurement will be recorded to an accuracy of 0.1 centimeters.

Only descriptive statistics are planned for this data.

4.8.1.4. Electrocardiogram (ECG)

Standard 12-lead ECGs will be performed at screening/baseline, Day 1, Day 2, Day 3, Month 3, Month 6, Month 9, Month 12, and Month 15 (Cohort 3 only) visits (or Early Termination) including heart rate, PR, QRS, QTcF. 12-lead ECG will also have QR included. 12-lead ECG tracings will be interpreted locally; however, the tracings will be submitted to a centralized interpreter for inclusion in the study dataset. Only descriptive statistics are planned for this data.

4.8.1.5. Echocardiogram

An echocardiogram will be performed at screening/baseline, and at the Month 3, Month 6, Month 9, Month 12, and Month 15 (Cohort 3 only) visits (or Early Termination). Echocardiograms will be interpreted locally; however, they will also be submitted to a centralized interpreter for inclusion in the study dataset. Only descriptive statistics are planned for this data.

4.8.1.6. 12-Lead Holter Monitor

Patients will have a 12-lead continuous Holter monitor attached 24-hours prior to the dose administration on Day -1. The Holter monitor will remain through 48 hours (Day 3). Serial ECG data will be pulled in triplicate from the Holter monitor data at the following time points:

- Pre-dose, 2 hour, 4 hour, 6 hour, 8 hour, 12 hour, 24 hour, 36 hour, 48 hour

Twenty-four hour Holter monitoring will also be performed at Months 1, 2, 3, 6, 9, 12, and 15 (Cohort 3 only) (or Early Termination).

4.9. Health-economics Endpoints

Not applicable to this SAP.

4.10. Other Endpoints

Not applicable to this SAP.

5. ANALYSIS SETS

5.1. Screened Set

The Screened Set will include all patients screened, regardless of whether they were given an AVXS-101 injection. Unless specified otherwise, this set will be used for summaries of screen failures, serious AEs, and AAV9 titers.

5.2. Enrolled Set

The Enrolled Set will include all patients enrolled (i.e., completed the informed consent process). Unless specified otherwise, this set will be used for patient listings and for summaries of patient disposition.

5.3. Safety Analysis Set

The Safety Analysis Set (SS) will include all patients who are given an AVXS-101 intrathecal injection. Patients will be analyzed according to actual dose received. The SS will be used for all analyses of safety endpoints and for the presentation of patients in all patient listings.

5.4. Intent-to-Treat or Full Analysis Set

5.4.1. Intent-to-Treat

The Intent-to-Treat (ITT) Set will include all enrolled patients who are given an AVXS-101 intrathecal injection. Patients will be analyzed according to the assigned dose. All efficacy analyses will be conducted using the ITT Set as the primary population, unless specified otherwise.

5.4.2. Full Analysis Set

The Full Analysis Set (FAS) will include all enrolled patients who are given an AVXS-101 intrathecal injection. The FAS includes the same patients as ITT Set.

5.4.3. Modified Intent-to-Treat

Not applicable for this SAP.

5.5. Per Protocol or Evaluable Set

5.5.1. Efficacy Completer Analysis Set

The Efficacy Completer Analysis Set (ECAS) consists of all treated patients who complete 12 months following AVXS-101 dose procedure. The end of study visit can be conducted either remotely or at the study site.

Patients who terminate the study early will not be included in ECAS.

5.5.2. Per Protocol Analysis Set

The Per Protocol (PP) Analysis Set consists of all enrolled patients who are given an AVXS-101 intrathecal injection and who did not have any major protocol violations which may have

impacted their efficacy or safety data. The determination of the criteria for which patients will be excluded from the PP Set will occur prior to database lock of the study. Specifically, if there is evidence at Screening that a patient is able to walk with support (according to Bayley-III Gross Motor Subtest #37) or that a patient does not have any clinical symptoms of SMA, they will be excluded from the PP Set.

The PP Set will be used for a sensitivity analysis of the primary efficacy endpoint of each cohort.

5.6. PNCR Population-Matched Control Population

A population-matched control cohort will be drawn from the PNCR Natural History dataset. The PNCR is a large natural history study developed from a 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 with any form of SMA, of any age, followed in PNCR site clinics and newly diagnosed patients were enrolled. All eligible patients were offered participation. 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-II) was defined as being able to sit independently for > 10 seconds, and walking alone was defined as having scored 2 points on item #20 of the HFMSE at any time. All patients with SMA type 2 or 3 who provided sufficient records and follow-up for evaluation and met the basic entry criteria for the two cohorts of the AVXS-101-CL-102 study (3 copies of *SMN2*, symptom onset before 12 months of age and baseline and follow-up visits within the age criteria for the study) were considered for possible inclusion in the natural history comparison dataset. The *SMN2* modifier mutation (c.859G>C) described by Prior and colleagues (Prior et al., 2009) was not assessed in the PNCR study cohort.

5.6.1. Primary analyses vs. PNCR

For the cohort of patients ≥ 6 months and < 24 months of age, patient-level data from a cohort of 51 patients drawn from the PNCR Network natural history study of SMA will serve as a "population-matched" control cohort. This comparison cohort encompasses all 51 patients enrolled in the PNCR study who met the criteria of having SMA Types 2 or 3, 3 copies of *SMN2* and symptom onset before 12 months of age and had at least one visit at or before 36 months of age. Of this cohort, 7/51 (14%) of the natural history cohort attained the ability to stand alone (defined as achieving a score of 2 on item #19 of the HFMSE). 5/51 (10%) attained the ability to walk alone (defined as achieving a score of 2 on item #20 of the HFMSE).

For the cohort of patients between 24 and <60 months of age, patient-level data from a cohort of 15 patients drawn from the PNCR Network natural history study of SMA will serve as a "population-matched" control cohort for the primary analysis. This comparison cohort encompasses all 15 patients enrolled in the PNCR study who met the criteria of having SMA Types 2 or 3, 3 copies of *SMN2*, symptom onset before 12 months of age, diagnosis before 24 months of age and unable to stand or walk at enrollment (baseline visit) and who received a HFMSE evaluation between 24 and 60 months of age ("baseline"), and a follow-up evaluation

(HFMS or HFMSE) performed between 12 and 14 months following that baseline evaluation. It is stated in the protocol that among the patients in this cohort, a mean change of -1.33 points (Standard deviation=4.32) was seen in HFMS. However, the primary endpoint for this cohort is HFMSE, not HFMS. As such, the comparison to PNCR will utilize HFMSE. Among patients in this PNCR cohort, a mean change of -1.13 points (Standard deviation=4.90) was seen in HFMSE, in line with other publications describing disease progression in SMA type 2 and 3 patients (Kaufman et al 2012, Mercuri et al 2016). From this point forward, this PNCR comparator group of 15 patients will be referred to as the "Primary PNCR" group.

5.6.2. Sensitivity analyses vs. PNCR

The primary PNCR group consists of 15 patients to be used for the analysis of efficacy in the older cohort patients, but one patient included in the cohort had an HFMSE score of 0 recorded at Baseline and all post-Baseline visits. Additionally, data collected more than 12 months after the Baseline assessment has occurred were being considered. The PNCR database was re-reviewed in order to identify a secondary PNCR population upon which to compare to AVXS-101 via sensitivity analyses. The secondary PNCR population consisting of 17 patients was identified as follows:

The PNCR database was filtered to identify individuals who matched eligibility criteria for CL-102 as closely as possible. Seventeen individuals were identified with age, clinical, and genetic criteria that were similar to CL-102 study patients. HFMSE scores were used to determine natural history of disease progression. The PNCR controls were 2-5 years of age. The first visit within the 2 to 5 year interval was defined as the baseline visit. Subsequent visits within a 12 month interval were used to determine change from baseline for HFMSE. Clinically, these individuals were able to sit without support but did not stand or walk. Genetically, patients harbored biallelic SMN1 deletions and 3 copies of SMN2. Not all patients in this group had a full 12 months of follow up data. Hence, this group underestimates decline during a 12 month period.

From this point forward, this PNCR comparator group of 17 patients will be referred to as the "Sensitivity PNCR" group.

5.7. Pharmacokinetic Set

Not applicable for this SAP.

5.8. Pharmacodynamic Set

Not applicable for this SAP.

5.9. Other Analysis Sets

Not applicable for this SAP.

5.10. Protocol Deviations

Protocol deviations identified by the site or the study monitor should be reported to the IRB according to the IRB's reporting guidelines. All deviations will be recorded in the MediData Rave database and will be categorized in accord with AveXis Standard Operating Procedures

(SOP)s. Protocol deviations will be reviewed on a regular basis by the appropriate study team members throughout the course of the study.

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. General Methods

In general, descriptive statistical methods will be used to summarize the data from this study. Hypothesis testing will be performed for the efficacy endpoints based upon the predetermined sample sizes. Unless stated otherwise, the term "descriptive statistics" refers to number of patients (n), mean, median, standard deviation, minimum, and maximum for continuous data and frequencies and percentages for categorical data. Unless noted otherwise, the data will be sorted first by dose (Dose A, then Dose B, then Dose C), age group, patient number, and then by date within each patient number.

Unless noted otherwise, all safety tables will be summarized using the SS, by the actual dose received and by age group.

All descriptive statistics of efficacy tables will be summarized by the assigned dose and age group. The efficacy analyses will be performed to compare with the efficacy endpoints of patients assigned to AVXS-101 and patients drawn from a widely (peer-reviewed) published natural history dataset collected by the PNCR network; comparisons to the PNCR data will be conducted for Dose B only. Efficacy data for Dose A and Dose C will only be summarized descriptively and will not be compared to the PNCR data.

Efficacy analyses will be conducted on the ITT or ECAS as specified within each section, with analyses on the ECAS produced only if the ECAS contains a subset of patients of the ITT. Since the FAS and the ITT Set include the same patients (SAP Section 5.3), the ITT Set is used to represent the efficacy analyses by the FAS stated in the protocol.

Unless specified otherwise, all statistical testing and confidence intervals (CI) will be 2-sided and will be performed using an alpha level of 0.05. No adjustments for multiple comparisons will be made.

All statistical analyses will be conducted with the SAS® software package version 9.4 or higher.

6.2. Key Definitions

6.2.1. Baseline Values

Unless otherwise specified, the baseline values of safety parameters and efficacy parameters of the patients enrolled in the study are defined as the last non-missing measurement or assessment prior to the dose of study medication. If multiple measurements are recorded on the same day, the last measurement recorded prior to the dose of study medication 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.

For patients ≥ 6 months and < 24 months at time of dosing who continue in study past 24 months of age, the score and change from baseline of HFMSE will also be the calculated. The baseline HFMSE will be defined as the patients' first measurement of HFMSE after passing 24 months of age.

The baseline values of parameters of patients from the PNCR are defined as those captured for the study-defined baseline visit. In cases where the baseline visit HFMSE assessment was not completed, the baseline value will be defined as the first non-missing assessment.

6.2.2. Study Day

For patients enrolled in the study, the only dose of study medication will be administered on study day 1. The study day for an event occurring on or after the dose date is defined as event date – dose date + 1. The study day for an event occurring prior to the dose date is defined as event date – dose date.

For patients from the PNCR dataset, the date of baseline assessment for the primary endpoint will be considered study day 1. The study day for an event occurring on or after the date of enrollment is defined as event date – enrollment date + 1. The study day for an event occurring prior to the date of enrollment is defined as event date – enrollment date.

6.2.3. Dose Date

The dose date, study day 1, will be the date of administration of the dose of study product.

6.2.4. Final Treatment Value

The final treatment value for each patient enrolled in the study is the last non-missing measurement collected after study day 1. For the patients from PNCR dataset, the final treatment value is the last non-missing measurement collected after study day 1 and on or prior to visit Month 12.

6.2.5. Final Study Value

The final study value for each patient enrolled in the study is the last non-missing measurement collected. For patients from PNCR dataset, the final study value is the measurement collected on or prior to visit Month 12.

6.2.6. Age at Baseline

Age at baseline for patients enrolled in the study is defined as the age at the dose date. Age at baseline for patients from the PNCR dataset is defined as age at baseline. Age will be defined/displayed in months.

6.3. Missing Data

Patients are allowed to withdraw from the study at any time. Analysis of quantitative and categorical variables will include data from patients with non-missing values. For continuous variables, a MMRM model may be used for the comparison between AVXS treated patients and the matching PNCR cohort.

Imputation of missing or incomplete dates will only be performed on AEs and concomitant medications for determining the timing relative to the dose of study product unless otherwise specified. The rules of imputation of missing dates are specified in Table 1 and Table 2. Partial or missing dates will be listed as recorded in the electronic case report form (eCRF). All imputed dates will be no earlier than the patients' birth date.

Table 1: Rules of Date Imputation: Pre-Dose Assessments

Partial Missing Start Date	Imputed Start 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
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
Missing month, but year and day are present	Missing month imputed as January

Table 2: Rules of Date Imputation: Post-Dose Assessments

Partial Missing Start Date	Imputed Start Date
Missing month and day, but the year is present	Date of dose
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
Missing month, but year and day are present	Month of dose

6.4. Derived and Transformed Data

6.4.1. Primary Safety Variables

The primary safety endpoints are defined as follows:

- Any AE
- Any serious AE
- Any AE related to study product
- Any AE with CTCAE Grade ≥ Grade 3

The AEs will be collected from eCRF based on the Schedule of Assessments in SAP Appendix 19.2.

6.4.2. Secondary Safety Variable

The secondary safety endpoint is defined as average number of hours per day of non-invasive ventilatory support.

The number of hours per day of non-invasive ventilatory support will be summarized by visit and cohort using descriptive statistics.

6.4.3. Primary Efficacy Variables

Bayley-III is a standardized, norm-referenced assessment tool used to identify developmental issues during early childhood. The gross and fine motor subtests will be completed within 30 days of dosing at baseline and then monthly through Month 12. The score of each scale/subtest will be captured in the eCRF. No missing scores will be imputed.

The achievement of significant developmental milestones will be assessed by the CE using a standard Developmental Milestone Checklist shown in Table 3 with definitions of each developmental milestone driven by Bayley-III. Developmental milestones will be assessed by the CE at the investigational site; the physical assessments will be captured on video. Video taken outside of the investigational site (i.e., at the patient's home) which demonstrates the achievement of a developmental milestone is also acceptable. All video evidence of developmental milestone achievement will then be reviewed and confirmed by an independent central reviewer. Aside from analysis of the developmental milestones defined in the primary and secondary efficacy objectives, only descriptive statistics are planned.

Table 3: Developmental Milestone Checklist

Developmental Milestone- Bayley Scales Item Number	Performance Criteria
Head Control – Gross Motor Subtest Item #4	Child holds head erect for at least 3 seconds without support
Rolls from Back to Sides – Gross Motor Subtest Item #20	Child turns from back to both right and left sides
Sits Without Support – Gross Motor Subtest Item #26	Child sits alone without support for at least 30 seconds
Stands With Assistance - Gross Motor Subtest Item #33	Child supports own weight for at least 2 seconds
Crawls – Gross Motor Subtest Item #34	Child makes forward progress of at least 5 feet by crawling on hands and knees
Pulls to Stand – Gross Motor Subtest Item #35	Child raises self to standing position using chair or other convenient object for support
Walks With Assistance – Gross Motor Subtest Item #37	Child walks by making coordinated, alternated stepping movements
Stands Alone – Gross Motor Subtest Item #40	Child stands alone for at least 3 seconds after you release his or her hands
Walks Alone – Gross Motor Subtest Item #43	Child takes at least five steps independently, displaying coordination and balance

The primary efficacy endpoint for the patients ≥ 6 months and < 24 months at time of dosing is the proportion of patients achieving the ability to stand alone. The ability to stand alone will be evaluated by the CE using the Bayley-III – Gross Motor Subtest # 40 at visits specified by the Schedule of Assessments. Patients who achieve standing alone at any post-procedure visit up to 12 months will be classified as responders. Otherwise, the patient will be classified as a non-responder.

The HFMSE was devised for use in children with SMA Type 2 and Type 3, age 24 months and above, to give objective information on motor ability and clinical progression. The HFMSE will be administered by a CE in accord with the Protocol Schedule of Assessments within 30 days of dosing and monthly through twelve (12) months for all patients ≥ 24 months of age. The primary efficacy endpoint for the patients ≥ 24 months and <60 months at time of dosing is the change from baseline in HFMSE. The change from baseline to the 12-month study visit will be calculated.

6.4.4. Secondary Efficacy Variables

The secondary efficacy variable is defined as follows for both patient strata (aged ≥ 6 and < 24 months at dosing, aged ≥ 24 and < 60 months at dosing):

- Ability to walk alone per Bayley-III Gross Motor Subtest # 43.

For the summary of each age group, the data from the historical dataset of PNCR network will also be included by the matched age group and analysis visits. The PNCR dataset evaluated the ability to walk alone, as per the HFMSE item #20. The HFMSE will not be started until patients reach 24 months of age; however, the Bayley-III will be assessed at Screening and all study visits.

[redacted]

6.5. Visit Windows

The time windows specified in Table 4.1 (Cohort 1 and 2) and Table 4.2 (Cohort 3) define how efficacy data will be assigned to protocol-specified time points, 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 4.1: Analysis Time Windows of Bayley Scales, HFMSE, Development Milestones and Pulmonary Exam – Cohort 1 and 2 Patients

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

Table 4.2: Analysis Time Windows of Bayley Scales, HFMSE, Development Milestones and Pulmonary Exam – Cohort 3 Patients

Scheduled Visit	Nominal Days (Study Day)	Acceptable Analysis Window in Study Days (Min Day – Max Day)
Baseline	-	< 1
Month 1	30	1 to 38
Day 44	44	39 to 49
Month 2	60	50 to 66
Day 72	72	67 to 77
Month 3	90	78 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

Scheduled Visit	Nominal Days (Study Day)	Acceptable Analysis Window in Study Days (Min Day – Max Day)
Month 13	390	375 to 404
Month 14	420	405 to 434
Month 15	450	≥435

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	Visit Month 0
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

If a PNCR patient is missing efficacy data at Baseline, then the earliest non-missing assessment collected post-Baseline will be re-mapped and considered their Baseline value, and subsequent visits occurring within 12 months after the re-mapped Baseline value will be included in the analysis.

For example, if a PNCR patient is missing their HFMSE assessment at Visit Month 0 and Visit Month 2 and their first non-missing HFMSE assessment occurred at Month 4, then their data would be re-mapped as follows:

- Visit Month 4 assessment is considered Baseline
- Month 6 is re-mapped as Month 2 (visit occurred 2 months after Baseline)
- Month 9 is remapped as Month 5 (visit occurred 5 months after Baseline)
- Month 12 is remapped as Month 8 (visit occurred 8 months after Baseline)
- Next available visit is >12 months after Baseline so it is not considered

6.6. Pooling of Centers

This is a multiple-center dose-comparison study. Given that the number of patients enrolled at any individual site is expected to be small, patients from all sites will be pooled in the analyses for the primary and secondary effectiveness endpoints. A site effect or a site-treatment interaction will not be examined due to the fact that the sites selected for this study are all high-level treatment centers with extensive experience in the management of SMA and, as such, are

expected to follow care management strategies closely aligned with the published standards of care.

6.7. Subgroups

There will be no subgroups created for the analysis.

6.8. Other Statistical Analysis

Not applicable to this SAP.

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1. Patient Disposition and Withdrawals

Patient disposition will be presented for all patients, which will include the following:

- The number of patients screened
- The number of patients who failed screening
- The number (%) of patients in the Enrolled Set
- The number (%) of patients in the ITT Set
- The number (%) of patients in the FAS
- The number (%) of patients in the SS
- The number (%) of patients in the ECAS
- The number (%) of patients in the PP Set
- The number (%) of patients who completed the study, including all patients with a final scheduled visit conducted either remotely or at the study site
    - The number (%) of patients who completed the study within 30 days of when the last study visit was scheduled to occur
    - The number (%) of patients who completed the study more than 30 days after when the last study visit was scheduled to occur
        - For patients in dose groups A and B, the last study visit was scheduled to occur at Month 12 (Day 360) and 30 days after the last scheduled study visit is Day 390. For patients in dose group C, the last study visit was scheduled to occur at Month 15 (Day 450) and 30 days after the last scheduled study visit is Day 480.
- The number (%) of patients who discontinued from the study and the associated reasons

Patient disposition will be summarized overall and by dose and age group. A listing of patient disposition will be provided. The inclusion/exclusion criteria for the patients who failed screening and all major protocol deviations will be listed. A separate listing will be produced which summarizes all protocol deviations related to COVID-19.

A listing of patients excluded from the PP Set, along with reason for exclusion, will be provided.

For patients who discontinued due to AE, a separate summary table will be produced in order to detail the type of AE that resulted in the discontinuation (whether serious fatal, non-serious fatal, or non-fatal).

7.2. Demographic and Other Baseline Characteristics

Demographics and baseline characteristics will be summarized for the PNCR dataset and separately for the SS overall and by dose and age group, with descriptive statistics including n, mean, standard deviation, median, minimum, and maximum for numeric variables and frequency and percentage for categorical variables.

The following characteristics will be summarized for the SS:

Demographics include age, gender, ethnicity, race, weight, length and body mass index.

Age (months) = (dose date - date of birth +1)/30

Length (cm) = Length (in inches) * 2.54

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

Race will be summarized as captured in the eCRF. Patients reporting multiple races will be summarized as 'Multiple'.

Baseline disease characteristics include the following:

- Familial history of SMA including affected siblings or parent carriers
- Gestational age at birth
- Length/weight and head circumference at birth
- Hospitalization information from time of birth including number, duration, and reason for hospitalizations including primary ICD-10 codes if available
- Historical ventilatory support, if any
- Historical feeding support, if any

All demographics and baseline characteristics will be listed for the SS.

The following characteristics will be summarized for each of the three PNCR populations being referenced in this study (refer to Section 5.6 of this SAP):

- Age at PNCR entry (months)
- Age (months) at first HFMSE assessment conducted after reaching 24 months of age
- Gender
- Ethnicity
- Race
- Gestational age at birth
- Height (cm) at PNCR entry
- Weight (kg) at PNCR entry

7.3. Medical History and Concomitant Diseases

A summary table of the number and percentage of patients by medical history system organ class (SOC) and preferred term (PT) will be produced for patients in the ITT. The summary will be provided overall and by dose and age group. Medical history will be sorted alphabetically by SOC and PT using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. For the summary tables, a patient may appear more than once if he/she has more than one medical history coded under the same PT and/or SOC categories. However, the patient will be counted only once in each category.

A summary table of SMA medical history will be produced for patients in the ITT. The summary will be provided overall and by dose and age group.

Listings for medical history and SMA medical history will also be provided. Medical history and concomitant diseases data were not collected in a similar fashion in the PNCR natural history study and therefore the study data regarding medical history and concomitant disease will not be compared with the PNCR natural history cohort.

7.4. Medication

7.4.1. Prior and Concomitant Medications

All prior and concomitant medications will be classified using the Anatomical Therapeutic Chemical (ATC) classification and preferred drug names from the World Health Organization (WHO) Drug Dictionary, version March 2014 or later. Prior medications are defined as medications which started prior to injection of AVXS-101. Concomitant medications are defined as medications ongoing at time of first injection of AVXS-101 or started after the injection.

Prior and concomitant medications will be summarized separately by ATC level 2 and preferred drug name for the SS. The prior and concomitant medications will be summarized overall and by dose and age group.

A separate listing for prior and concomitant medications will also be provided. Prior and concomitant medication information is not available for the PNCR population matched cohort.

7.4.2. Specific Medication Subgroup

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. Only the data recorded on the prednisolone dosing log will be used in this derivation.

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 30, then on Day 31, dose is lowered to 0.5 mg/kg until Day 42. On Day 43, the dose is lowered to 0.25 mg/kg and continues until Day 56 when prednisolone dosing stops. For this patient,

Total cumulative dose= (1.0 mg/kg x 30 days) +
(0.5 mg/kg x 12 days) +
(0.25 mg/kg x 14 days) = 39.5 mg/kg

Exposure will be summarized overall and by actual dose received and age group for the SS.

A listing of AEs will be produced for patients who did not follow the protocol-defined taper, defined as those patients with less than 56 days of total time of prednisolone dosing.

7.4.3. Compliance to Study Product

Refer to Section 11.1 and Section 11.2 of this SAP.

7.4.4. Measurement of Treatment Compliance

Refer to Section 11.1 and Section 11.2 of this SAP.

7.4.5. Data Display Treatment and Other Sub-Group Description

Not applicable for this SAP.

7.4.6. 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 in a table. Listings will be provided.

8. EFFICACY

8.1. Primary Efficacy Endpoints and Analysis

8.1.1. Proportion of patients ≥ 6 months and < 24 months at time of dosing that achieve the ability to stand alone at any post-baseline visit up to 12 months

The developmental milestone stands alone as assessed by Bayley-III Gross Motor Subtest #40 will be assessed at the scheduled visits in accord with the Schedule of Assessments for evaluating patient's ability to stand alone. The developmental milestone achievement of each patient in the study is based on the video evidence reviewed and confirmed by an independent central reviewer, as specified in SAP Section 6.4.3. The proportion of patients ≥ 6 months and < 24 months of age at time of dosing that achieve the developmental milestone at any post-baseline visit up to 12 months will be summarized overall and by dose.

The proportion of patients achieving the corresponding developmental milestone "stand unsupported" assessed using the HFMSE item #19 within 12 months in the historical dataset of PNCR network will also be included by the matched age group. PNCR patients with an HFMSE item #19 score of 2 at either the Baseline visit or at any post-Baseline visit within 12 months of Baseline will be considered to have achieved the milestone. The HFMSE will not be started until patients reach 24 months of age; however, the Bayley-III will be assessed at Screening and all study visits as indicated in the Schedule of Assessments. An additional summary will be produced to present the proportion of patients achieving the developmental milestone at each visit; this will be summarized overall and by dose.

The corresponding p-value from Fisher's exact test will be computed for the comparison between AVXS-101 Dose B and PNCR data and this is the primary analysis for this endpoint. The summary and statistical analysis will be conducted using the ITT Set and will be repeated using the PP Set as a sensitivity analysis. The difference of the proportions between AVXS-101 and PNCR will be summarized and the exact 95% CIs will be provided accordingly.

As a supporting analysis to the primary analysis, the time to achieving ability to stand alone will be summarized for patients overall and by dose in the ITT Set. The study day will be used as the

time variable. Age at baseline will be used as a covariate. The probability of the ability to stand alone over time will be estimated using Kaplan-Meier methods. A Cox regression model will be used to obtain the hazard ratio with 95% CI for AVXS-101 Dose B to the data from PNCR. In this analysis, patients will be censored at the date of their End of Study visit.

All of the efficacy analyses stated above may be repeated using the ECAS as a sensitivity analysis, in the event the ECAS contains a subset of patients of the ITT Set.

If necessary, an additional set of sensitivity analyses may be conducted to include patients who demonstrated the developmental milestone of standing alone (Bayley-III, Gross Motor Subtest #40) which occurred after but within 3 months of the upper bound of the Month 12 visit window (day 374) due to COVID-19 disruptions.

In the first sensitivity analysis, the proportion of patients ≥ 6 months and < 24 months of age at time of dosing that achieve the developmental milestone at any post-baseline visit (considering the expanded 3-month window) will be summarized overall and by dose. The corresponding p-value from a Fisher's exact test will be computed for the comparison between AVXS-101 Dose B and PNCR data. The summary and statistical analysis will be conducted using the ITT Set. The difference in the proportions between AVXS-101 and PNCR will be summarized and the exact 95% CIs will be provided accordingly.

In the second sensitivity analysis, the time from dosing to achieving the ability to stand alone will be summarized for patients overall and by dose in the ITT Set. The study day will be used as the time variable. Age at baseline will be used as a covariate. The probability of the ability to stand alone over time will be estimated using Kaplan-Meier methods. A Cox regression model will be used to obtain the hazard ratio with 95% CI for AVXS-101 Dose B and PNCR. In this analysis, patients who demonstrated the developmental milestone within the expanded 3-month window after Month 12 will be censored at the last attended visit prior to when the Month 12 visit was scheduled to occur.

8.1.2. Change from Baseline in HFMSE at the 12 Month study visit for patients ≥ 24 months and < 60 months of age at time of dosing

The baseline, post-baseline, and change from baseline values in HFMSE will be summarized for patients overall and by dose. The summary and primary statistical analysis will be conducted using the ITT Set, and will be repeated using the PP Set as a sensitivity analysis. The patient data from the Primary PNCR group will also be included in the descriptive summary and analyses by the matched age group and analysis visits. The change from baseline to 12-month visit will be analyzed using a mixed model with repeated measurement (MMRM). The model will include the change from baseline as the dependent variable, fixed effect of cohort (AVXS-101 and PNCR), visit, and covariates of baseline HFMSE and age at baseline, and interactions of cohort*age at baseline, baseline HFMSE*visit, baseline HFMSE*cohort, and cohort*visit. A compound symmetry covariance structure will be assumed initially to model the within-patient errors; however, if compound symmetry results non-convergence, the variance component will be used. The unadjusted means, least squares (LS) means, differences between LS means, a 95% 2-sided CIs for each difference and the p-values from model effects will be reported for each scheduled visit.

A sensitivity analysis may be performed using the ECAS, in the event the ECAS contains a subset of patients of the ITT Set.

A sensitivity analysis will also be performed using the Sensitivity PNCR group and will be based on the ITT Set. This analysis may be repeated using the ECAS, in the event the ECAS contains a subset of patients of the ITT Set.

8.2. Secondary Efficacy Endpoint and Analyses

8.2.1. Proportion of patients that achieve ability to walk alone at any post-Baseline visit up to 12 Months

The developmental milestone walks alone as assessed by Bayley-III Gross Motor Subtest #43 will be assessed at the scheduled visits in accord with the Schedule of Assessments. The developmental milestone achievement of each patient in the study is based on the video evidence reviewed and confirmed by an independent central reviewer, as specified in SAP Section 6.4.3. The proportion of patients ≥ 6 months and < 24 months and the proportion of patients ≥ 24 and < 60 months at time of dosing who achieve the ability to walk alone up to 12 months will be summarized separately. The summaries will be done by dose and overall.

For the summary of each age group, the data from the historical dataset of PNCR network will also be included by the matched age group and analysis visits. The PNCR dataset evaluated the ability to walk alone per HFMSE item #20. PNCR patients with an HFMSE item #20 score of 2 at either the Baseline visit or at any post-Baseline visit within 12 months of Baseline will be considered to have achieved the developmental milestone. The HFMSE will not be started until patients reach 24 months of age; however, the Bayley-III will be assessed at Screening and all study visits. All patients who are able to walk alone at any post-baseline visit up to Month 12 will be classified as responders. All other patients will be classified as non-responders.

The corresponding p-value from Fisher's exact test will be computed for the comparison between AVXS-101 Dose B and PNCR data for each age group. The summary and statistical analysis will be done using the ITT Set. In each age group, the actual proportions as well as the difference of the proportions between two data sources will be summarized and the exact 95% CI will be provided accordingly.

For each age group, the time to achieving ability to walk alone will be summarized for patients overall and by dose using the ITT Set. The study day will be used as the time variable. Age at baseline will be used as covariate. A Cox regression model will be used to obtain the hazard ratio with 95% CI of AVXS-101 to the data from PNCR.

All efficacy analyses stated above may also be performed using the ECAS as a sensitivity analysis in the event the ECAS contains a subset of patients of the ITT Set. Additionally, a sensitivity analysis will be performed for patients aged ≥ 24 and < 60 months at time of dosing using the Sensitivity PNCR group. This sensitivity analysis will be based on the ITT Set and separately using the ECAS in the event the ECAS contains a subset of patients of the ITT Set.

If necessary, an additional set of sensitivity analyses may be conducted to include patients in the ≥ 6 months and < 24 months group who demonstrated the developmental milestone of walking alone which occurred after but within 3 months of the upper bound of the Month 12 visit window (day 374) due to COVID-19 disruptions.

In the first sensitivity analysis, the proportion of patients that achieve the developmental milestone at any post-baseline visit (considering the expanded 3-month window) will be summarized overall and by dose. The corresponding p-value from a Fisher's exact test will be

computed for the comparison between AVXS-101 Dose B and PNCR data. The summary and statistical analysis will be conducted using the ITT Set. The difference in the proportions between AVXS-101 and PNCR will be summarized and the exact 95% CIs will be provided accordingly.

In the second sensitivity analysis, the time from dosing to achieving the ability to walk alone will be summarized for patients overall and by dose in the ITT Set. The study day will be used as the time variable. Age at baseline will be used as a covariate. The probability of the ability to walk alone over time will be estimated using Kaplan-Meier methods. A Cox regression model will be used to obtain the hazard ratio with 95% CI for AVXS-101 Dose B and PNCR. In this analysis, patients who demonstrated the milestone within the expanded 3-month window after Month 12 will be censored at the last attended visit prior to when the Month 12 visit was scheduled to occur.

8.4. Sensitivity Analysis of the Primary Endpoint

The primary analyses described in the SAP Section 8.1.1 and Section 8.1.2 may be conducted on the ECAS as a sensitivity analysis, in the event that the ECAS contains a subset of patients of the ITT Set.

The primary and secondary analyses for patients aged ≥ 24 and < 60 months at time of dosing will be conducted on the Sensitivity PNCR group as a sensitivity analysis.

8.4.1. Proportion of patients with a ≥3-point increase from baseline in HFMSE score among patients ≥ 24 months and < 60 months of age at time of dosing

The proportion of patients that achieve ≥3-point increase from baseline in HFMSE score at any post-baseline visit up to 12 months will be summarized overall and by dose. The proportion of patients achieving a ≥3-point increase from baseline in HFMSE within 12 months of their baseline visit in the historical dataset of PNCR network will also be summarized.

The corresponding p-value from Fisher's exact test will be computed for the comparison between AVXS-101 Dose B and PNCR data. The difference between the proportions between AVXS-101 and PNCR will be summarized and the exact 95% CIs will be provided. The summary and statistical analysis will be conducted using the ITT Set and repeated for the ECAS, in the event the ECAS contains a subset of patients of the ITT Set, for both the Primary PNCR and Sensitivity PNCR groups.

8.4.2. Change from Baseline in HFMSE across all available assessments (Months 1-12) among patients ≥ 24 months and < 60 months of age at time of dosing

The HFMSE total score at baseline and the weighted mean change from baseline in HFMSE total score considering all post-baseline visits through Month 12 will be summarized for patients overall and by dose. All change from baseline HFMSE scores across all available post-baseline visits (Months 1-12) will be averaged together for this measure and summarized. The number of available post-baseline HFMSE scores available for each patient will be used as the weight for this calculation. For the PNCR patients, the weighted mean change from baseline in HFMSE total score recorded across all visits through 12 months after the patient's baseline assessment will be summarized. The number of available post-baseline HFMSE scores available for each patient will be used as the weight for this calculation. For patients where only a single post-baseline HFMSE score is available, the single value will be used.

The scores will be analyzed using an Analysis of Covariance (ANCOVA) model which will include the weighted mean change from baseline HFMSE score as the dependent variable, fixed effect of cohort (AVXS-101 and PNCR), and baseline HFMSE score and age at baseline as covariates. The unadjusted means, LS means, differences between LS means, a 95% 2-sided CIs for each difference and the p-values from model effects will be reported.

This analysis will be repeated in the subset of patients that achieve ≥3-point increase from baseline in HFMSE and separately in the subset of patients that achieve a <3-point increase from baseline in HFMSE, defined as follows:

- AVXS-101 treated patients with a weighted mean change from baseline in HFMSE total score of ≥3 points considering all available post-baseline visits through Month 12
- AVXS-101 treated patients with a weighted mean change from baseline in HFMSE total score of <3 points considering all available post-baseline visits through Month 12
- PNCR patients with a weighted mean change from baseline in HFMSE total score of ≥3 points considering all available HFMSE scores recorded across all visits through 12 months after the patient's baseline assessment

- PNCR patients with a weighted mean change from baseline in HFMSE total score of <3 points considering all available HFMSE scores recorded across all visits through 12 months after the patient's baseline assessment

The summary and statistical analysis will be conducted using the ITT Set and repeated for the ECAS, in the event the ECAS contains a subset of patients of the ITT Set, using both the Primary PNCR and Sensitivity PNCR groups.

8.4.3. Change from Baseline in HFMSE across all available assessments (Months 1-6 vs. Months 7-12) among patients ≥ 24 months and < 60 months of age at time of dosing

The weighted mean change from baseline in HFMSE total score considering all post-baseline visits from Months 1 through 6 and separately considering all post-baseline visits from Months 7 through 12 will be summarized for patients overall and by dose. All change from baseline HFMSE scores available across all post-baseline visits during the first 6 months of the trial (Months 1-6) will be averaged together for one measure, and all change from baseline HFMSE scores available across all post-baseline visits during the last 6 months of the trial (Months 7-12) will be averaged together for the second measure. The number of available post-baseline HFMSE scores available for each patient within each window (Months 1-6, Months 7-12) will be used as the weight for this calculation.

The difference between scores (Months 1-6 vs. Months 7-12) will be analyzed using an ANCOVA model which will include the weighted mean change from baseline HFMSE score as the dependent variable, time period (Months 1-6, Months 7-12), and baseline HFMSE score and age at baseline as covariates. The unadjusted means, LS means, differences between LS means, a 95% 2-sided CIs for each difference and the p-values from model effects will be reported.

This analysis will be repeated in the subset of subset of patients that achieve a ≥3-point increase from baseline in HFMSE (Months 1-6 vs. Months 7-12) and separately in the subset of subset of patients that achieve a <3-point increase from baseline in HFMSE (Months 1-6 vs. Months 7-12), defined as follows:

- AVXS-101 treated patients with a weighted mean change from baseline in HFMSE total score of ≥3 points considering all post-baseline visits from Months 1 through 6
- AVXS-101 treated patients with a weighted mean change from baseline in HFMSE total score of <3 points considering all post-baseline visits from Months 1 through 6
- AVXS-101 treated patients with a weighted mean change from baseline in HFMSE total score of ≥3 points considering all post-baseline visits from Months 7 through 12
- AVXS-101 treated patients with a weighted mean change from baseline in HFMSE total score of <3 points considering all post-baseline visits from Months 7 through 12

The summary and statistical analysis will be conducted using the ITT Set and repeated for the ECAS, in the event the ECAS contains a subset of patients of the ITT Set.

9. ANALYSIS OF PHARMACOKINETICS

Not applicable for this SAP.

10. ANALYSIS OF PHARMACODYNAMICS

Not applicable for this SAP.

11. SAFETY

The population used for safety analyses will be the SS. Safety will be assessed on the basis of AEs, clinical laboratory data, physical examinations, non-invasive ventilatory support use, vital signs and related exams. All safety analyses will be summarized overall and by actual dose received and age group. Safety data will not be compared with the PNCR natural history cohort as AE data, study product exposure, laboratory assessments, vital sign, ECG, 12-lead Holter monitor, physical examination, echocardiogram, pulmonary exam, ventilatory support and viral shedding were not collected in a comparable manner during the natural history study.

11.1. Extent of Exposure

The planned volume to be administered, total volume administered, duration of injection and post-injection procedure of the patients' injection of study product on the dosing date will be summarized overall and by actual dose received and age group for all patients.

Planned volume to be administered is calculated as follows: [(Cohort-specific dose for patient) ÷ (titer associated with lot number of actual administered dose)], where:

- The dose administered in Cohort 1 is 6.0 x 10^{13} vg (Dose A)
- The dose administered in Cohort 2 is 1.2 x 10^{14} vg (Dose B)
- The dose administered in Cohort 3 is 2.4 x 10^{14} vg (Dose C)

Duration of injection is calculated as (injection stop time – injection start time) and is expressed in seconds. If a patient's injection start time = injection stop time, then the duration of injection will be set as 60 seconds. If a patient's injection start time or stop time is missing, then the duration of injection will not be calculated.

A listing of injections of AVXS-101 will be provided.

11.2. Treatment Compliance

The treatment compliance of each patient will calculated as:

Percentage of compliance (%) = 100 * (total volume administered – 1.5 mL contrast) / (planned volume administered)

Treatment compliance will be summarized by dose and by age group.

11.3. Adverse Events / Adverse Drug Reactions

11.3.1. Adverse Events / Adverse Drug Reactions

Adverse events will be coded using MedDRA. TEAEs are defined as any event that begins or worsens in severity after the first injection of study product through the last study visit. If an incomplete or missing onset date was collected for an AE, the imputation method of missing data specified in Section 6.3 will be applied. The AE will be defined as TEAE if its imputed onset date is after the date and time of injection of study product through last study visit.

The Common Terminology Criteria for Adverse Event (CTCAE) version 4.03 will be applied for determining the severity of each AE. The classifications of CTCAE 4.03 are outlined in Table 6.

Table 6: Adverse Event Classification

Grade	Classification
1	Mild adverse event; did not require treatment
2	Moderate adverse event; resolved with treatment
3	Severe adverse event; inability to carry on normal activities; required professional medical attention
4	Life-threatening or permanently disabling adverse event
5	Fatal adverse event

The relationship to study treatment for each AE will be classified as 'Unrelated', 'Possibly Related', 'Probably Related', or 'Definitely Related'. AEs classified as 'Possibly', 'Probably' or 'Definitely' related will be analyzed as 'Related' in the AE summaries. Data listings, patient narratives, etc. will present the relationship to study treatment as collected on the CRF.

11.3.2. Tabulations of Treatment-Emergent Adverse Events

Adverse event data will be summarized and presented using primary MedDRA SOCs and 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 SOCs will be presented in alphabetical order and the PTs will be presented in alphabetical order within each SOC.

Adverse events will be presented overall and by actual dose received and age group.

11.3.2.1. Adverse Event Overview

An overview of AEs will be presented by the actual treatment received overall and by dose and age group consisting of the number and percentage of patients experiencing at least one event for the following AE categories:

- Any TEAEs
- TEAEs related to study treatment
- TEAEs of Grade III (severe) severity or higher
- Serious TEAEs
- Serious TEAEs related to study treatment
- TEAEs leading to discontinuation of patient from study
- TEAEs leading to death

11.3.2.2. Adverse Events by SOC and PT

The following summaries of AEs will be generated:

- Incidence of TEAEs

- Incidence of TEAEs related to study treatment
- Incidence of serious TEAEs
- Incidence of serious TEAEs related to study treatment
- Incidence of TEAEs in Grade 2 (moderate) or Grade 3 (severe) severity
- Incidence of TEAEs in Grade 3 (severe) severity
- Incidence of TEAEs in Grade 3 (severe) or Grade 4 (life-threatening) severity
- Incidence of TEAEs leading to discontinuation of patient from study
- Incidence of TEAEs leading to death
- Incidence of TEAEs related to study treatment and leading to death
- Incidence of TEAEs leading to concomitant medication use
- Incidence of non-serious TEAEs

For all AE summaries, the number and percentage of patients experiencing TEAEs will be tabulated according to SOC and PT for each actual drug/product received. Patients reporting more than one AE 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), although each event will be counted individually. Patients reporting more than one AE within an SOC at a study period will be counted only once for that SOC.

A listing by dose of TEAEs grouped by SOC and PT with patient numbers will be created.

11.3.2.3. Adverse Events by PT

The number and percentage of patients experiencing TEAEs will be tabulated according to PT and sorted by overall frequency. Similar summaries will be provided for Grade 3 and Grade 4 TEAEs and TEAEs related to study drug/product.

11.3.2.4. Adverse Events of Special Interest

The following specific TEAEs of special interest, which are primarily defined by using Standardized MedDRA queries (SMQ), will be summarized:

- Hepatotoxicity, identified via the following SMQ:
  - Hepatic disorders (SMQ)
- Thrombocytopenia, identified via the following CMQ:
  - Transient thrombocytopenia (CMQ)
- Cardiac events, identified via the following SMQs:
  - Ischemic heart disease (SMQ)
  - Cardiomyopathy (SMQ)
  - Cardiac arrhythmias (SMQ)

- Embolic and thrombotic events (SMQ)
- Myocardial infarction (SMQ)

- Thrombotic microangiopathy, identified via the following approach:
  - Criteria #1: cases with **any one** of the following PTs: thrombotic microangiopathy **OR** haemolytic uraemic syndrome **OR** atypical haemolytic uraemic syndrome
  - Criteria #2: cases with **at least one PT** from **EACH** of the following SMQs representing thrombocytopenia, hemolysis and relevant renal events respectively:
    - Haematopoietic thrombocytopenia (SMQ)
    - Haemolytic disorders (SMQ)
    - Acute renal failure (SMQ) **OR** Renovascular disorders (SMQ)
- Sensory abnormalities suggestive of ganglionitis, identified via the following CMQ:
  - DRG Cell Inflammation (CMQ)

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 and by actual dose received and age group. AEs of interest will be summarized by SOC and PT overall, by actual dose received, and age group.

11.3.2.5. Adverse Events by Maximum Severity

Treatment-emergent adverse events will be summarized by maximum CTCAE grade of each PT. Each PT will be assigned to a grade level, as assessed by the investigator, based on the CTCAE version 4.03 for grading severity of AEs. If a patient has an AE with an 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.

11.3.2.6. Adverse Events by Maximum Relationship

Treatment-emergent adverse events will be summarized by maximum relationship of each PT to study product (AVXS-101), as assessed by the investigator. Events with an assessment of 'Possibly Related', 'Probably Related' or 'Definitely Related', will be summarized as 'Related' in the table. Events with an assessment of 'Unrelated' will be summarized as 'Unrelated' in the table. If a patient has more than one occurrence of the same event, and one is 'related' and the other is 'unrelated', then the 'related' event is considered to be the one having the maximum relationship to study drug. If a patient has an AE with unknown relationship, then the patient will be counted in the relationship category of "unknown". The only exception is if the patient has another occurrence of the same AE with a relationship present. In this case, the patient will be counted under the maximum relationship category.

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

11.4. Laboratory Evaluations

11.4.1. Variables and Criteria Defining Abnormality

Hematology variables include: Hematocrit, Hemoglobin, Red Blood Cells, White Blood Cells, Platelets, Neutrophils, Lymphocytes, Monocytes, Basophils, and Eosinophils.

Clinical Chemistry variables include: AST, ALT, Gamma glutamyl transferase (GGT), Alkaline phosphatase, Total creatinine kinase, Direct bilirubin, Serum total bilirubin, Glucose, Electrolytes (Sodium, Potassium, Chloride, CO_2), Albumin, Creatinine, BUN, CK-MB, and Troponin I.

Coagulation variables include: Prothrombin time, Partial prothrombin time, and International normalized ratio

Urinalysis variables include: Color, Clarity/turbidity, pH, Specific gravity, Glucose, Ketones, Nitrites, Leukocyte esterase, Bilirubin, Blood, Protein, Red blood cells, White blood cells, Squamous epithelial cells, Casts, Crystals, Bacteria, Yeast

Virus Serology variables include: Human immunodeficiency virus, Hepatitis B, Hepatitis C, and Zika virus

Capillary Blood Gas variables include: pH, pCO_2, pO_2, TCO_2

Immunology variables include: Serum antibody to AAV9 (Anti-AAV9), Serum antibody to SMN (Anti-SMN Ab), and Interferon Gamma (IFN-γ) ELISpot measurement of T-cell response to AAV9 and SMN.

The Criteria for Potentially Clinically Significant (PCS) values are generally based upon CTCAE version 4.03 criteria for Grade 2 or higher AEs. Age-related differences in normal ranges of some analytes in pediatric (vs adult) populations were taken into account in defining PCS Values.

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

11.4.2. Statistical Methods

Clinical laboratory tests at each scheduled visit will be summarized overall and by actual dose received and age group. The baseline value will be the last measurement on or before the day of the injection of study product. Mean changes from baseline to each post-baseline visit will be summarized for each protocol-specified hematology, clinical chemistry, coagulation, and capillary blood gas laboratory parameter with the baseline mean, visit mean, change from baseline mean, standard deviation, minimum, maximum, and median.

Immunology and virus serology data will be summarized using descriptive statistics appropriate for categorical variables (i.e. number and percentage of patients with each reported result at each visit). Urinalysis data will only be presented in listings.

Chemistry, hematology, and coagulation 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 treatment values 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 meeting the specified criteria for PCS laboratory values will be summarized overall and by actual dose received and age group. A post-baseline value must be more extreme than the baseline value to be considered a PCS finding. A listing will be provided to present the entire set of lab values for a patient for the parameter meeting PCS criteria during treatment.

For hemoglobin and the liver function enzyme (LFE) tests of ALT, AST, and alkaline phosphatase, the number and percentage of patients in each age/dose 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 study will be summarized. All LFE 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 a Grade 3 laboratory abnormality. Accompanying listings of all ALT, AST, total serum bilirubin, direct bilirubin, and alkaline phosphatase will be created for any patients who had at least a Grade 3 ALT, AST, or alkaline phosphatase value. A listing of hematology results will be provided for patients with hemoglobin abnormalities.

The number and percentage of patients meeting the following criteria will be summarized overall and by dose and age group:

- ALT >3x ULN, ALT >5x ULN, ALT >10x ULN, ALT >20x ULN
- AST >3x ULN, AST >5x ULN, AST >10x ULN, AST >20x ULN
- ALT or AST >3x ULN, ALT or AST >5x ULN, ALT or AST >8x ULN, ALT or AST >10x ULN, ALT or AST >20x ULN
- Total bilirubin >2x ULN, Total bilirubin >3x ULN
- ALT or AST >3x ULN and Total bilirubin >2x ULN
- ALT or AST >3x ULN and Total bilirubin >2x ULN and Alkaline phosphatase ≥2x ULN
- ALT or AST >3x ULN and Total bilirubin >2x ULN and Alkaline phosphatase <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 the last three combination categories, the values do not need to have been collected at the same assessment. 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.

11.4.3. 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), the 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 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 ALT 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 study patients showing such AT elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum Total Bilirubin (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.

A listing of patients meeting the ALT >=3xULN and TBL >=2xULN will be produced.

For patients enrolled in this study these criteria will be assessed in order to determine both general LFE changes according to change from baseline and over course of study. In addition, changes in ALT or AST relative to Total Bilirubin will be assessed to determine whether a signal related to DILI has occurred in any individual or group of patients.

11.5. Vital Signs

Vital signs will include blood pressure, respiratory rate, pulse, heart rate, pulse oximetry and axillary temperature. Body weight and length and/or height will also be collected.

Vital signs will be examined at each scheduled visit and time point. The baseline value will be the last measurement before date and time of the injection of study drug. Mean changes from baseline to each post-baseline visit and time point will be summarized with the baseline mean, visit/time point mean, change from baseline mean, standard deviation, minimum, maximum, and median. Summaries will be presented overall and by actual dose received and age group.

In addition, vital signs results will be flagged as PCS if they meet the pre-specified criteria which are defined outside of this SAP. The number and percent of patients meeting each PCS criterion at each scheduled visit and time point will be summarized overall and by actual dose received and age group. For body weight, the PCS criteria are based on percentile weights for age and sex as defined by the World Health Organization Child Growth Standards. These definitions extend

through 60 months of age. If a patient is >60 months of age at the time of their weight assessment, they will not be assessed for PCS weight values.

11.6. ECG

A 12-lead ECG will be conducted at scheduled visits of Screening/Baseline, Day 1, Day 2, Day 3, Month 3, Month 6, Month 9, and Month 12 (or Early Termination), and assessed by a central reviewer. The baseline value will be the last measurement on or before the day of injection of study drug. 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 as measured by the central reviewer.

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 and by actual dose received and age group.

11.7. 12-Lead Holter Monitor

Patients will have a 12-lead continuous Holter monitor attached 24 hours prior to dose administration on Day -1 and the Holter will remain in place through 48 hours post-dose (Day 3). Serial ECG data from Holter monitor will be pulled in triplicate 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 and by dose and age group.

Twenty-four-hour Holter monitoring will also be performed as per the Schedule of Assessments.

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'.

11.8. Physical Examination

Shift tables summarizing the shift of physical examination results ('Normal', 'Abnormal Not Clinically Significant', 'Abnormal Clinically Significant') in head, eyes, ears, nose and throat, lungs/thorax, cardiovascular, abdomen, musculoskeletal, neurologic, dermatologic, lymphatic, and genitourinary 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.

11.9. 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.

Pulmonary exam results will be presented in a listing.

11.10. 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.

Additionally, echocardiogram data will be provided to an external cardiologist for centralized review; this will be considered the primary echocardiogram source data.

Clinically significant, treatment-emergent findings 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.

11.11. 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 and by dose and age group using descriptive statistics. Ventilatory support data will not be compared with the PNCR natural history cohort as that data was not collected and is not available for comparison.

11.12. 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 dose.

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. Vector shedding data will not be compared with the PNCR natural history cohort as that data was not collected and is not available for comparison.

11.13. Values of Clinical Concern

Not applicable for this SAP.

12. HEALTH ECONOMICS

Not applicable for this SAP.

13. INTERIM SAFETY REVIEWS

Up to three (3) safety reviews by the DSMB will be conducted. The DSMB will review the safety data extract from the database. The safety analysis specified in this SAP is not planned for the DSMB.

The first DSMB interim safety review will take place after three (3) participants in Cohort 1 have been dosed. The consideration for this review is terminating the study for safety. In the absence of a termination recommendation, a recommendation to escalate enrollment to the higher dose is made.

The second DSMB interim safety review will take place after three (3) participants in Cohort 2 have been dosed (6 total dosed). The consideration for this review is terminating enrollment in Cohort 2 due to safety concerns. In the absence of a termination recommendation, a recommendation to expand the current Cohort 2 is made.

The third DSMB interim safety review may take place after three (3) patients have been enrolled in Cohort 3. The consideration for this review is terminating enrollment in Cohort 3 due to safety concerns. In the absence of a termination recommendation, a recommendation to expand the current Cohort 3 is made.

14. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

15. REFERENCE LIST

Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 4.03, DCTD, NCI, NIH, DHHS (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm), Publish Date: Jun 14, 2010.

Kaufman et al; Prospective cohort study of spinal muscular atrophy types 2 and 3; Neurology. 2012 Oct 30; 79(18): 1889–1897.

Mercuri E., Finkel R., Montes J., et al. Patterns of disease progression in type 2 and 3 SMA: Implications for clinical trials. Neuromuscular Disorders 2016 FEB; 26(2) 126-131.

Prior TW, Krainer AR, Yimin H, Swoboda KJ, Snyder PC, et al. A Positive Modifier of Spinal Muscular Atrophy in the SMN2 Gene. American Journal of Human Genetics 2009; 85, 408-413.

16. PROGRAMMING CONSIDERATIONS

See TLF Documentation for Details.

17. QUALITY CONTROL

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. The CRO's SOPs provide an overview of the development of such SAS programs.

The CRO's SOPs describe the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

For all data sets, tables and listings generated by SAS, the CRO will create SAS codes independently, and then use SAS PROC COMPARE procedure to perform 100% electronic comparison for all numerical and character values. In addition, the Lead Biostatistician, Lead Programmer and Senior Statistical Reviewer will review all Tables, Listings, and Figures (TLFs) for consistency and accuracy.

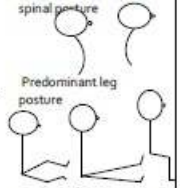
Deliveries of datasets, SAS programs, and output from the CRO to AveXis will occur via a secure file transfer platform.

18. MOCK-UPS

Refer to TLF Mock-ups which are maintained in a separate document.

19. APPENDICES

19.1. Hammersmith Functional Motor Scale - Expanded

Smartnet & PNCR	Hammersmith Functional Motor Scale for SMA (HFMS)						07/03/09
Name			DOB				
Date of assessment			Time taken to complete				
Date of spinal surgery			Evaluator				
Please circle highest current level of independent mobility							LBC = Limited by contracture
None Rolls Bottom shuffles creeps /crawls Walks with crutches / frame /rollator Walks with KAFO's / AFO's Independent walking							
Comment.....							
Test	***Instruction***	**2**	**1**	**0**	**L B C**	**S =**	**Comments** **S = score**
1 Plinth /chair sitting Can be over edge of plinth or on plinth / floor. Record best you see	*Can you sit on the plinth /chair without using your hands for support for a count of 3?(Back unsupported /feet +/- support)*	Able to sit using no hand support for a count of 3 or more	Needs one hand support to maintain balance for a count of 3	Needs two hand support to maintain balance Unable to sit			**Item 1** Predominant spinal posture  Predominant leg posture Circle predominant spinal posture and leg position
2 Long sitting Legs straight = knees maybe flexed, knee caps pointing upwards, ankles <10cm apart	*Can you sit on the floor/plinth without using your hands for support and with your legs straight for a count of 3?*	Able to sit on floor/plinth with legs straight without hand support for a count of 3	Able to sit on floor/plinth with legs straight propping with one hand support for a count of 3	Able to long sit using two hands for a count of 3 Or unable to sit with straight legs			
3 One hand to head in sitting Hand touch head above level of ears	*Can you get one hand to your head without bending your neck*	Able to bring one hand to head. Head and trunk remain stable	Can only bring hand to head by flexing head	Unable to bring hand to head even using head and trunk movement			R / L
4 Two hands to head in sitting Hands touch head above level of ear	*Can you lift both hands up at the same time, to your head, without bending your neck?*	Able to place both hands on head arms free from side. Head and trunk remain stable	Able to place hands on head but only using head flexion or side tilt or crawling hands up or one at a time	Unable to place both hands on head			
5 Supine to side-lying	*Can you roll onto your side in both directions? Try not to use your hands*	Able to ½ roll from supine both ways	Can ½ roll only one way R / L	Unable to half roll either way			Shoulders perpendicular to floor. Trunk and hips in line with body
6 Rolls prone to supine over R	*Can you roll from your tummy to your back in both directions?*	Turns to supine with free arms to the right	Turns to supine using arms to push/ pull with	Unable to turn into supine			
7 Rolls prone to supine over L		Turns into supine with free arms to the left	Turns to supine using arms to push/ pull with	Unable to turn into supine			
8 Rolls supine to prone over R	*Can you roll from your back to your front in both directions?*	Turns to prone with free arms to the right	Turns to prone by pulling/ pushing on arms	Unable to turn into prone			
9 Rolls supine to prone over L		Turns to prone with free arms to the left	Turns to prone by pulling/ pushing on arms	Unable to turn into prone			
10 Sitting to lying	*Can you lie down in a controlled way from sitting?*	Able to lie down in a controlled fashion through side lying or using clothes	Able to lie down by flopping forwards and rolling sideways	Unable or falls over			
11 Props on forearms	*Can you prop yourself on your forearms and hold for a count of 3?*	Able to achieve prop on elbows with head up for a count of 3	Holds position when placed for a count of 3	Unable			
12 Lifts head from prone	*Can you lift you head up keeping your arms by your side for a count of 3?*	Able to lift head up in prone arms by side for a count of 3	Lift head with arms in a forward position for a count of 3	Unable			
13 Prop on extended arms	*Can you prop yourself up with straight arms for a count of 3?*	Able to prop on extended arms, head up for a count of 3	Can prop on extended arms if placed for a count of 3	Unable			
14 Lying to sitting	*Can you get from lying to sitting without rolling to your tummy?*	Able by using side lying	Turns into prone or towards floor	Unable			
15 Four-point kneeling	*Can you get onto your hands and knees with your head up and hold for a count of 3?*	Achieves four-point kneeling – head up for a count of 3	Holds position when placed for a count of 3	Unable			

Test	*Instruction*	2	1	0	L B C	S =	Comments S = score
16 Crawling	*Can you crawl forwards?*	Able to crawl forwards – moves all four points twice or more	Moves all four points only once	Unable			
17 Lifts head from supine	*Can you lift your head to look at your toes keeping your arms folded for a count of 3*	In supine, head must be lifted in mid-line. Chin moves towards chest. Held for a count of 3	Head is lifted but through side flexion or with no neck flexion Held for a count of 3	Unable			
18 Supported standing	*Can you stand using one hand for support for a count of 3?*	Can stand using one hand support for a count of 3	Able to stand with minimal trunk support (not hip) for a count of 3	Can stand with hand support but needs knee/hip support in addition for a count of 3 Or unable			
19 Stand unsupported	*Can you stand without holding onto anything for a count of 3?*	Can stand independently for the more than a count of 3	Stands independently for a count of 3	Stands only momentarily (less than a count of 3) Or unable			
20 Stepping	*Can you walk without using any help or aids? Show me*	Able to take more than 4 steps unaided	Able to take 2 – 4 steps unaided	Unable			
SCORE		**No of 2's =**	**No of 1's =**	**No of 0's =**	**TOTAL =**		**/40**
Comments							

PNCR	Expanded Hammersmith Functional Motor Scale for SMA (HFMSE) *add-on module*						07/03/09
Test	*Instruction*	2	1	0	L B C	S =	Comments S = score
21 Right hip flexion in supine	*Can you bring your right knee to your chest?*	Full hip flexion achieved	Initiates right hip and knee flexion (more than 10% of available range of motion)	Unable			
22 Left hip flexion in supine	*Can you bring your left knee to your chest?*	Full hip flexion achieved	Initiates left hip and knee flexion (more than 10% of available range of motion)	Unable			
23 High kneeling to right half kneel	*Can you bring your **left** leg up so that your foot is flat on the ground without using your arms and hold for a count of 10?*	Arms used for transition, maintains arms free in half kneel for a count of 10	Maintains half kneel with arm support for a count of 10	Unable			
24 High kneeling to left half kneel	*Can you bring your **right** leg up so that your foot is flat on the ground without using your arms and hold for a count of 10?*	Arms used for transition, maintains arms free in half kneel for a count of 10	Maintains half kneel with arm support for a count of 10	Unable			
25 High kneeling to stand leading with left leg	*Can you stand up from this position starting with your left leg without using your hands? May need demonstration*	Able with arms free	Able to shift weight off both knees (with or without arm support)	Unable			
26 High keeling to stand leading with right leg	*Can you stand up from this position starting with your right leg without using your hands? May need demonstration*	Able with arms free	Able to shift weight off both knees (with or without arm support)	Unable			
27Stand to sit	*Can you sit on the floor, in a controlled way? Try not to use your arms.*	Able to sit down with arms free and no collapse	Sits on floor but uses arms or crashes	Unable			
28Squat	*Can you squat? Pretend you are going to sit in a very low seat.*	Squats with arms free (at least 90° of hip and knee flexion)	Initiates squat (more than 10%) , uses arm support	Unable to initiate			
29 Jump 12" forward	*Can you jump as far as you can, with both feet, from this line all of the way to the other line?*	Jumps at least 12", both feet simultaneously	Jumps between 2-11", both feet simultaneously	Unable to initiate jump with both feet simultaneously			
30 Ascends stairs with rail	*Can you walk up the steps? You can use one railing*	Ascends 4 stairs with railing, alternating feet	Ascends 2-4 stairs, one rail, any pattern	Unable to ascend 2 stairs one rail			
31 Descends stairs with rail	*Can you walk down the steps? You can use one railing*	Descends four stairs , with railing, alternating feet	Descends 2-4 stairs, one rail, any pattern	Unable to descend 2 stairs with one rail			
32 Ascends stairs without rail	*Can you walk up the steps? This time try not to use the railing*	Ascends four stairs, arms free, alternating feet	Ascends 2-4 stairs, arms free, any pattern	Unable to ascend 2 stairs arms free			
33 Descends stairs without rail	*Can you walk down the steps? This time try not to use the railing*	Descends four stairs, arms free, alternating feet	Descends 2-4 stairs, arms free, any pattern	Unable to descend 2 stairs arms free			
SCORE		No of 2's =	No of 1's =	No of 0's =			TOTAL = /66

19.2. Schedule of Assessments

Table 3: Schedule of Assessments[1]

Study Interval	Baseline Screening	Vector (AVXS-101) Injection (Inpatient)			Follow-up (Outpatient)									Notes
Study Day	-60 to -2	-1	1	2-3	7	14	21	30	44	60	72	Monthly Through M12[1]	M15/ EOS	
Window					± 2							± 7		
Informed Consent	X													
Spinal X-ray	X													
Demographics/ Medical History	X		X	(X)	X	X	X	X		X		X	X	Medical history collected at baseline; review of systems conducted at each study visit. (X): Patients to remain inpatient 48 hours post-dose for observation and AE monitoring.
Physical Exam	(X)		X	X	X	X	X	X		X		X	X	Includes measuring head circumference. (X): Baseline procedure must be completed within 30 days of dosing.
Vitals/Weight/ Length/Height	(X)		X	X	X	X	X	X		X		X	X	Vital signs will include BP, respiratory rate, pulse, and axillary temperature. Vitals including BP, respiratory rate, pulse axillary temperature, pulse oximetry and HR will be monitored and recorded every 15 minutes (± 5 minutes) from dosing for four hours and every hour (± 15 minutes) for 24 hours following the AVXS-101 dosing procedure. (X): Baseline procedure must be completed within 30 days of dosing.
Pulse Oximetry	(X)		X	X	X	X	X	X		X		X	X	(X): Baseline procedure must be completed within 30 days of dosing.
Pulmonary Exam	(X)							X		X		X	X	

[1] Patients who reached the Month 12 visit prior to Protocol Amendment 7 had their EOS assessments conducted at Month 12.

Study Interval	Baseline Screening	Vector (AVXS-101) Injection (Inpatient)			Follow-up (Outpatient)									Notes
Study Day	-60 to -2	-1	1	2-3	7	14	21	30	44	60	72	Monthly Through M12[1]	M15/ EOS	
Window					± 2							± 7		
12-Lead ECG	X		X	X								(X)	X	Irrespective of study schedule, after signing the updated informed consent, all patients enrolled prior to the Amendment 5 version of the protocol should have ECG, 24-hour Holter monitoring, and echocardiogram done at the next scheduled visit and then in conformity with the study SoA. (X): Months 3, 6, 9, and 12 visits.
12-Lead Holter Monitor	X	X	X	X				X		(X)		(X)	X	ECGs extracted from Holter by central reader in triplicate at the following time points: pre-dose, 2h, 4h, 6h, 8h, 12h, 24h, 36h, and 48h during the patient's inpatient stay. (X): Months 2, 3, 6, 9, and 12 visits.
Echocardiogram	X											(X)	X	Irrespective of study schedule, after signing the updated informed consent, all patients enrolled prior to the Amendment 5 version of the protocol should have echocardiogram done at the next scheduled visit and then in conformity with the study SoA. (X): Months 3, 6, 9, and 12 visits.
Capillary Blood Gas		X		(X)										(X): Laboratory samples collected on Day 2.
HFMS- Expanded (with video)	(X)							X				X	X	Will be conducted for patients ≥ 24 months of age; patients < 24 months of age at study entry will begin HFMS-E at such time that 24 months of age is reached. (X): Baseline procedure must be completed within 30 days of dosing.
Bayley III (with video)	(X)							X		X		X	X	Gross and fine motor sections will be performed at screening and monthly through 15 months. (X): Baseline procedure must be completed within 30 days of dosing.

Study Interval	Baseline Screening	Vector (AVXS-101) Injection (Inpatient)			Follow-up (Outpatient)									Notes
Study Day	-60 to -2	-1	1	2-3	7	14	21	30	44	60	72	Monthly Through M12[1]	M15/ EOS	
Window					± 2							± 7		
Motor Milestone Development Survey (with video)	(X)							X		X		X	X	
Hematology / Chemistry	(X)	(X)*		(X)$	X	X	X	X	(X)†	X	(X)†	X	X	(X): Baseline procedure must be completed within 30 days of dosing. (X)*: Laboratory samples collected prior to dosing are to be processed locally. (X)$: Laboratory samples collected on Day 2. (X)† Liver function test (AST, ALT, total bilirubin, alkaline phosphatase, GGT) only.
Coagulation	(X)	(X)*		(X)$	X	X	X	X		X		X	X	
Urinalysis	(X)	(X)*		(X)$	X	X	X	X		X		X	X	
CK-MB	X				X			X		X		(X)	X	Troponin I will be measured instead of CK-MB in new patients who are screened and enrolled after amendment 5 (protocol version 6.0) goes into effect. Participants who have been screened and enrolled but who have not yet received gene replacement therapy (visit #2) at the time that amendment 5 (protocol version 6.0) goes into effect will have baseline troponin I testing prior to treatment with AVXS-101, and will have troponin I testing in place of CK-MB. CK-MB will be collected from all other participants. (X): Months 2, 6, 9, and 12 visits.
Troponin I	X				X			X		X		(X)	X	
Virus Serology	(X)													(X): Baseline procedure must be completed within 30 days of dosing.
Blood for diagnostic confirmation testing	X													To be performed by central laboratory.

Study Interval	Baseline Screening	Vector (AVXS-101) Injection (Inpatient)			Follow-up (Outpatient)									
Study Day	-60 to -2	-1	1	2-3	7	14	21	30	44	60	72	Monthly Through M12[1]	M15/ EOS	
Window					± 2							± 7		Notes
Saliva, Urine, and Stool Samples (for viral shedding)		X		(X)	(X)	(X)		(X)						(X): Sites participating in the viral shedding sub-study will collect 24-hour full volume samples for urine and feces through 24 and 48 hours. All other sites will collect singular urine and feces samples within 24 hours and 48 hours of dosing. Full urine and feces samples will be collected for patients ≥ 48 months who are no longer in diapers.
Baseline Screening of Biological Mother (Anti-AAV9 Ab)	(X)													Serum sample collected at screening for anti-AAV9 antibodies. (X): Baseline procedure must be completed within 30 days of dosing. (X)*: Additional sampling may be performed at subsequent time points if ELISpot value(s) continue to be elevated, based on further discussion with the PI and Medical Monitor.
Immunology Labs (Anti-AAV9/SMN)	(X)				X	X	X	(X)						
Immunology Labs (IFN-γ T-cells)					X	X	X	(X)						(X): Additional sampling may be performed at subsequent time points if ELISpot value(s) continue to be elevated, based on further discussion with the PI and Medical Monitor.
Prophylactic Prednisolone		X	X	X	X	X	X	X	X	X	X			See Section 9.2.1. Daily dosing from 24 hours prior to scheduled AVXS-101 dose and continued as per protocol.
Study Product Administration with fluoroscopic / radiographic guidance			X											
Photograph Injection Site			X		X	X	X	X						
Adverse Events	X	X	X	X	X	X	X	X		X		X	X	

Study Interval	Baseline Screening	Vector (AVXS-101) Injection (Inpatient)			Follow-up (Outpatient)									
Study Day	-60 to -2	-1	1	2-3	7	14	21	30	44	60	72	Monthly Through M12[1]	M15/ EOS	
Window					± 2							± 7		Notes
Prior and Concomitant Medications	*To be collected from 2 weeks before study dosing until final study visit*													

AE = adverse event, ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK-MB = Creatinine kinase-MB (isozyme MB); ECG = electrocardiogram; ELISpot = enzyme-linked ImmunoSpot; GGT = gamma glutamyl transferase; IFN-γ = interferon gamma; PI = Principal Investigator; SoA = Schedule of Assessments;

19.3. 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.

Protocol Amendments 5 and 6 introduced the potential for patients to be dosed with Dose C. The addition of Dose C to the study meant that the previous wording used throughout the SAP of

"AVXS-101 at the optimal dose" was no longer relevant. This wording has been removed throughout and, in its place, clarifying text has been added to document the plan for comparing both Dose B and Dose C (separately) to PNCR database, as well as comparing Dose B and Dose C combined to the PNCR database.

The approval signature page was updated to remove [redacted] as Clinical Operations signatory and to add [redacted] as Clinical Operations signatory.

Section 2.1 was updated to remove [redacted] as the responsible CRO for statistical and programming support.

Section 2.2.1 was updated to detail when the primary analyses for efficacy and safety would be conducted; and to detail that an additional analysis of efficacy and safety data would be conducted once the last Cohort 2 patient has completed the 12 month visit.

Section 3.5 was updated to include details regarding Dose C, including the additional clinic visits for Dose C patients on Days 44 and 72.

Section 3.7 was updated to include details regarding Dose C.

Section 3.10 was updated to reflect an updated version of the study flowchart (Figure 1). The schedule of study assessments was moved to Appendix 22.3.

Section 4.8.1.3 was updated to include measurement of head circumference.

Section 4.8.1.4 was updated to reflect the timepoints for ECG assessment.

Section 4.8.1.5 was updated to reflect the timepoints for echocardiogram assessment.

Section 4.8.1.6 was added to provide the details of 24-hour Holter monitoring.

Section 5 was updated to expand the definition of the Enrolled Set to be based on patients who received an injection of AVXS-101.

Section 5.4.2 was added to document the definition of the Per Protocol Analysis Set.

Section 5.5 was updated to clarify the PNCR control group for the older patient cohort consisted of 15 patients, not 12 patients; to clarify that the PNCR control group for the younger cohort may have demonstrated the milestones of interest at any point, not at or before turning 36 months of age; to include the sensitivity analysis for the older patient cohort using a different group of 15 PNCR patients.

Section 6.1 was updated to state that no adjustments for multiple comparisons would be made.

Section 6.5 was updated to define the visit windows for Cohort 3 patients, and to include rules for remapping of efficacy data for PNCR patients which have data missing at the Baseline visit.

Section 7.1 was updated to include a summary table for patients who discontinued due to AE, and to clarify that a listing of major protocol deviations would be produced; to indicate that the number (%) of patients in the PP Set would be summarized.

Section 7.2 was updated to clarify which demographic characteristics would be summarized for the PNCR populations.

Section 7.3 was updated to indicate the table of SMA medical history should be based on the FAS.

Section 7.4.2 was updated to include a listing of AEs for patients who did not follow the protocol-prescribed taper for prednisolone.

Section 8.1.1 was updated to remove the sample SAS code; to clarify that patients in the PNCR group who achieved the milestone at either the Baseline visit or at a post-Baseline visit within 12 months of Baseline would be considered to have met the milestone; to indicate that the analysis of the primary endpoint will be repeated using the PP Set as a sensitivity analysis.

Section 8.1.2 was updated to remove the sample SAS code, and to include a sensitivity analysis based on the Sensitivity PNCR group; to indicate that the analysis of the primary endpoint will be repeated using the PP Set as a sensitivity analysis.

Section 8.2.1 was updated to remove the reference to sample SAS code; to include a sensitivity analysis based on the Sensitivity PNCR group; to clarify that patients in the PNCR group who achieved the milestone at either the Baseline visit or at a post-Baseline visit within 12 months of Baseline would be considered to have met the milestone.

Section 8.3.1 was updated to remove the sample SAS code; the text related to the comparison to PNCR data for this endpoint was removed as Bayley Scale scores are not available in the PNCR dataset.

Section 8.3.2 was updated to state the summary would be based on descriptive statistics only; to state that change from baseline at each visit and maximum change from baseline will be summarized.

Section 8.4 was updated to include details regarding a sensitivity analysis for patients aged ≥ 24 and < 60 months at time of dosing.

Sections 8.4.1, 8.4.2, and 8.4.3 were added to describe additional sensitivity analyses based on HFMSE.

Section 11.1 was updated to include details regarding Dose C and to include the derivation for duration of injection; text was added to state that duration of injection would not be calculated if either the start or stop time of the injection was missing.

Section 11.3.2.2 was updated to include 3 additional AE tables needed for CT.gov reporting purposes: incidence of serious TEAEs by relationship, incidence of TEAEs leading to death by relationship, incidence of non-serious TEAEs.

Section 11.3.2.4 was updated to detail the full set of AEs of special interest for the AVXS-101 program.

Section 11.4.1 was updated to include CK-MB and Troponin I as chemistry parameters assessed for this study; to remove the tables of PCS values for labs as this will be maintained outside of the SAP.

Section 11.4.2 was updated to clarify that urinalysis data would only be presented in listings; text was added to clarify that the listing of PCS laboratory values would include all of the results for only the parameter(s) meeting PCS criteria; to clarify how elevated LFTs would be summarized.

Section 11.5 (Table 11) was removed as definitions for PCS values are maintained outside of the SAP.

Section 11.6 was updated to reflect the full set of timepoints for ECG assessment; to add a statement to indicate that definitions for PCS values are maintained outside of the SAP.

Section 11.7 was updated to reflect the full set of timepoints for 24-hour Holter monitoring.

Section 11.8 was updated to include a table summarizing head circumference data.

Section 11.9 was updated to reflect the full set of timepoints for echocardiogram assessment.

Section 11.2 was updated to refer to Vector Shedding instead of Viral Shedding.

Section 13 was updated to include details regarding Cohort 3.

[redacted]

Section 16 was updated to remove [redacted] as the responsible CRO for statistical and programming support.

The section below highlights content changes represented in version 6.0 of the SAP.

Text was updated throughout the SAP to indicate that no formal statistical comparisons would be made for Dose C (alone) to PNCR, and that no summaries of data would be produced for Dose B+C combined.

Text was added throughout to define COVID-related analyses to be conducted in necessary.

Text was updated throughout to clarify that summaries of data would only be produced for the ECAS in instances where the ECAS reflects a subset of the ITT Set.

Section 5 was updated to include the definition of the Screened Set.

Section 5.5.2 was updated to clarify the definition of the PP Set.

Section 5.4.1 was updated to clarify the end of study visit could occur remotely or at the study site.

Section 7.1 was updated to include a separate listing which summarizes all protocol deviations related to COVID-19; to clarify how completed patients are defined; and to add a summary of completions within and outside of a 30-day window of the last study visit.

Sections 11.1 and 11.2 were updated to clarify the calculation of planned volume to be administered and treatment compliance. Section 11.1 was updated to state duration of injection is expressed in seconds, rather than minutes.

Section 11.3 was updated to include serious TEAEs related to study treatment in the AE overview table.

Section 11.3.2.4 was updated to reflect the updated approach to identifying AESIs.

Section 11.4.2 was updated to reflect the updated approach to identifying elevated liver function tests.

Section 11.5 was updated to clarify that for body weight, the PCS criteria are based on percentile weights for age and sex as defined by the World Health Organization Child Growth Standards.

These definitions extend through 60 months of age. If a patient is >60 months of age at the time of their weight assessment, they will not be assessed for PCS weight values.

The appendices of proposed lists of tables, listings, and figures were removed.

Appendix 22.2 (Lot Titers) was removed because this information is being maintained outside of the SAP.