AVXS-101

AVXS-101-LT-001

IND Number:	15699
Protocol Title:	A Long-term Follow-up Safety Study of Patients in the AVXS-101-CL-101 Gene Replacement Therapy Clinical Trial for Spinal Muscular Atrophy Type 1 Delivering AVXS-101
Indication Studied:	Spinal Muscular Atrophy Type 1
Sponsor Address:	AveXis, Inc. 2275 Half Day Road Bannockburn, IL 60015
Protocol Version/Date:	Amendment 2.0 / Protocol Version 3.0 / 07 May 2018

The study will be completed according to the guidelines of Good Clinical Practice. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

Confidentiality Statement

The information in this document contains trade and commercial information that is privileged or confidential and may not be disclosed unless such disclosure is required by federal or state law or regulations. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you which is indicated as privileged or confidential.

1. ADMINISTRATIVE INFORMATION

1.1. Approval

REPRESENTATIVES FROM AveXis:

This trial will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical trial protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki
- International Council for Harmonization and the Harmonized Tripartite Guideline for Good Clinical Practice E6
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations

SIGNATURES (may be applied electronically and will therefore be maintained in the electronic system):

[Name], MD [Contact] AveXis, Inc.	Date (ddMmmyyyy)
[Name], MD [Contact] AveXis, Inc.	Date (ddMmmyyyy)
[Name] Ph.D. [Contact], [Contact] AveXis, Inc.	Date (ddMmmyyyy)
[Name] [Contact], [Contact] AveXis, Inc.	Date (ddMmmyyyy)

1.2. Investigators Agreement

I have received and read the Investigator's Brochure for AVXS-101. I have read the AVXS-101-LT-001 protocol and agree to conduct the study in accordance with the relevant current protocol(s). I agree to maintain the confidentiality of all information received or developed in connection with this protocol. I agree to personally conduct or supervise the investigation(s). I also agree to promptly report to the Institutional Review Board (IRB) / Independent Ethics Committee (IEC) all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to human subjects. I agree to protect the safety, rights, privacy, and well-being of study participants. I agree to comply with:

- The ethical principles that have their origin in the Declaration of Helsinki
- International Council for Harmonization, E6 Good Clinical Practice: Consolidated Guideline
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations including but not limited to Informed Consent 21 CFR Part 56, Institutional Review Board Review in 21 CRF Part 56, Adverse Event Reporting as defined in Section 12.4 and in 21 CFR 312.64, Adequate/accurate and accessible records in accordance with 21CFR 312.62 and 312.68.
- Terms outlined in the study site agreement
- Responsibilities of the Investigator (per regulatory guidelines and applicable regulations) I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in this protocol.

Confidentiality Statement

The confidential information in this document is provided to you as a Principal Investigator or Consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

_____
Printed Name of Investigator

_____
Signature of Investigator

_____
Date (ddMmmyyyy)

1.3. Summary of Changes

See Appendix 5.

1.4. Contact Information

Table 1 Important Study Contact Information

Role in Study	Name/ Address and Telephone number
Clinical Study Leader	Please see Project Communication Plan in the Trial Master File (TMF) or Study Contact list in the Investigator Site File (ISF)
Responsible Physician	Please see Project Management Plan in TMF or Study Contact list in ISF
SAE Reporting	Please see Project Management Plan in TMF or Study Contact list in ISF
24-Hour Emergency Contact	Please see Study Contact list in ISF

Table 2 Study Vendor Listing

Role in Study	Name
Clinical Research Organization	Please see Project Management Plan in TMF
Autopsy	Regional Pathology and Autopsy Services

2. SYNOPSIS

Name of Sponsor/Company: AveXis, Inc.

Name of Investigational Product: Not applicable

Name of Active Ingredient: Not applicable

Title of Study: A Long-term Follow-up Safety Study of Patients in the AVXS-101-CL-101 Gene Replacement Therapy Clinical Trial for Spinal Muscular Atrophy Type 1 Delivering AVXS-101

Study centers: Nationwide Children's Hospital

Investigators: Jerry Mendell, MD

Studied period (years):	**Phase of development:**
Estimated date first patient enrolled: Q2 2017 Estimated date last patient completed: Q4 2033	Long-term follow-up

Objectives:

Primary:

To collect long-term follow-up safety data of patients with spinal muscular atrophy (SMA) Type 1 who were treated with AVXS-101 in the AVXS-101-CL-101 study.

Methodology:

This is a long-term, safety follow-up study of patients in the AVXS-101-CL-101 gene replacement therapy clinical trial for SMA Type 1 delivering AVXS-101. Patients will roll over from the parent study into this long-term study for continuous safety monitoring for up to 15 years. The last visit of the parent study or early discontinuation from the parent study may serve as the visit at which the informed consent form process is conducted for the AVXS-101-LT-001 long-term follow-up safety study. Patients will return annually for follow-up study visits for five (5) years, and then will be contacted via phone annually for ten (10) years. Additionally, patient record transfers from their local physician and/or neurologist will be requested in conjunction with the annual study visits and phone contacts for review by the investigator.

If the patient is unable to return to the original investigative site, the sponsor will arrange with the patients' local established physician to serve as an additional investigator to conduct the required assessments.

Number of patients (planned): Up to 15 patients.

Diagnosis and main criteria for inclusion:

Inclusion Criteria

- Patient who received AVXS-101 in the AVXS-101-CL-101 gene replacement therapy clinical trial for SMA Type 1.
- Parent/legal guardian willing and able to complete the informed consent process and comply with study procedures and visit schedule.

Exclusion Criteria

- Parent/legal guardian unable or unwilling to participate in the long-term follow-up safety study.

Investigational product, dosage and mode of administration: Not applicable
Duration of treatment: Not applicable
Reference therapy, dosage and mode of administration: Not applicable
Criteria for evaluation: **Safety Assessments:** • Medical history and record review • Physical examinations, including height, weight, vital signs, ventilation, and nutritional support • Clinical laboratory evaluations • Pulmonary assessments **Efficacy Assessments:** • Physical examinations to assess developmental milestones o New milestones demonstrated by patients which were not documented during the AVXS-101-CL-101 study must be supported by video evidence
Statistical methods: This is a long-term follow-up study with safety as the primary measure. Sample size was not determined through statistical justification.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 3 Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADL	Activities of Daily Living
AE	Adverse event
AESI	Adverse Events of Special Interest
CBC	Complete blood cell count
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	Electronic case report form
ELISpot	Enzyme-linked ImmunoSpot
EMR	Electronic medical record
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFP	Green fluorescent protein
GGT	Gamma-glutamyltransferase
GLP	Good Laboratory Practice
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
ISF	Investigator Site File
MGRS	Multicentre Growth Reference Study
NIH	National Institutes of Health
PBMCs	Peripheral blood mononuclear cells
PBS	Phosphate-buffered saline
RSV	Respiratory syncytial virus
SAE	Serious adverse event
scAAV	Self-complimentary adeno-associated virus

Abbreviation or Specialist Term	Explanation
scAAV9.CB.SMN	Self-complimentary adeno-associated virus serotype 9.chicken-β-actin-hybrid.survival motor neuron
SMA	Spinal muscular atrophy
SMN	Survival motor neuron
SMN1	Survival motor neuron 1 gene
SMN2	Survival motor neuron 2 gene
TMF	Trial Master File
WHO	World Health Organization
WT	Wild type. Wild type mice are those not affected with SMA.

5. INTRODUCTION

The Phase 1 AVXS-101-CL-101 clinical trial was the first clinical gene therapy trial for spinal muscular atrophy (SMA). The survival motor neuron (SMN) gene was transferred using self-complementary adeno-associated virus (scAAV) type 9 under control of the chicken-β-actin hybrid promoter.

Preclinical studies have demonstrated survival of the SMN-Δ7 mouse model for SMA from a median of 15.5 days to over 1 year, following intravenous delivery of AVSX-101 to the facial vein. The AVXS-101-CL-101 clinical trial was an open-label, single injection ascending dose study in which AVXS-101 was delivered one time through a venous catheter inserted into a peripheral vein (arm, leg, or scalp) in SMA Type 1 patients with 2 copies of *SMN2*. The ongoing clinical study has demonstrated improved muscle function and development milestone achievement following delivery of AVXS-101.

This study is a long-term safety follow-up study of the patients who received AVXS-101 treatment in the AVXS-101-CL-101 gene replacement therapy clinical trial for SMA Type 1.

5.1. Background and Preliminary Data

Spinal muscular atrophy is a genetic neurodegenerative disorder caused by a loss or mutation in the survival motor neuron 1 gene (*SMN1*) on chromosome 5q13, which leads to reduced SMN protein levels and a selective dysfunction of motor neurons. Spinal muscular atrophy is an autosomal recessive, early childhood disease with an incidence of 1:10,000 live births [1]. Spinal muscular atrophy is the leading cause of infant mortality due to genetic diseases. Disease severity and clinical prognosis depends on the number of copies of survival motor neuron 2 gene (*SMN2*). In its most common and severe form (Type 1), hypotonia and progressive weakness are recognized in the first few months of life, leading to diagnosis by 6 months of age and then death due to respiratory failure by age 2 years. Spinal muscular atrophy Type 1 is the leading genetic cause of infant death. Motor neuron loss in SMA Type 1 is profound in the early post-natal period (or may even start in the pre-natal period), whereas motor neurons in Type 2 and Type 3 patients adapt and compensate during development and persist into adult life. The findings from various neurophysiological and animal studies have shown an early loss of motor neurons in the embryonic and early post-natal periods [2,3,4]. From a clinical perspective, these findings emphasize the importance of targeting the SMA Type 1 group for gene replacement of *SMN2* in hopes of rescuing neurons at this critical stage. Our goal is to modify the SMA Type 1 phenotype, which will hopefully lead to a milder disease course and prolonged survival as seen in SMA Type 2 and Type 3 patients.

Therapeutic efforts in SMA have focused on the potential for small molecules to increase SMN levels. These include deacetylase inhibitors, such as, valproic acid, sodium butyrate, phenylbutyrate, and trichostatin A. These agents activate the *SMN2* promoter, resulting in increased full-length SMN protein in SMA animal models [5,6]. However, clinical trials employing several of these agents, most notably phenylbutyrate, valporic acid, and hydroxyurea, have not resulted in clinical benefit [7,8]. Nusinersen is an antisense oligonucleotide (ASO) drug designed to increase the production of the SMN protein by modulating the splicing of the *SMN2* gene, thereby compensating for the underlying genetic defect. Although clinical trials have

shown some modest promise in improving motor function, the treatment must be administered indefinitely on a quarterly basis via intrathecal injection.

The AVXS-101-CL-101 dose escalation trial of self-complimentary adeno-associated virus serotype 9.chicken-β-actin-hybrid.survival motor neuron (scAAV9.CB.SMN) will provide information for the potential gene replacement has in treating Type 1 SMA patients and will hopefully show promise for success in modifying the disease prognosis.

This study is a long-term safety follow-up study of patients who received AVXS-101 treatment in the gene replacement therapy clinical trial AVXS-101-CL-101 for SMA Type 1. It is expected that all 15 patients in the parent study will continue in this follow-up study.

5.2. Rationale for Gene Replacement Therapy to SMA Type 1 Patients

There is no therapy administered in this trial.

Patients with SMA Type 1 were chosen as the target population for the AVXS-101-CL-101 gene therapy study. There is a strong rationale for this based on studies of the natural history of this disease. The classification of SMA is shown below (Table 4) in which SMA Types 0 to 4 are described. Spinal muscular atrophy is conventionally classified into 4 phenotypes on the basis of age of onset and highest motor function achieved, with an additional phenotype (Type 0) to describe the severe forms of antenatal-onset SMA.

Table 4 Spinal Muscular Atrophy Classification

Type	Age at Symptom Onset		Maximum Motor Function	Life Expectancy	*SMN2* Copy No.
0	Fetal		Nil	Days-Weeks	1
1	< 6 Months	1A: B-2 Weeks 1B: < 3 Months 1C: > 3 Months	Never sits	< 2 years	1, 2, 3
2	6 - 18 Months		Never walks	20-40 years	2, 3, 4
3	1.5 - 10 Years	3A: < 3 Years 3B: > 3 Years	Walks, regression	normal	3, 4, 5
4	>35 Years		Slow decline	normal	4, 5

Source = Adapted from Kolb[10]
SMN2 = survival motor neuron 2 gene

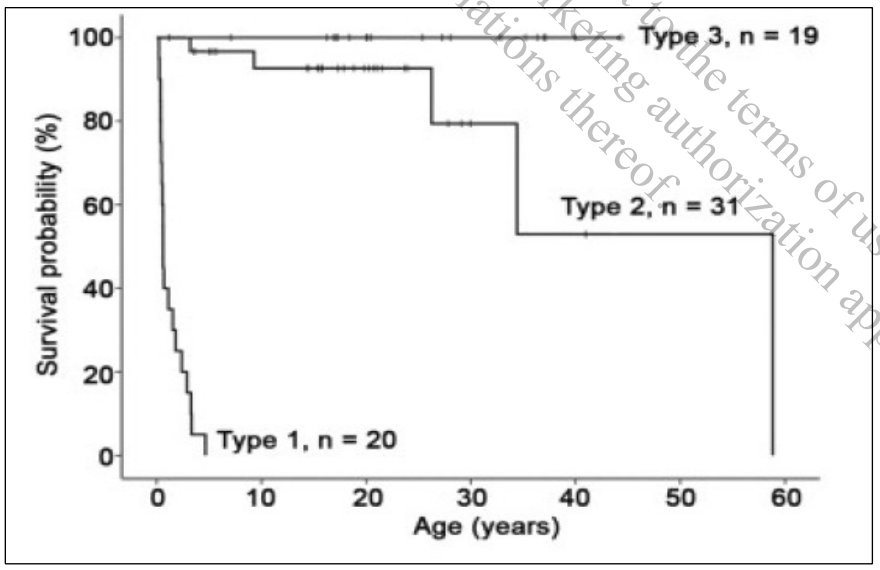
Spinal muscular atrophy Type 1 patients, by definition, never attain independent sitting and have hypotonia within the first 6 months of life. Spinal muscular atrophy Type 1 is the leading genetic cause of infant death. In contrast, SMA Type 2 manifests within the first 18 months, and children afflicted with this condition are able to maintain sitting unassisted but never walk independently. Spinal muscular atrophy Type 3 patients attain the ability to walk unaided (Type 3a have onset < 3 years of age; Type 3b have onset > 3 years of age). Spinal muscular atrophy Type 4 is an adult onset disease. The genetic cause for SMA is well established and is

intimately involved with one's prognosis. All forms of SMA are autosomal recessive in inheritance and are caused by deletions or mutations of the *SMN1* gene.

Humans also carry a second nearly identical copy of the *SMN1* gene called *SMN2* [11]. Both the *SMN1* and *SMN2* genes express SMN protein; however, the amount of functional full-length protein produced by *SMN2* is only 10 to 15% of that produced by *SMN1* [11,12,13]. Although *SMN2* cannot completely compensate for the loss of the *SMN1* gene, patients with milder forms of SMA generally have higher *SMN2* copy numbers [14,15]. Quantitative analysis of *SMN2* copies in 375 patients with Type 1, Type 2, or Type 3 SMA showed a significant correlation between *SMN2* copy number and SMA type, as well as duration of survival; 80% of patients with Type 1 SMA carry one or two *SMN2* copies, 82% of patients with Type 2 SMA carry three *SMN2* copies, and 96% of patients with Type 3 SMA carry three or four *SMN2* copies. In a large early study by Feldkotter et al 2002, 2 copies of *SMN2* was 97% predictive for developing SMA Type 1, 3 copies of *SMN2* was 83% predictive for developing SMA Type 2, and 4 copies of *SMN2* was 84% predictive of SMA Type 3 [16]. As these percentages do not reflect the possible impact of modifier mutations such as that described by Prior et al 2009 [17], they may understate the relationship between copy number (in the absence of a genetic modifier) and clinical phenotype. Among 113 patients with Type 1 SMA, 9 with one *SMN2* copy lived < 11 months, 88/94 with two *SMN2* copies lived < 21 months, and 8/10 with three *SMN2* copies lived 33 to 66 months. Even more refined data describing this relationship has been generated and has also influenced our choice of the study target group. The median survival for patients with SMA Type 1 is 7.4 months with the age of onset being the most predictive factor in survival [18].

The severity of SMA Type 1 is demonstrated by prognosis as illustrated in Kaplan-Meier survival curves shown in Figure 1.

Figure 1 Kaplan-Meier Survival Curves and Survival Probabilities for SMA Types 1, 2, and 3



n = number of patients
Source: Farrar 2013 [18]

In Figure 1, the relative stability of the clinical course of SMA Type 2 and Type 3 is dramatically illustrated. Perhaps most importantly, these findings show that outcome differences are related to the number of *SMN2* copies that enable motor neurons to adapt and compensate during the growth of the child and persist into adult life. This contrasts with SMA Type 1 where motor neuron loss is profound in the early post-natal period (or may even start in the pre-natal period, especially for SMA Type 1 patients presenting in first 3 months of life). The findings in Figure 1 confirm other pieces of evidence from neurophysiological studies and animal studies that also show early loss of motor neurons in the embryonic and early post-natal periods [2,3,4]. From a clinical trials perspective these findings emphasize the importance of targeting SMA Type 1 for gene replacement of *SMN2* in hopes of rescuing neurons at this critical stage. Ultimately, the goal is to modify the SMA Type 1 phenotype leading to a milder course and prolonged survival, as we see in SMA Type 2 or Type 3 patients.

These findings more clearly provided the rationale for the AVXS-101-CL-101 clinical gene replacement therapy trial in the younger patients, making it more difficult to justify even Phase I safety trials in older (SMA Type 2 or 3) patients. Based upon what we know about the natural history of SMA, gene replacement in the older, less severe SMA types (Type 2, Type 3, and Type 4), is less likely to have a significant, clinical effect than it would in the younger Type 1 patients. Since the motor neuron pool is stable in older patients due to higher copy number of *SMN2*, asking Type 2, Type 3, and Type 4 patients to undergo safety trials with possibly only minimal benefit is highly unreasonable. It is much more appropriate and safe to prove tolerability in the younger SMA Type 1 group, in which death is the unequivocal outcome. Also, the poor prognosis of the SMA Type 1 patients, who only have 2 copies of *SMN2*, warrants the rescue of their lives as our top priority at this time.

There have been few safety issues of concern when targeting the SMA Type 1 group for the AVXS-101-CL-101 clinical gene therapy trial. Overexpression of SMN has been shown to be well tolerated in both mice and non-human primates, and in humans a high copy number of *SMN2* poses no risk (as seen in Type 2, Type 3, and Type 4 patients who have high *SMN2* copy number). This allows us to utilize robust, ubiquitous expression systems (like the CB-promoter) to ensure sustained, high-level SMN expression. Additionally, it is important to point out that recombinant scAAV could be employed because of the small size of the SMN gene. This enabled efficient packaging and allowed for efficient gene replacement with lower viral titers (a safety consideration), compared with prototypical single-stranded AAV vectors.

Studies using scAAV9.CB.SMN show a robust post-natal rescue of SMA mice with correction of motor function, neuromuscular electrophysiology and survival after a onetime delivery of vector [19]. Intravenous scAAV9 is able to transduce neurons, muscle, and vascular endothelium, all of which have been proposed as target cells for SMA treatment.

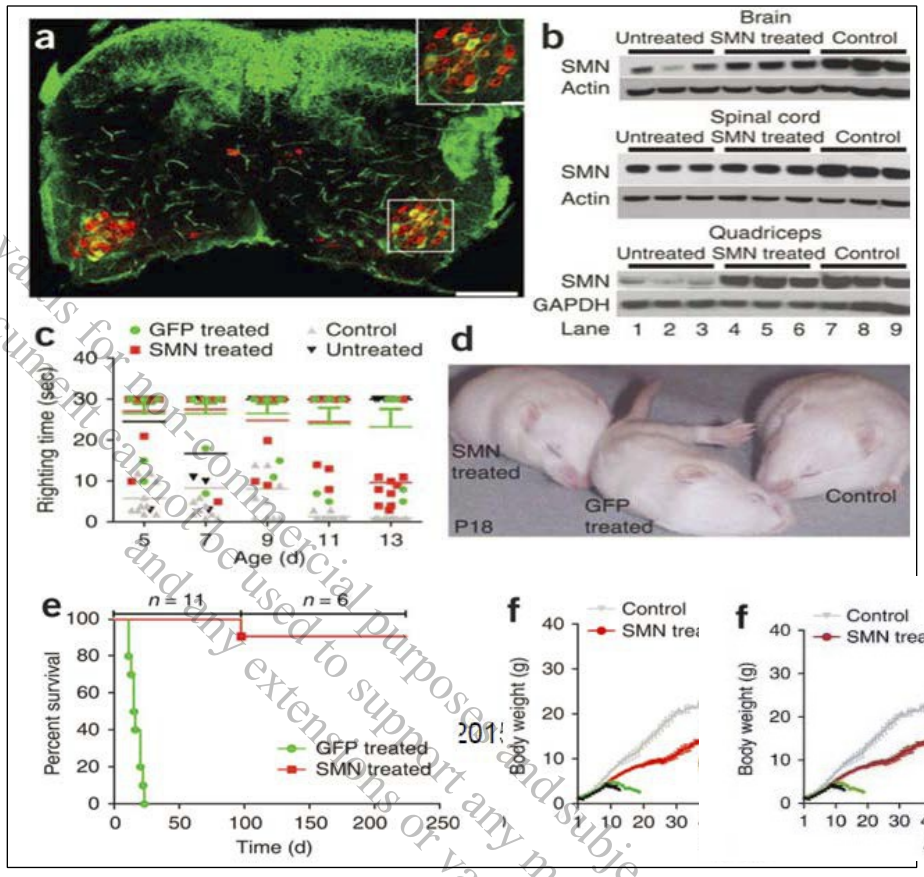
5.3. Non-clinical Studies

A mouse model was developed by the Arthur Burghes Laboratory after a generation of multiple variants. It was found that the double transgenic, referred to as the SMN-Δ7 mouse, provided the most suitable model to study gene replacement [20]. Studies performed in the Kaspar laboratory have shown that injecting 5×10^{11} viral genomes of scAAV9.CB.SMN into the facial vein on Day 1 old mice rescues the SMN-Δ7 mouse model [19]. Figure 2 shows the results of these studies, including staining of transduced spinal motor neurons, SMN expression levels, righting

ability, and weight and survival curves. Approximately 42 ± 2% of lumbar spinal motor neurons were transduced in scAAV9.CB.SMN treated mice. The SMN levels were increased as well, in brain, spinal cord, and muscle of scAAV9.CB.SMN-treated animals, compared with untreated SMA mice (although lower than wild type [WT] controls). Spinal muscular atrophy animals treated with either scAAV9.CB.SMN or scAAV9.CB.GFP on P1 were assessed for their righting ability and were compared to WT control mice and untreated mice. Wild type controls could right themselves quickly, whereas the SMN- and green fluorescent protein (GFP)-treated SMA animals showed difficulty at P5. However, by P13, 90% of SMN-treated animals could right themselves compared with 20% of GFP-treated controls and 0% of untreated SMA animals. At P18, SMN-treated animals were larger than GFP-treated animals, but smaller than WT controls. Locomotive ability of the SMN-treated mice was nearly identical to WT controls, as assayed by open field testing and wheel running.

Survival of SMN-treated SMA animals compared with GFP-treated SMA animals was significantly improved. No GFP-treated control animals survived past P22 and had a median life span of 15.5 days. The weights of GFP mice peaked at P10 and then precipitously declined until death, while SMN mice showed a steady weight gain until around P40 with it stabilizing at 17 g (about half the weight of WT controls). The smaller size of corrected animals is likely related to the tropism and incomplete transduction of scAAV9, resulting in a 'chimeric' animal in which some cells were not transduced. Additionally, the smaller size suggests an embryonic role for SMN. Most remarkably, SMN-treated mice survived well past 250 days of age.

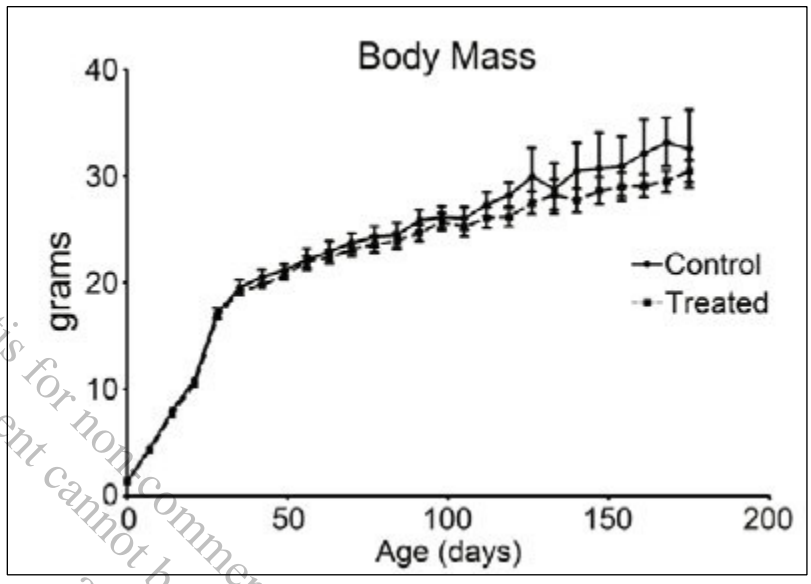
Figure 2 Study Results, Including Staining of Transduced Spinal Motor Neurons, SMN Expression Levels, Righting Ability, and Weight and Survival Curves



Source: Foust 2010 [19]
CNS = central nervous system; GFP = green fluorescent protein; SMN = survival motor neuron; WT = wild type
a) Shows transduced motor neurons in lumbar spinal cord.
b) Western Blots of SMN expression in CNS and muscle.
c) Improved righting ability of SMN-treated- similar to WT controls by P13.
d) SMN-treated are larger than GFP-treated at P18.
e) Survival of SMN-treated markedly improved compared to GFP- treated.
f) Body weight increased in SMN-treated vs GFP.

Toxicology bio-distribution studies were generated by the Kaspar laboratory. In the non-Good Laboratory Practice (GLP) studies, 24 mice and 4 non-human primates were injected, by way of vascular delivery, with scAAV9.CB.SMN. To assess toxicity and safety scAAV9.CB.SMN was injected into P1 WT FVB mice with either vehicle (phosphate-buffered saline [PBS]) (3 males/6 females) or 3.3×10^{14} vg/kg of scAAV9.CB.SMN (6 males/9 females) via the facial temporal vein. This dose was previously shown to be most efficacious in the Δ7 mouse model of SMA16. The P1 mice were used in anticipation of simulating potential clinical studies in infants, which is the planned population for the first-in-human clinical trial. All mice survived the injection procedure and the initial 24-hour observation period without any signs of distress or weight loss. Body mass was measured and hands-on observations were performed weekly for the remainder of the study; neither revealed any difference between control and treated cohorts (Figure 3).

Figure 3 Body Mass of Treated and Control Mice Showed No Difference



At 60, 90, and 180 days post-injection, blood from the mice was collected for hematology studies and clinical chemistries assessment (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, creatinine, blood urea nitrogen, electrolytes, and creatine kinase. All were normal except for 1 variant at the 90-day time point. This difference appeared to be due to a technical problem relating to the site of blood draw, which differed from that of all other mice. For histopathology, 13 mice were necropsied at 120 days post-injection and 8 mice at 180 days. All organs were normal; in particular there was no inflammation seen in any section from any organ (heart, liver, kidney, muscle, gonads, brain, lung, lymph nodes, and intestines).

In the safety study for the 4 male Cynomolgus Macaques, patients were injected at 90 days of age to closely mimic the likely age of administration of treatment in SMA Type 1 infants. The scAAV9.CB.SMN vector was administered one time by catheterization of the saphenous vein with a dose of 6.7×10^{13}/kg, which corresponds to the lowest dose tested for which SMN-Δ7 mice showed a significant increase of survival. Animals were followed for 6 months until they were sacrificed at approximately 9 months of age. No adverse effects were seen, and all clinical chemistries were normal. T-cell immune response was tested using Enzyme-linked ImmunoSpot (ELISpot) in peripheral blood mononuclear cells (PBMCs), and all were negative at 6 months post-injection.

These mouse and monkey studies can be summarized as follows. The serum chemistry and hematology studies were unremarkable as was the histopathology assessment. The non-human primate patients mounted appropriate immune responses to capsid (but not to transgene), with very high transgene expression persisting at 6 months post-injection. In conclusion, these studies provide strong evidence that systemically-delivered scAAV9.CB.SMN is safe and well tolerated, even at the high doses required for penetration of the blood-brain barrier [19].

When newborn FVB mice were given a single IV injection of scAAV9.CB.SMN at levels up to 3.3×10^{14} vg/kg on Day 1, there was neither test article-related mortality nor evidence of toxicity seen at time points up to 24 weeks after administration. Treatment-related decreases in mean

body weight and mean body weight gain, as well as lower activated partial thromboplastin time (APTT) values, were mild effects of treatment, but did not result in toxicity. Activity of the scAAV9.CB.SMN was demonstrated by the biodistribution and the presence of a specific transgene ribonucleic acid (RNA) expression in brain and spinal cord, the main targeted therapeutic tissues. Low levels of antibodies to the AAV9 capsid were found after 12 and 24 weeks in males and females given 3.3×10^{14} vg/kg (Group 3). No alteration was observed in clinical pathology and histopathology analyses. Based on these results, the no observable adverse effect level (NOAEL) of scAAV9.CB.SMN in newborn male and female mice is considered to be 3.3×10^{14} vg/kg.

5.4. Clinical Studies

First in-human study AVXS-101-CL-101 is an ongoing 2-year study evaluating the safety and efficacy of AVXS-101 in 15 SMA Type 1 patients with 2 copies of *SMN2*. All patients have received a single IV dose of AVXS-101 in 2 cohorts: Cohort 1 (n = 3) received 6.7×10^{13} vg/kg and Cohort 2 (n = 12) received 2.0×10^{14} vg/kg (proposed therapeutic dose).

Preliminary data as of 15 September 2016 indicate that treatment with AVXS-101 results in broad improvements in survival, motor function, pulmonary function, and nutritional function. All patients in Cohort 2 (proposed therapeutic dose) showed improvements in survival, as defined by Finkel et al 2014 [25], with no deaths or requirements for permanent ventilation ≥ 16 hours/day for ≥ 14 consecutive days through 15 September 2016. The median age at last follow-up for Cohort 2 was 17.3 months, with the oldest patient at 27.4 months of age. One patient in Cohort 1 (low-dose cohort) had a pulmonary event after [****]. The patient had increased use of bi-level positive airway pressure in advance of surgery related to hypersalivation, a condition experienced by some SMA patients. The event was determined by independent review to represent progression of disease and not related to AVXS-101.

Improvements in motor function, as assessed by the CHOP-INTEND scores, were observed with mean increases of 9.0 points in Cohort 1 and 24.8 points in Cohort 2. The CHOP-INTEND scores in Cohort 2 were ≥ 40 points for 11/12 patients, ≥ 50 points for 9/12 patients, and ≥ 60 points (normal) for 3/12 patients.

Patients in Cohort 2 consistently achieved and maintained key developmental motor milestones as summarized below:

- 11/12 patients achieved head control, 7/12 patients could roll over (completely), 11/12 patients could sit with support, and 8/12 patients could sit unassisted, including 1 patient whose achievement of this milestone was confirmed after 15 September 2016
- 7 patients were able to feed themselves, including 1 patient whose achievement of this milestone was confirmed after 15 September 2016, and 5 patients were speaking (1 bilingual)
- 2 patients were walking independently, including 1 patient whose achievement of this milestone was confirmed after 15 September 2016. These 2 patients each achieved earlier and important developmental milestones such as crawling, standing with support, standing alone, and walking with support

AVXS-101 appears to have a favorable safety profile and appears to be generally well-tolerated in this study. A total of 118 treatment-related AEs was reported (34 serious adverse events

[SAEs] and 84 non-serious adverse events [AEs]). Two SAEs were deemed treatment-related in 2 patients, and 3 AEs were deemed treatment-related in 2 patients. All treatment-related events consisted of clinically asymptomatic liver enzyme elevations that resolved with prednisolone treatment. There were no clinically significant elevations of gamma-glutamyl transferase (GGT), alkaline phosphatase or bilirubin, and as such, Hy's Law was not met. Other non-treatment-related AEs were expected and were associated with SMA.

In summary, the consistently positive clinical observations are remarkably different from that described in extensive natural history studies, clinical publications, the experience of seasoned clinicians and concurrent SMA Type 1 studies with other therapies. These significant and clinically meaningful responses in patients treated with AVXS-101 indicate preliminary clinical evidence of a treatment effect that addresses an unmet need in this devastating pediatric disease.

A full understanding of all the risks associated with AVXS-101 is not known at this time. Elevated liver function tests have been observed in the ongoing AVXS-101-CL-101 study, which is believed to be a T-cell immune response to the AAV9 vector. None of the liver enzyme abnormalities observed in the study were accompanied by clinical sequelae. Patients could experience an allergic response to AVXS-101. Patients could also develop an immune response to the AAV9 viral vector, which could prevent future use of gene transfers using this vector.

Taken together, results from the clinical and non-clinical studies support further clinical investigation of the efficacy and safety of AVXS-101 in patients with SMA Type 1.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

The primary objective is to collect long-term safety data of patients with SMA Type 1 who were treated with AVXS-101 in the AVXS-101-CL-101 gene replacement therapy clinical trial.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

In accord with National Institutes of Health (NIH) and Food and Drug Administration (FDA) Guidance for Industry: Gene Therapy Clinical Trials - Observing Subjects for Delayed Adverse Events [27], this is a long-term, safety follow-up study of patients in the AVXS-101-CL-101 gene replacement therapy clinical trials for SMA Type 1 delivering AVXS-101. Patients will be asked to roll over from the previous study into this study for long-term safety monitoring. Patients will be enrolled in the study for 15 years of follow-up. The study will consist of an initial 5-year phase, during which subjects will be seen annually for evaluation of long-term safety, followed by a 10-year observational phase.

The last visit of the parent study or early discontinuation may serve as the visit at which the informed consent process is completed for this AVXS-101-LT-001 long-term safety study. Qualifying safety events occurring prior to entry in this study but after completion of the AVXS-101-CL-101 study will be captured in this study, after the informed consent process is complete. During the initial 5-year phase, patients will return to the investigative site for yearly follow-up study visits. If the patient is unable to visit the investigative site, the sponsor will arrange with the patients' local established physician to serve as an additional investigator to conduct the required assessments.

At each study visit, safety and efficacy assessments will be conducted including:

- Medical history and record review;
- Physical examination including an assessment of ventilation and nutritional support (Table 5) and review of developmental milestones checklist (see Appendix 1);
    - New milestones demonstrated by patients which were not documented during the AVXS-101-CL-101 study must be supported by video evidence, obtained either during the course of the clinical visit or provided by parents/caregivers from home video.
- Height, weight, and vital sign measurements;
- Clinical laboratory evaluation;
- Pulmonary assessment.

Additionally, patient record transfers from their local physician and/or neurologist will be requested in conjunction with the annual study visits for review by the investigator.

Upon completion of the initial five years of follow-up visits, patients will be contacted via phone annually for the remaining 10-year follow-up period. During the 10-year observational phase, caregivers and patients will be contacted at least once a year and site staff will review a yearly questionnaire designed to elicit information regarding medical history, adverse events, and other clinical conditions. Additionally, patient record transfers from their local physician and/or neurologist will be requested in conjunction with the annual phone contacts for review by the investigator.

Throughout the 15-year study, the Investigator will maintain detailed patient records to include the following:

- Serious Adverse Events (SAEs) and hospitalizations
- Adverse Events of Special Interest
- Exposures to SMA treatment clinical trial(s) or receipt of an investigational or approved product or therapy received with the intent to treat SMA
- Exposures to mutagenic agents and other medicinal products

The Investigator, patients and families, and other medical providers will report adverse events, including unexpected illness and hospitalization.

Patients/families/caregivers will be instructed to report adverse events and conditions directly to the investigative site. Caregivers will be instructed to record all AEs and SAEs, conditions, and medications and to make these available to the Investigator on an annual basis.

Study design is displayed in Figure 4.

Figure 4 Study Design

AVXS-101-CL-101 STUDY **AVXS-101-LT-001 STUDY**

AVXS-101 INFUSION	AVXS-101-LT-001 ICF	15-YEAR LONG-TERM SAFETY FOLLOW-UP	
Day -1 to 2	Last Study Visit or Early Discontinuation[a]	Initial 5-Year Phase Annual Safety Follow-up Study Visits	10-Year Observational Phase Annual Contact by Telephone and Questionnaire

[a] Last study visit or early discontinuation from the parent study is the visit at which the informed consent process maybe completed for the AVXS-101-LT-001 study

7.2. Number of Patients

Up to 15 patients are expected to enroll. The study population will consist of patients who have participated in the AVXS-101-CL-101 gene replacement therapy clinical trial for SMA Type 1 delivering AVXS-101.

7.3. Treatment Assignment

This is a long-term safety follow-up study. Patients will not receive study treatment.

7.4. Criteria for Study Termination

The trial may be terminated for the following reasons:

1. Study is terminated by Sponsor
2. Regulatory authority recommendation

8. SELECTION AND WITHDRAWAL OF PATIENTS

Patients in the AVXS-101-CL-101 gene replacement therapy clinical trial for SMA Type 1 delivering AVXS-101 will roll over from the previous study into the AVXS-101-LT-001 study for continuous safety monitoring for up to 15 years.

8.1. Patient Inclusion Criteria

1. Patient who received AVXS-101 in the AVXS-101-CL-101 gene replacement therapy clinical trial for SMA Type 1.
2. Parent/legal guardian willing and able to complete the informed consent process, comply with study procedures and visit schedule.

8.2. Patient Exclusion Criteria

1. Parent/legal guardian unable or unwilling to participate in the long-term follow-up safety study.

8.3. Patient Withdrawal Criteria

Patients will be withdrawn from the study for the following reasons:

- Death
    - Autopsies will be requested of any patient that expires following participation in a gene replacement therapy study as per the National Institutes of Health's Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (see Autopsy Plan, Appendix 4).
- Withdrawal of consent and/or assent from further participation by the parent/legal guardian or the patient
    - If consent or assent is withdrawn, no further data will be collected for that patient.
- Lost to follow-up
    - The primary reason for withdrawal from the study should be documented on the appropriate electronic case report form (eCRF).

9. TREATMENT OF PATIENTS

9.1. Description of Study Drug

Patients will not receive study treatment.

9.2. Concomitant Medications

Capture of all concomitant medications is not required; however, exposures to SMA treatment clinical trial(s) or receipt of an investigational or approved product or therapy received with the intent to treat SMA as well as mutagenic agents will be captured. Mutagenic agents are defined as chemicals including alkylating agents, cross-linking agents, and polycyclic aromatic hydrocarbons (PAHs) as well as physical agents such as ionizing radiation.

9.3. Treatment Compliance

Not applicable.

9.4. Randomization and Blinding

Not applicable.

A schedule of assessments is presented in Table 5.

Table 5 Schedule of Assessments

	Initial 5-Year Follow-up Phase[a] Annual Study Visits						10-Year Observational Phase Annual Telephone Contact
Year	**0[b]**	**1**	**2**	**3**	**4**	**5**	**6-15**
Informed consent/assent[g]	X						
Inclusion/exclusion	X						
Demographic and medical history	X						
Review of medical history since previous visit		X	X	X	X	X	X
Gene therapy-related delayed adverse events, Serious adverse events, and other adverse events of interest	X	X	X	X	X	X	X
SMA treatments/mutagenic agents	X	X	X	X	X	X	X
Vital signs[d]	X	X	X	X	X	X	
Height and weight	X	X	X	X	X	X	
Physical examination[e]	X	X	X	X	X	X	
Clinical laboratory assessments[f]	X	X	X	X	X	X	
Developmental milestone checklist	X	X	X	X	X	X	
Pulmonary Assessment	X	X	X	X	X	X	X[h]
Telephone contact							X
Observational phase questionnaire							X

[a] Study visits will take place annually (± 6 weeks). Patients will remain in the study for 15 years or until withdrawal.
[b] The last visit of the parent study or early discontinuation may be the timepoint at which the informed consent process is completed
[c] The End of Study visit will take place 15 years after the date on which the patient enrolled in the study.
[d] Vital signs include blood pressure, respiratory rate, pulse, axillary temperature, and pulse oximetry.
[e] Physical examination includes review of the following systems: head, ears, eyes, nose and throat; lungs/thorax; cardiovascular; abdomen; musculoskeletal; neurologic; dermatologic; lymphatic; and genitourinary. Assessment of ventilation and nutritional support and review of developmental milestones (through Year 5) will be reviewed and documented as part of the physical examination.
[f] Clinical laboratory assessments include hematology and blood chemistry.
[g] Informed assent process to be completed at the visit following the timepoint at which the subject reaches the age of assent, as per state legislation or institutional requirements of the investigative site. If during the 10–year observational period, assent will be completed via phone interview, as allowed per IRB guidelines/regulations.
[h] Pulmonary assessment during 10–year observational phase including only phone contact will include only patient-reported daily ventilatory support usage.

10. ASSESSMENT OF SAFETY

10.1. Safety Parameters

The primary outcome for this clinical trial is safety. Safety assessments will be performed at the study visits during the first five (5) years as defined below.

10.1.1. Demographic and Medical History

Patient demographics and prior medical history information will be collected at baseline and captured in the eCRF.

10.1.2. Concomitant Medications

Concomitant medications will not be captured, however, patients are encouraged to follow all routinely scheduled immunizations as recommended by the Center for Disease Control (CDC) or equivalent organization outside of the United States. Seasonal vaccinations that include palivizumab prophylaxis (also known as Synagis) to prevent respiratory syncytial virus (RSV) infections are also recommended in accordance with American Academy of Pediatrics [26].

Exposures to SMA treatment clinical trial(s) or receipt of an investigational or approved product or therapy received with the intent to treat SMA as well as mutagenic agents should be captured through Year 15. Mutagenic agents are defined as chemical including alkylating agents, cross-linking agents, and polycyclic aromatic hydrocarbons (PAHs) as well as physical agents such as ionizing radiation.

10.1.3. Vital Signs

Vital signs will be measured at each study visit through Year 5. Vital sign measurements will include blood pressure, respiratory rate, pulse, axillary temperature, and pulse oximetry.

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

10.1.4. Height and Weight

Height and weight will be measured at each visit through Year 5.

10.1.5. Physical Examination

A physical examination will be performed at each on-site visit through Year 5 and includes review of the following systems: head, ears, eyes, nose and throat; lungs/thorax; cardiovascular; abdomen; musculoskeletal; neurologic; dermatologic; lymphatic; and genitourinary. Evaluation of ventilation and nutritional support will be included as part of the physical examination as well as review of developmental milestones as per the Developmental Milestone Checklist (Appendix 1).

For any patients enrolled under the version of the protocol that excluded completion of the Developmental Milestone Checklist for patients opting to initiate an investigational or approved product or therapy received with the intent to treat SMA, an additional visit must be completed

as soon as possible following IRB approval of the amended protocol within the first year of the study to complete this assessment. If the milestone assessment was completed and documented as per standard of care at a previous office visit, this data can be captured in the eCRF and applicable videos can be collected once each applicable patient completes the informed consent form, as appropriate.

10.1.6. Laboratory Assessments

Blood samples will be collected for hematology, including complete blood count, and chemistry, at each study visit.

10.1.6.1. Hematology

Hematology analysis will include a complete blood cell count (CBC) with differential and platelet with smear.

10.1.6.2. Clinical Chemistry

Chemistry analysis will include the following:

- Serum gamma-glutamyltransferase (GGT)
- Alanine aminotransferase/aspartate aminotransferase
- Serum total bilirubin
- Direct bilirubin
- Albumin
- Glucose
- Total creatine kinase
- Creatinine
- Blood urea nitrogen
- Electrolytes
- Alkaline phosphatase
- Amylase

10.1.7. Pulmonary Assessment

Pulmonary examinations will be performed by a pulmonologist or appropriate individual as per standard institutional practice at each scheduled visit during the 5-year period requiring on-site visits.

During the study patients may be provided ventilatory support at the discretion of the pulmonologist or appropriate individual as per standard institutional practice and/or Investigator. Patients requiring non-invasive ventilatory support will be asked to summarize the hours per day usage in the month prior to the study visit.

During the 10-year observational period when patients are contacted annually via phone, the parent/legal guardian/patient will be asked to summarize the hours per day usage in the month prior to the study visit.

10.1.8. Medical Records Transfer

At the time of enrollment into the study the patients' local physician and/or neurologist contact information will be collected.

Patient record transfers from the local physicians and/or neurologists will be requested in conjunction with the annual study visits and phone contacts for review by the investigator. The investigator will review the local physician's and/or neurologist's record of the patient for an additional objective and accurate safety assessment of the patient.

10.1.9. Observational Phase Questionnaire

Patients will be contacted via telephone annually Years 6-15. Study staff will review the Observational Phase Questionnaire (Appendix 2) with the parent(s)/guardian(s) or patient and document responses in the patient's chart. The investigator will follow-up accordingly for safety concerns raised during the telephone contact.

11. ASSESSMENT OF EFFICACY

11.1.1. Developmental Milestones

In the case that a new developmental milestone is demonstrated during the physical examination (Section 10.1.5) for which the patient had not previously documented achievement in the AVXS-101-CL-101 study, video evidence will be captured either at the site or by collecting video from the parent(s)/legal guardian(s). Milestone achievement (Appendix 1) is defined as per the WHO-Multicentre Growth Study (WHO-MGRS) definitions [23] or Bayley Scales of Infant and Toddler Development, 3rd Ed. [24]; video documentation should demonstrate performance that satisfies the criteria for the specific item as defined by the relevant scale described in Appendix 1 (Developmental Milestone Checklist).

11.1.2. Video Evidence

AveXis, Inc. (AveXis) will provide a secure and confidential upload process for transfer and storage of the videos from investigational sites to a contracted third-party vendor that will compile and arrange videos as per AveXis requirements. Any/all videos received at AveXis or the contracted vendor will be treated as confidential study data and will be the sole property of AveXis. AveXis and the contracted vendor will provide this secure, encrypted transfer and storage solution to properly protect the identities of patients/families on the videos, which may be shared with regulatory agencies, the medical community, and/or in appropriate venues to discuss the results of this clinical study.

Videos may be provided to an independent, centralized reviewer for unbiased assessment of developmental milestone achievement. The independent reviewer will document whether the video displays evidence of having achieved each developmental milestone. The date of developmental milestone achievement will be computed as the earliest date on which video evidence demonstrates the achievement of the specified milestone.

Additionally, the Parent(s)/legal guardian(s) may submit additional videos demonstrating achievement of developmental milestones at any time during the study. These videos will be handled in the same manner in which the study-derived videos are handled.

12. ADVERSE AND SERIOUS ADVERSE EVENTS

12.1.1. Definition of Adverse Events

12.1.1.1. Adverse Event

An adverse event (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. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

In this study, only SAEs (as defined in Section 12.1.1.2) or Adverse Events of Special Interest (as defined in Section 12.1.1.3) since the previous visit will be collected. The Investigator will document the SAE on the form provided and report the SAE as outlined in Section 12.4 Reporting Adverse Events.

12.1.1.2. Serious Adverse Event

An SAE is an AE occurring during the study that fulfils one or more of the following:

- Results in death
- It is immediately life-threatening
- It requires in-patient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

Any SAE that occurs after a patient has been enrolled, whether or not it is related to the study, must be recorded on forms provided by AveXis,

12.1.1.3. Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) identified by the Drug Safety Physician and if applicable also by the Clinical Study Team Physician may be captured and reported to AveXis or designee if deemed necessary.

The identified AESI include:

- Gene-therapy related delayed AEs
- Liver Function Enzyme (LFE) elevations
- New malignancies
- New incidence or exacerbation of a preexisting neurologic disorder
- New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
- New incidence of hematologic disorder

12.2. Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each SAE/AESI (Unrelated, Possibly Related, Probably Related, or Definitely Related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related."

If the relationship between the SAE/AESI and the investigational product is determined to be "possible" or "probable" the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

12.3. Recording Serious Adverse Events

Serious adverse events spontaneously reported by the patient 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.

Serious AE information will be collected from signing of the consent form until the last study visit. Any AEs that occurred during the parent study and are ongoing at the time of enrollment in the AVXS-101-LT-001 will be followed until resolution or until the last study visit.

The SAE term should be reported in standard medical terminology when possible. For each SAE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the patient to discontinue the study.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 12.1.1.2. An AE of severe intensity may not be considered serious.

Events will be graded in accord with the Common Terminology Criteria for Adverse Events (CTCAE) 4.03 shown in Table 6.

Table 6 Common Terminology Criteria for Adverse Events

1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a].
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b].
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to AE.

Abbreviation: ADL = activity of daily living.
[a] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
Source: National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). [22]

Should a pregnancy occur, it must be reported and recorded on AveXis' or designee's pregnancy form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

12.4. Reporting Serious Adverse Events

All SAEs (related and unrelated) will be recorded from the signing of consent form until the last study visit. Any SAEs considered possibly or probably related to the investigational product and discovered by the Investigator at any time after the study should be reported. All SAEs must be reported to AveXis, Inc. or designee within 24 hours of the first awareness of the event. The Investigator must complete, sign and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send notification to AveXis, Inc. or designee, as per the Safety Management Plan.

Additional follow-up information, if required or available, should all be provided to AveXis, Inc. or designee within 24 hours of receipt for events that are unexpected and/or possibly/probably/definitely related to the investigational product. This information should be provided on a follow-up SAE form and placed with the original SAE information and kept with the appropriate section of the eCRF and/or study file. Follow-up information for events that are not unexpected and are not related to the investigational product should be provided to AveXis, Inc. or designee within 5 calendar days of receipt.

AveXis, Inc. is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) of all SAEs that occur at his or her site, as per the IRB/IEC's reporting guidelines.

13. STATISTICS

As this is a long-term follow-up study safety data will be summarized and described.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

During the study, a monitor from AveXis, Inc. or representative will have regular contact with the investigational site, for the following:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol and International Council on Harmonisation (ICH)/Good Clinical Practice (GCP) guidelines, and that data are being accurately recorded in the eCRFs.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g., clinic charts) including access to the site's Electronic Medical Record (EMR) and the videos captured during specified visit assessments.
- Record and report any protocol deviations not previously sent to AveXis, Inc.
- Confirm SAEs/AESIs have been properly documented on eCRFs and confirm any SAEs have been forwarded appropriately and those SAEs that met criteria for reporting have been forwarded to the IRB/IEC.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

14.2. Audits and Inspections

Authorized representatives of AveXis, Inc., a regulatory authority, or an IRB/IEC may visit the site to perform audits or inspections, including source data verification. The purpose of an AveXis, Inc. audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. The Investigator should contact AveXis, Inc. immediately if contacted by a regulatory agency about an inspection.

14.3. Institutional Review Board

The Principal Investigator must obtain IRB/IEC approval for the investigation. Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, AveXis, Inc. may conduct a quality assurance audit. Please see Section 14.2 for more details regarding the audit process.

Qualified individuals designated by the Sponsor will monitor all aspects of the study according to GCP, standard operating procedures (SOPs), and for compliance with applicable government regulations. Please see Section 16.1 for more details regarding the quality control and monitoring process. AveXis may also conduct a quality assurance audit anytime during or after the completion of the study. The investigator agrees to allow these Sponsor representatives direct access to the clinical data and if requested, agrees to cooperate fully or assist the sponsor representative. The investigator and staff are responsible for being present or available for consultation during routinely scheduled site visits conducted by the Sponsor or its designees.

Noncompliance with the protocol, ICH, GCP, or local regulatory requirements by an investigator, site staff, or representatives of the Sponsor will lead to prompt action by the sponsor to secure compliance. Continued noncompliance may result in termination of the corresponding party's involvement in the study. The IRB/ IEC and relevant regulatory authority will also be informed.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate.

The Principal Investigator is responsible for informing the IRB/IEC of any amendment to the protocol in accordance with local requirements. The protocol must be re-approved by the IRB/IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB/IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. AveXis, Inc. will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB/IEC according to local regulations and guidelines

16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (please see Appendix 3) and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and AveXis' policy on Bioethics.

16.3. Informed Consent/Assent

The Principal Investigator(s) at each center will ensure that the parent(s) and guardian(s) of the patient, and the patient when applicable, is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Parent(s) and guardian(s) must also be notified that they are free to discontinue from the study at any time. The parent(s) and guardian(s) of the patient, and the patient when applicable, should be given the opportunity to ask questions and allowed time to consider the information provided.

A signed and dated informed consent must be obtained from the parent(s)/guardian(s) of the patient before conducting any study procedures. At such time that a patient reaches the age of assent or consent as per state legislation or institutional guidelines, a signed and dated assent form or informed consent form must be obtained before further study procedures are completed.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form and Assent Form. A copy of the signed Informed Consent Form and Assent Form must be given to the parent/guardian and patient, respectively.

17. DATA HANDLING AND RECORDKEEPING

17.1. Electronic Case Report Forms

Adequate and accurate case records will be maintained and all relevant observations and data related to the study will be recorded. This will include medical history/physical examination, hematology, clinical chemistry, and serology results, a checklist of inclusion and exclusion criteria, a record of sample collection, hemodynamic measurements, clinical assessments, AEs, and final evaluation.

Electronic CRFs will be used in this study. The eCRF will be electronically signed and dated by the Principal Investigator or his designee after his/her review. After the completion of the study, completed eCRFs will be retained in the archives.

Completed eCRFs will be reviewed by the study monitor against the source documentation for accuracy and completeness. Once signed by the Investigator, the monitor will transmit the completed eCRFs to data management for data validation and database analysis.

17.2. Inspection of Records

AveXis will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect patient charts, study source documents, and other records relative to study conduct.

17.3. Retention of Records

All primary data that are a result of the original observations and activities of the study and that are necessary for the reconstruction and evaluation of any study report will be retained in a secure archive at the study site for a period not less than 2 years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have lapsed since the formal discontinuation of the clinical development of the investigational product. All country/region specific requirements that may be more stringent than the 2 years (e.g., 25 years in Canada) included in ICH shall be followed.

The site will maintain a Clinical Study Document Binder, which will be maintained at the study site. In this binder, there will be tabbed sections for study documents including the following: study personnel identification and signature list, patient / subject screening records, patient / subject roster (names omitted), protocol and amendments or administrative changes, FDA Form 1572 (if required), study staff Curricula Vitae, IRB/IEC documentation, an approved sample ICF, drug / product accountability records, correspondence, site monitoring reports, blank Data Documentation form, and lab accreditations and normal values. The site must keep this binder current and available for review by the Sponsor, IRB/IEC, and/or regulatory bodies.

18. PUBLICATION POLICY

The Investigator is obliged to provide the Sponsor with complete test results and all data derived by the Investigator from the study. During the study, only the Sponsor may make study information available to other study Investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the Sponsor.

The Sponsor may publish any data and information from the study (including data and information generated by the Investigator) without the consent of the Investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

If the study is being conducted as part of a multicenter clinical study, data from all sites participating in the study will be pooled and analyzed by the Sponsor or the Sponsor's designee. The first publication of the study results shall be made in conjunction with the results from other study sites as a multicenter publication. If a multicenter publication is not forthcoming within 24 months of completion of the study at all sites, the Investigator may publish or present the results generated at his or her site.

The Investigator will provide the Sponsor with a copy of any proposed publication or presentation for review and comment at least 60 days prior to such presentation or submission for publication. The Sponsor shall inform the Investigator in writing of any changes or deletions in such presentation or publication required to protect the Sponsor's confidential and proprietary technical information and to address inaccurate data or inappropriate interpretations in the context of any pooled multicenter results. At the expiration of such 60-day period, the Investigator may proceed with the presentation or submission for publication unless the Sponsor has notified the institution or the Investigator in writing that such proposed publication or presentation discloses the Sponsor's confidential and proprietary technical information. Further, upon the request of the Sponsor, the Investigator will delay the publication or presentation for an additional 90 days to permit the Sponsor to take necessary actions to protect its intellectual property interests.

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20. APPENDICES

APPENDIX 1. DEVELOPMENTAL MILESTONE CHECKLIST

Current Status: Achieved	Developmental Milestone: Bayley Scales of Infant and Toddler Development©/WHO-MGRS[23]
YES/NO	Child holds head erect for at least 3 seconds without support[24]
YES/NO	Sitting with support[24]
YES/NO	Sitting without support[23]
YES/NO	Ability to crawl[23]
YES/NO	Pulls to stand[24]
YES/NO	Stand with assistance[23]
YES/NO	Stand alone[23]
YES/NO	Walk with assistance[23]
YES/NO	Walk alone[23]

APPENDIX 2. OBSERVATIONAL PHASE QUESTIONNAIRE

Patient ID: _____

Date of Family Contact: _____/_____/_____
DD MMM YYYY

Contact made with: ☐ Mother ☐ Father ☐ Other, specify: _____

ADVERSE EVENTS (AE)

Have there been any changes in the patient's health since the last visit/telephone call?
☐ Yes* ☐ No
If Yes, describe:

If patient experienced an SAE complete/update the SAE worksheet and applicable eCRF.

HOSPITALIZATIONS

Has the patient had any hospitalizations since the last visit/telephone call? ☐ Yes* ☐ No
**If Yes, complete/update the Hospitalization worksheet and Hospitalization eCRF.*

CONCOMITANT MEDICATIONS

Have there been any changes to the patient's concomitant medications since the last visit/telephone call? ☐ Yes ☐ No

If yes, has the patient received SMA treatment in a clinical trial(s) or an investigational or approved product or therapy aimed at treating SMA? ☐ Yes* ☐ No
**If Yes, complete/update the Concomitant Medication worksheet and Concomitant Medication eCRF*

Has the patient received mutagenic agents? ☐ Yes* ☐ No
**If Yes, complete/update the Concomitant Medication worksheet and Concomitant Medication eCRF.*

VENTILATORY SUPPORT

Has the patient had any change in their non-invasive ventilator use since the last visit/telephone call? ☐ Yes* ☐ No
If yes, describe:

FEEDING SUPPORT

Has the patient had any change in their feeding support? ☐ Yes* ☐ No
If yes, describe:

Comments:

_____ _____
Signature Date

APPENDIX 3. DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving Human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving Human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving Human subjects.

6. The primary purpose of medical research involving Human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all Human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research patients.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research patients. The responsibility for the protection of research patients must always rest with the physician

or other health care professionals and never with the research patients, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving Human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research patients set forth in this Declaration.
11. Medical research should be conducted in a manner that minimizes possible harm to the environment.
12. Medical research involving Human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research patients.
15. Appropriate compensation and treatment for patients who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving Human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research patients.
17. All medical research involving Human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving Human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving Human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving Human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for patients and information regarding provisions for treating and/or compensating patients who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research patients set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research patients and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as patients in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving Human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the

study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential patients as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research patients should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

30. Research involving patients who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving patients with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all patients who still need an intervention identified as beneficial in the trial. This information must also be disclosed to patients during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving Human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on Human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

APPENDIX 4. AUTOPSY PLAN

A third–party contract company that provides autopsy and tissue collection services, will perform autopsy and tissue collection for the patients in the clinical trial. This company will deploy a pathology assistant to the funeral home of the deceased to perform the autopsy and tissue collection. Standard autopsy incisions are used to perform the autopsy and pathology necessary to determine the cause of death, which will be completed by the contracted autopsy service.

During the procedure, multiple tissues along with the entire spinal cord will be collected for research purposes. Up to 7 sections or pieces from each organ and each region of the spinal cord will be collected and provided to AveXis, Inc. for analysis. Analysis of the tissue will be done to determine whether the vector transduced the expected motor neurons and if the SMN gene was expressed. These results demonstrate whether the vector delivered the therapeutic gene as expected. Tissue samples collected will also be available for histology and immunohistochemistry, allowing the state of the motor neurons and muscles to be examined.

Specifically, tissue samples from the following organs and regions of the spinal cord and brain will be collected (see Table 7 below). Tissue sample will be frozen or fixed (e.g., 2% paraformaldehyde) for appropriate analysis.

Families will be asked to consent to the autopsy and tissue collection prior to any sign of moribund or death by the clinical team conducting the trial. There are distinct consent forms for the formal autopsy and for the research tissue collection. This allows the families the flexibility to participate in one or both of the research activities.

Table 7 Tissue Samples for Analysis

Brain	Spinal Cord	Muscles	Organs
Motor cortex	Cervical spinal cord	Diaphragm	Spleen
Layer 5 motor cortex	Thoracic spinal cord	#6/#7 Rib with intercostal muscle and nerve	Kidney
Brain stem	Lumbar spinal cord	Psoas muscle	Small intestine
	Sacral spinal cord		Large intestine
	Dorsal root		Pancreas
	Cervical level		Stomach
	Ventral root		Lung
	Cervical level		Heart
	DRG root		Liver
	Cervical level		Inguinal lymph node
	Cerebrospinal fluid		Gonads

APPENDIX 5. SUMMARY OF CHANGES

The section below highlights content changes represented in this version of the protocol. Language deleted from Protocol version 1.0 appears in ~~red strike through~~. Language added to Protocol version 2.0 appears in **bold**.

Section 2 Synopsis

The synopsis was updated to reflect changes consistent with the protocol revisions.

Section 7.1 Overall Study Design

At each study visit, safety **and efficacy** assessments will be conducted including:

- Medical history and record review;
- Physical examination including an assessment of ventilation and nutritional support (Table 5) and review of developmental milestones checklist (see Appendix 1);
    - ~~Capture of developmental milestone data will be discontinued for patients opting to initiate an investigational or approved product or therapy received with the intent to treat SMA~~
    - **New milestones demonstrated by patients, which were not documented during the AVXS-101-CL-101 study, must be supported by video evidence, obtained either during the course of the clinical visit or provided by parents/caregivers from home video.**
- Height, weight, and vital sign measurements;
- Clinical laboratory evaluation;
- **Pulmonary assessment.**

Rationale for Change

Milestone achievements will be captured for all patients, regardless of alternative SMA therapy treatments and a pulmonary assessment will be added to include details of patient long-term respiratory status.

Section 9.4 Randomization and Blinding

Table 5 Schedule of Assessments

	Initial 5-Year Follow-up Phase[a] Annual Study Visits						10-Year Observational Phase Annual Telephone Contact
Year	**0[b]**	**1**	**2**	**3**	**4**	**5**	**6-15**
Informed consent/assent[g]	X						
Inclusion/exclusion	X						
Demographic and medical history	X						
Review of medical history since previous visit		X	X	X	X	X	X

	Initial 5-Year Follow-up Phase[a] Annual Study Visits						10-Year Observational Phase Annual Telephone Contact
Gene therapy-related delayed adverse events, Serious adverse events, and other adverse events of interest	X	X	X	X	X	X	X
SMA treatments/mutagenic agents	X	X	X	X	X	X	X
Vital signs[d]	X	X	X	X	X	X	
Height and weight	X	X	X	X	X	X	
Physical examination[e]	X	X	X	X	X	X	
Clinical laboratory assessments[f]	X	X	X	X	X	X	
Developmental milestone checklist	X	X	X	X	X	X	
Pulmonary Assessment	**X**	**X**	**X**	**X**	**X**	**X**	**X[h]**
Telephone contact							X
Observational phase questionnaire							X

[i] Study visits will take place annually (± 6 weeks). Patients will remain in the study for 15 years or until withdrawal.
[j] The last visit of the parent study or early discontinuation may be the timepoint at which the informed consent process is completed
[k] The End of Study visit will take place 15 years after the date on which the patient enrolled in the study.
[l] Vital signs include blood pressure, respiratory rate, pulse, axillary temperature, and pulse oximetry.
[m] Physical examination includes review of the following systems: head, ears, eyes, nose and throat; lungs/thorax; cardiovascular; abdomen; musculoskeletal; neurologic; dermatologic; lymphatic; and genitourinary. Assessment of ventilation and nutritional support and review of developmental milestones (through Year 5) will be reviewed and documented as part of the physical examination.
[n] Clinical laboratory assessments include hematology and blood chemistry.
[o] Informed assent process to be completed at the visit following the timepoint at which the subject reaches the age of assent, as per state legislation or institutional requirements of the investigative site. If during the 10–year observational period, assent will be completed via phone interview, as allowed per IRB guidelines/regulations.
[p] **Pulmonary assessment during 10–year observational phase including only phone contact will include only patient-reported daily ventilatory support usage.**
[q] ~~Capture of developmental milestone data will be discontinued for patients opting to initiate an investigational or approved product or therapy received with the intent to treat SMA~~

Rationale for Change

Milestone achievements will be captured for all patients, regardless of alternative SMA therapy treatments.

Section 10.1.5 Physical Examination

A physical examination will be performed at each on-site visit through Year 5 and includes review of the following systems: head, ears, eyes, nose and throat; lungs/thorax; cardiovascular; abdomen; musculoskeletal; neurologic; dermatologic; lymphatic; and genitourinary. Evaluation of ventilation and nutritional support will be included as part of the physical examination as well as review of developmental milestones as per the Developmental Milestone Checklist (Appendix 1).

For any patients enrolled under the version of the protocol that excluded completion of the Developmental Milestone Checklist for patients opting to initiate an investigational or approved product or therapy received with the intent to treat SMA, an additional visit must be completed as soon as possible following IRB approval of the amended protocol within the first year of the study to complete this assessment. If the milestone assessment was completed and documented as per standard of care at a previous office visit, this data can be captured in the eCRF once each applicable patient completes the informed consent form, as appropriate.

~~Capture of developmental milestone data will be discontinued for patients opting to initiate an investigational or approved product or therapy received with the intent to treat SMA.~~

Rationale for Change

Developmental milestone achievements were not captured for patients who initiated alternative SMA therapy prior to completing the first AVXS-101-LT-001 visit in Year 1. The protocol will now capture milestone achievements for all patients, regardless of treatment; to ensure a complete dataset, all patients for whom milestones achievements were not assessed thus far in Year 1 will return for an additional visit to complete this assessment.

Section 10.1.7 Pulmonary Assessment

Pulmonary examinations will be performed by a pulmonologist or appropriate individual as per standard institutional practice at each scheduled visit during the 5-year period requiring on-site visits.

During the study patients may be provided ventilatory support at the discretion of the pulmonologist or appropriate individual as per standard institutional practice and/or Investigator. Patients requiring non-invasive ventilatory support will be asked to summarize the hours per day usage in the month prior to the study visit.

During the 10-year observational period when patients are contacted annually via phone, the parent/legal guardian/patient will be asked to summarize the hours per day usage in the month prior to the study visit.

Rationale for Change

Pulmonary assessments will be added to include details of patient long-term respiratory status.

Section 11 EFFICACY ASSESSMENTS

Section 11.1.1 Developmental Milestones

In the case that a new developmental milestone is demonstrated during the physical examination (Section 10.1.5) for which the patient had not previously documented achievement in the AVXS-101-CL-101 study, video evidence will be captured either at the site or by collecting video from the parent(s)/legal guardian(s). Milestone achievement (Appendix 1) is defined as per the WHO-Multicentre Growth Study (WHO-MGRS) definitions [23] or Bayley Scales of Infant and Toddler Development, 3rd Ed. [24]; video documentation should demonstrate performance that satisfies the criteria for the specific item as defined by the relevant scale described in Appendix 1 (Developmental Milestone Checklist).

Rationale for Change

Video evidence will be collected to verify achievement of new milestones, to maintain consistency with the global AVXS-101 development program and ensure rigorous assessment of all developmental milestone achievement claims.

Section 11.1.2 Video Evidence

AveXis, Inc. (AveXis) will provide a secure and confidential upload process for transfer and storage of the videos from investigational sites to a contracted third-party vendor that will compile and arrange videos as per AveXis requirements. Any/all videos received at AveXis or the contracted vendor will be treated as confidential study data and will be the sole property of AveXis. AveXis and the contracted vendor will provide this secure, encrypted transfer and storage solution to properly protect the identities of patients/families on the videos, which may be shared with regulatory agencies, the medical community, and/or in appropriate venues to discuss the results of this clinical study.

Videos may be provided to an independent, centralized reviewer for unbiased assessment of developmental milestone achievement. The independent reviewer will document whether the video displays evidence of having achieved each developmental milestone. The date of developmental milestone achievement will be computed as the earliest date on which video evidence demonstrates the achievement of the specified milestone.

Additionally, the Parent(s)/legal guardian(s) may submit additional videos demonstrating achievement of developmental milestones at any time during the study. These videos will be handled in the same manner in which the study-derived videos are handled.

Rationale for Change

Video evidence will be collected to verify achievement of new milestones, to maintain consistency with the global AVXS-101 development program and ensure rigorous assessment of all developmental milestone achievement claims.

Section 121.1.1.1 Adverse Event

An adverse event (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** ~~casually~~ related to the product. In clinical studies, an AE can include an undesirable medical condition occurring at any time, including baseline or washout periods, even if no study treatment has been administered.

Rationale for Change

Correction of typographical error and change in section number due to addition of efficacy assessments section.

Section 12.2 Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each SAE/AESI (Unrelated, ~~Unlikely Related,~~ Possibly Related, Probably Related, or Definitely Related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If no valid reason exists for suggesting a relationship, then the AE should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related."

Rationale for Change

AveXis revised SOPs require removal of "unlikely related" as a relationship to IP option for clinical studies.

Appendix 1 Developmental Milestone Checklist

Current Status: Achieved	Developmental Milestone: Bayley Scales of Infant and Toddler Development©/WHO-MGRS[23]
YES/NO	Child holds head erect for at least 3 seconds without support[24]
YES/NO	Sitting with support[24]
YES/NO	Sitting without support[23]
YES/NO	Ability to crawl[23]
YES/NO	Pulls to stand[24]
YES/NO	Stand with assistance[23]
YES/NO	Stand alone[23]
YES/NO	Walk with assistance[23]
YES/NO	Walk alone[23]

Rationale for Change

Clarification added for reference source for each milestone definition.