

Application Type	Original BLA
STN	125694
CBER Received Date	October 9th, 2018
PDUFA Goal Date	June 1 st , 2019
Division / Office	DCGT/OTAT
Committee Chair	Andrew Byrnes
Clinical Reviewer	Mark Singer
Project Manager	Candace Jarvis
Priority Review	Yes
Reviewer Name(s)	Xue Lin
Review Completion Date / Stamped Date	
Supervisory Concurrence	Min (Annie) Lin, Ph.D. Acting Team Leader, FDA/CBER/OBE/DB/TEB
	Boguang Zhen, Ph.D. Branch Chief, FDA/CBER/OBE/DB/TEB
	John Scott, Ph.D. Director, FDA/CBER/OBE/DB
Applicant	AveXis, Inc.
Established Name	AVXS-101
(Proposed) Trade Name	ZOLGENSMA
Pharmacologic Class	adeno-associated virus serotype 9 expressing the human Survival Motor Neuron gene
Dosage Form(s) and Route(s) of Administration	Single intravenous infusion
Dosing Regimen	1.1E14 vector genomes (vg)/kg
Indication(s) and Intended Population(s)	adeno associated virus (AAV) vector-based gene therapy indicated for the treatment of pediatric patients with infantile-onset spinal muscular atrophy (SMA) with confirmed biallelic mutations in the <i>SMN1</i> gene

Table of Contents

Glossary	3
1. Executive Summary	4
2. Clinical and Regulatory Background.....	5
2.1 Disease or Health-Related Condition(s) Studied	5
2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)	5
2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission	5
3. Submission Quality and Good Clinical Practices	5
3.1 Submission Quality and Completeness.....	6
5. Sources of Clinical Data and Other Information Considered in the Review	6
5.1 Review Strategy	6
5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review.....	6
5.3 Table of Studies	6
6. Discussion of Individual Studies/Clinical Trials	7
6.1 AVXS-101-CL-101.....	7
6.1.2 Design Overview.....	7
6.1.3 Population	7
6.1.4 Study Treatments or Agents Mandated by the Protocol.....	7
6.1.6 Sites and Centers	7
6.1.7 Surveillance/Monitoring.....	7
6.1.8 Endpoints and Criteria for Study Success	8
6.1.9 Statistical Considerations & Statistical Analysis Plan	8
6.1.10 Study Population and Disposition	8
6.1.11 Efficacy Analyses.....	9
6.1.12 Safety Analyses	16
6.2 AVXS-101-CL-001.....	17
6.3 AVXS-101-CL-303.....	18
10. Conclusions.....	19
10.1 Statistical Issues and Collective Evidence	19
10.2 Conclusions and Recommendations.....	20
11. REFERENCES.....	20

GLOSSARY

Abbreviation	Definition
AAV	Adeno-associated virus
AAV9	Adeno-associated virus serotype 9
ACTIVE-mini	Ability Captured Through Interactive Video Evaluation – mini
ADaM	Analysis data model
AE	Adverse event
AESI	Adverse event of Special Interest
ASO	Antisense oligonucleotide
BiPAP	Bi-level positive airway pressure
CDISC	Clinical data interchange standards consortium
CHOP-INTEND	Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data safety monitoring board
FAS	Full analysis set
FDA	Food and Drug Administration
GMP	Good manufacturing practice
ITT	Intent-to-treat
IV	Intravenous
Max	Maximum
Min	Minimum
mITT	Modified intent-to-treat
NA	Not applicable
NCH	Nationwide children’s hospital
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
NIV	Noninvasive ventilation
SDTM	Study data tabulation module
SMA	Spinal muscular atrophy
SMN	Survival motor neuron
<i>SMN1</i>	Survival motor neuron 1
<i>SMN2</i>	Survival motor neuron 2
SOC	System Organ Class
SS	Safety analysis set
TEAE	Treatment emergent adverse events
US	United States
USPI	United States prescribing information
vg	Vector genome
WHO	World Health Organization

1. EXECUTIVE SUMMARY

ZOLGENSMA is a gene therapy. It consists of adeno associated virus (AAV) vector expressing the human Survival Motor Neuron (SMN) gene. This Biologics License Application (BLA) seeks licensure of ZOLGENSMA for the treatment of pediatric patients with infantile-onset spinal muscular atrophy (SMA) with confirmed biallelic mutations in the *SMN1* gene. Spinal muscular atrophy (SMA) is an early childhood disease with an incidence of approximately 1: 10,000 live births, of which approximately 45-60% cases are SMA Type 1. Spinal muscular atrophy is the leading cause of infant mortality due to genetic disease.

The primary source of evidence to support this application is a Phase I, single center, single arm, single dose, dose escalation study (AVXS-101-CL-101). Fifteen (15) subjects were enrolled, and 3 subjects were treated at the low dose of 6.7×10^{13} vg/kg (Cohort 1) and the other 12 were treated at the proposed therapeutic dose of 2.0×10^{14} vg/kg (Cohort 2).

For Cohort 2 (n=12), no subjects died or needed permanent ventilation within 24 months after infusion. In comparison, in a natural history study¹ only 8% of patients were alive and permanent ventilation-free by 24 months of age. Eleven subjects (92%) reached the developmental milestone of holding head erect for at least 3 seconds unsupported, 9 (75%) were able to roll back to side from both sides, 9 (75%) were able to sit alone for at least 30 seconds, 2 subjects were able to stand alone and walk independently. In addition, the mean Chop-INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders) score increased from baseline of 28.2 (standard error=3.5) to 49.6 (standard error=3.8) at 6 months, 53.6 (standard error=1.8) at 12 months, and 55.5 (standard error=0.5) at 24 months. In general clinical practice, untreated SMA Type 1 children 6 months of age or older do not surpass a score of 40 points on the CHOP-INTEND². Furthermore, an average decline of 10.7 points between the ages of 6 and 12 months were reported amongst untreated infants in the natural history study¹.

For Cohort 1 (n=3), one subject needed permanent ventilation (defined as at least 16-hour per day of ventilation support for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative use). No subject developed any major developmental milestone. Their CHOP-INTEND scores only changed slightly over the course of the trial.

No deaths occurred during the 24 months follow-up after dosing in study AVXS-101-CL-101. All 3 subjects in Cohort 1 (6.7×10^{13} vg/kg) had at least one serious treatment emergent adverse event (TEAE). Ten (83.3%) subjects in Cohort 2 (2.0×10^{14} vg/kg) had at least one serious TEAE. The most common serious TEAEs were in the category of infections and infestations. Three (100%) subjects in Cohort 1 and 9 (75%) subjects in Cohort 2 had AEs in this category.

The statistical analysis results provide evidence to support the applicant's proposed indication for ZOLGENSMA in this BLA.

2. CLINICAL AND REGULATORY BACKGROUND

Insert text here

2.1 Disease or Health-Related Condition(s) Studied

Spinal muscular atrophy (SMA) is a neurogenetic disorder caused by a loss or mutation in the survival motor neuron 1 gene (*SMN1*) on chromosome 5q13, which leads to reduced SMN protein levels. Deficiency of SMN protein correlates directly with death of the individual's motor neurons. Loss of motor neurons leads to secondary effects on muscle strength and function, leading to progressive loss of muscle control, strength and function, swallowing, breathing and, ultimately, death in the most severe forms of the disease.

Spinal muscular atrophy (SMA) has an incidence of approximately 1: 10,000 live births, of which approximately 45-60% cases are SMA Type 1. Spinal muscular atrophy is the leading cause of infant mortality due to genetic disease.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

SPINRAZA is an FDA approved drug designed to increase the production of the SMN protein. SPINRAZA requires clinical monitoring. It is recommended that platelet count, coagulation laboratory testing, and quantitative spot urine protein testing be performed at baseline and prior to each administration of nusinersen. Furthermore, the need for repeat lumbar punctures may be challenging as SMA patients are likely to develop scoliosis, contractures, and often require spinal rod surgery and/or spinal fusion surgeries for continued survival and function.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Table 1 summarizes the major regulatory activities associated with this BLA.

Table 1. Summary of major Pre-and Post-submission regulatory activities

Date	Milestone
8/6/2013	IND 15699 submission
9/27/2013	Fast Track granted
9/30/2014	Orphan Drug Designation granted
7/15/2016	Breakthrough Therapy Designation granted
6/14/2018	Pre-BLA Meeting
8/21/2018	Rare Pediatric Disease Designation granted
10/9/2018	BLA 125694 submission
11/28/2018	BLA filed. Filing Letter issued to Applicant
2/6/2019	120 day update
6/1/2019	PDUFA Action Due Date

(Source: adopted Table 1 BLA 125694/0.1 module 1 Reviewer's guide, FDA statistical reviewer)

3. Submission Quality and Good Clinical Practices

3.1 SUBMISSION QUALITY AND COMPLETENESS

The submission was adequately organized for conducting an in-depth and complete statistical review without unreasonable difficulty.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The primary source of evidence to support the efficacy and the safety of the proposed product comes from study AVXS-101-CL-101, which is the focus of this review memo.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

The basis of this statistical memo includes review of

- Clinical study reports and data sets submitted in module 5 of BLA 125694/0.0
- Efficacy and safety 120-day update submitted in BLA 125694/0.32

5.3 Table of Studies

Table 2 summarizes the five studies included in the BLA submission. Results from study AVXS-101-CL-101 form the primary evidence of safety and efficacy of AVXS-101 for the BLA application.

Table 2. Studies in the BLA submission

Study code	Study design+ Study population	Study status	# of subjects treated*
AVXS-101-CL-101 (pivotal)	Phase 1, single center, single arm, single dose, dose escalation SMA Type 1	completed	15
AVXS-101-CL-102	Phase 1, US multicenter, single dose, dose escalation, intrathecal trial in SMA Type 2 and Type 3	ongoing	4
AVXS-101-CL-303	Phase 3, US multicenter, single arm, single dose, IV trial in SMA Type 1	ongoing	12
AVXS-101-CL-304	Phase 3, Global multicenter, single arm, single dose, IV presymptomatic trial in SMA Type 1 and Type 2	ongoing	1
AVXS-101-LT-001	long-term follow-up of patients from the AVXS-101-CL-101 study	ongoing	11

* Data cutoff date = May 8, 2018

(Source: FDA statistical reviewer's summary)

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 AVXS-101-CL-101

6.1.1 Objectives

Primary:

- Determination of safety based on the development of unacceptable toxicity: defined as the occurrence of any one Grade III or higher, unanticipated, treatment-related toxicity.

Secondary:

- The time from birth until death or until patient requires at least 16-hour per day of ventilation support for breathing for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative use.

6.1.2 Design Overview

This was a Phase 1, open-label, single-infusion, single-center, dose-escalation clinical trial of AVXS-101 injected intravenously through a peripheral limb vein.

6.1.3 Population

Six months of age and younger at day of vector infusion with Type 1 SMA as defined by the following features:

- Diagnosis of SMA based on gene mutation analysis with bi-allelic SMN1 mutations (deletion or point mutations) and 2 copies of SMN2.
- Onset of disease at birth: up to 6 months of age.
- Hypotonia by clinical evaluation with delay in motor skills, poor head control, round shoulder posture and hypermobility of joints

6.1.4 Study Treatments or Agents Mandated by the Protocol

- Cohort 1 (Low Dose): 6.7×10^{13} vg/kg (n=3)
- Cohort 2A (Intermediate Dose): 2.0×10^{14} vg/kg ($n \geq 3$ and $n \leq 6$)
- Cohort 2B (Intermediate Dose): 2.0×10^{14} vg/kg (n=3)
- Cohort 3 (High Dose): 3.3×10^{14} vg/kg (n=3)

The protocol specified that 3 to 6 patients would be enrolled in Cohort 2A, and 3 patients each would be enrolled in Cohort 2B and Cohort 3. However, by mutual decision of the investigator, Sponsor, and Data Safety Monitoring Board (DSMB), Cohort 2B was expanded to include additional patients and Cohort 2a and Cohort 2b combined treated a total of 12 subjects. The study did not escalate to Cohort 3.

6.1.6 Sites and Centers

Nationwide Children's Hospital was the center that conducted the trial.

6.1.7 Surveillance/Monitoring

An independent DSMB continuously monitored the safety of patients and the DSMB meetings were to occur on a quarterly basis. The DSMB reviewed reports describing the status of the study, patient safety data, and any other key information related to

safety/conduct of the study. The DSMB could recommend early termination of the study for safety reasons. Study enrollment could be halted by the investigator and/or Sponsor when any patient experienced a Grade 3 or higher AE toxicity that was possibly, probably, or definitely related to the AVXS-101. This included any patient death, important clinical laboratory finding, or any severe local complication in the injected area related to the administration of AVXS-101.

6.1.8 Endpoints and Criteria for Study Success

Safety:

- Incidence of Grade III or higher, unanticipated, treatment-related toxicity.

Efficacy:

- Permanent ventilation free survival, which is defined as time to death or until patient requires at least 16-hour per day of ventilation support for breathing for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative use
- Score change in CHOP-INTEND from baseline
- Achievement of significant development milestones including but not limited to the ability to sit alone and roll over unassisted

6.1.9 Statistical Considerations & Statistical Analysis Plan

Due to the nature of the single arm, Phase I study, statistical analyses were descriptive.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

6.1.10.1.1 Demographics

Demographics of subjects who were enrolled in study AVXS-101-CL-101 are summarized in Table 3.

Table 3. AVXS-101-CL-101 subject demographics

	Cohort 1 (N=3)	Cohort 2 (N=12)	Combined (N=15)
Age (months)			
Mean (SD)	6.3 (0.75)	3.4 (2.1)	4 (2.2)
Median	5.9	3.1	4.1
Min, Max	5.9, 7.2	0.9, 7.9	0.9, 7.9
Sex n (%)			
Female	2 (67%)	7 (58%)	9 (60%)
Male	1 (33%)	5 (42%)	6 (40%)
Ethnicity n (%)			
Hispanic or Latino	0	2 (17%)	2 (13%)
Not Hispanic or Latino	3 (100%)	10 (83%)	13 (87%)
Race n (%)			
White	3 (100%)	11 (92%)	14 (93%)
Other	0	1 (8%)	1 (7%)

(Source: FDA statistical reviewer's analysis)

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 4 summarizes the medical history of the enrolled subjects.

Table 4. Medical history of each enrolled subjects

Subjects ID/baseline age (Month)	Cohort	Age of Symptom Onset (Month)	Family History	Baseline SMA Symptom				
				HYPOTONIA	LIMB WEAKNESS	PNEUMONIA OR RESPIRATORY SYMPTOMS	SWALLOWING OR FEEDING DIFFICULTIES	TONGUE FASCICULATIONS
(b) (6) 5.9	1	3	Yes	√	√	√		
5.9	1	1	No	√	√			
7.2	1	1	No	√			√	
5.6	2	3	Unknown	√	√			
4.2	2	1	No	√	√			
1.9	2	1	Yes	√	√			
3.6	2	1	No	√	√		√	
7.9	2	2	No	√	√		√	
4.9	2	3	No	√	√		√	
0.9	2	0	No	√				
2.3	2	1	No	√	√			
2.6	2	2	Yes	√	√			
0.9	2	0	Yes	√	√			
4.1	2	2	No	√	√		√	
2.1	2	1	No	√	√		√	

(Source: AVXS-101-CL-101 study report Listing 16.2.4.2-14 with minor adaption)

6.1.10.1.3 Subject Disposition

Three subjects (Cohort 1) were treated with the low dose (6.7×10^{13} vg/kg) and 12 subjects (Cohort 2) were treated with the intermediate dose (2.0×10^{14} vg/kg). All 15 subjects completed the 24-month follow-up period.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Efficacy Endpoint #1

Permanent ventilation free survival

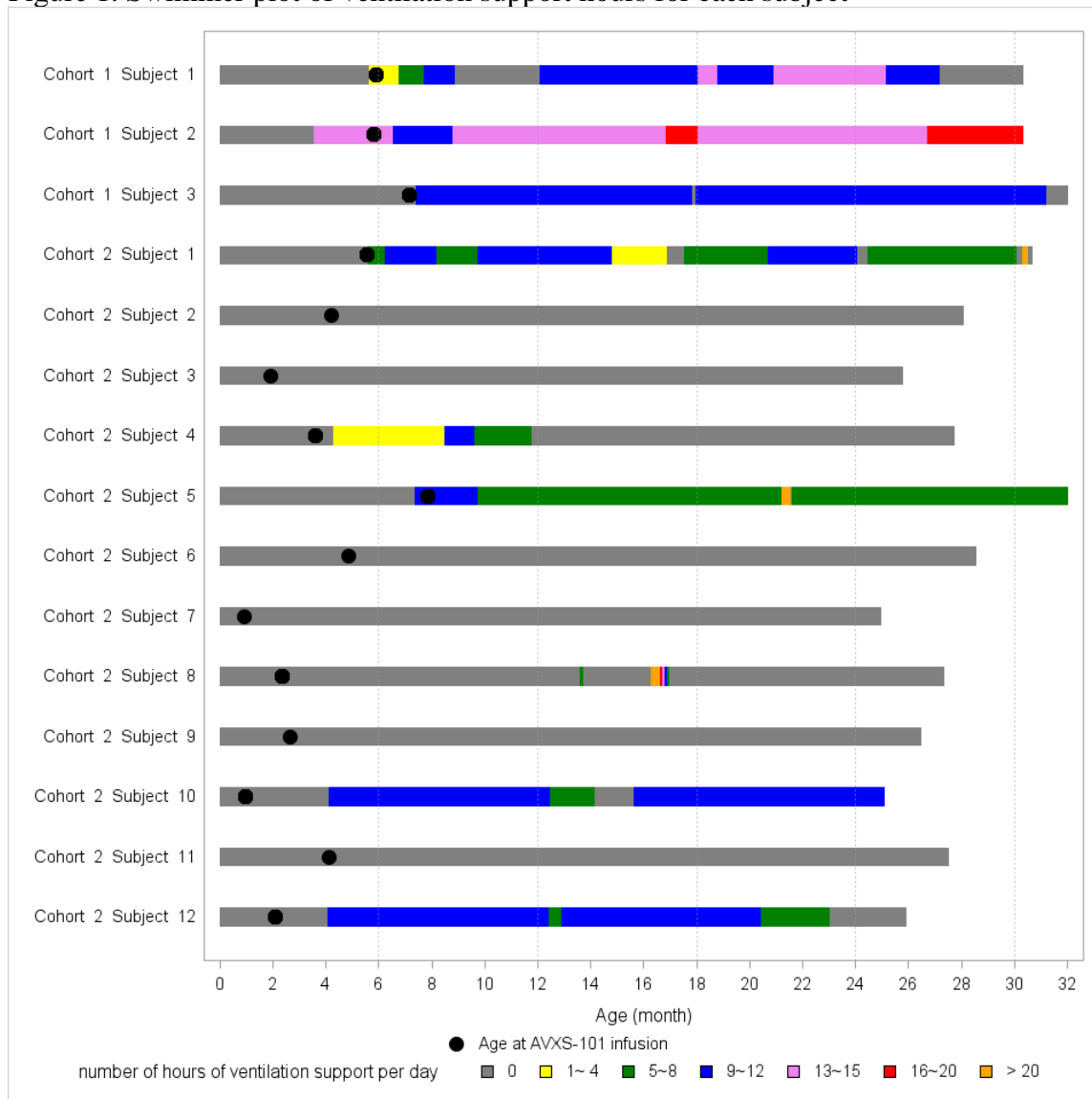
Figure 1 shows the swimmer plot of ventilation support for each subject. The follow-up time were between 713 and 765 days. Subjects who had no ventilation support are represented by a grey bar. For those with ventilation support, the number of hours of ventilation support per day is color coded.

Four subjects had over 16 hours of ventilation support per day for at least one day, one of whom met the efficacy endpoint of over 16 hours of ventilation support per day for 14 or more consecutive days.

- Subject AVXS-101-CL-101-(b) (6) was on 16 hours of ventilation support per day from 2015-07-27 to 2015-08-30 and then 20 hours of ventilation support per day from 2016-05-23 to 2016-09-08. Therefore, this subject had an event for the endpoint of permanent ventilation free survival.

- Subject AVXS-101-CL-101-(b) (6) had 24 hours of ventilation support per day from 2016-12-24 to 2016-12-28.
- Subject AVXS-101-CL-101-(b) (6) had 24 hours of ventilation support per day from 2016-06-29 to 2016-07-07.
- Subject AVXS-101-CL-101-(b) (6) had 24 hours of ventilation support per day from 2016-12-11 to 2016-12-19, 18 hours of ventilation support per day from 2016-12-19 to 2016-12-21, and then 17 hours of ventilation support per day from 2016-12-21 to 2016-12-22.

Figure 1. Swimmer plot of ventilation support hours for each subject



(Source: FDA statistical reviewer's analysis)

6.1.11.2 Analyses of Other Efficacy Endpoints

Achievement of significant development milestones

None of the Cohort 1 subjects had reached any milestone.

Table 5 summarizes the percentage of subjects reaching each milestone in Cohort 2.

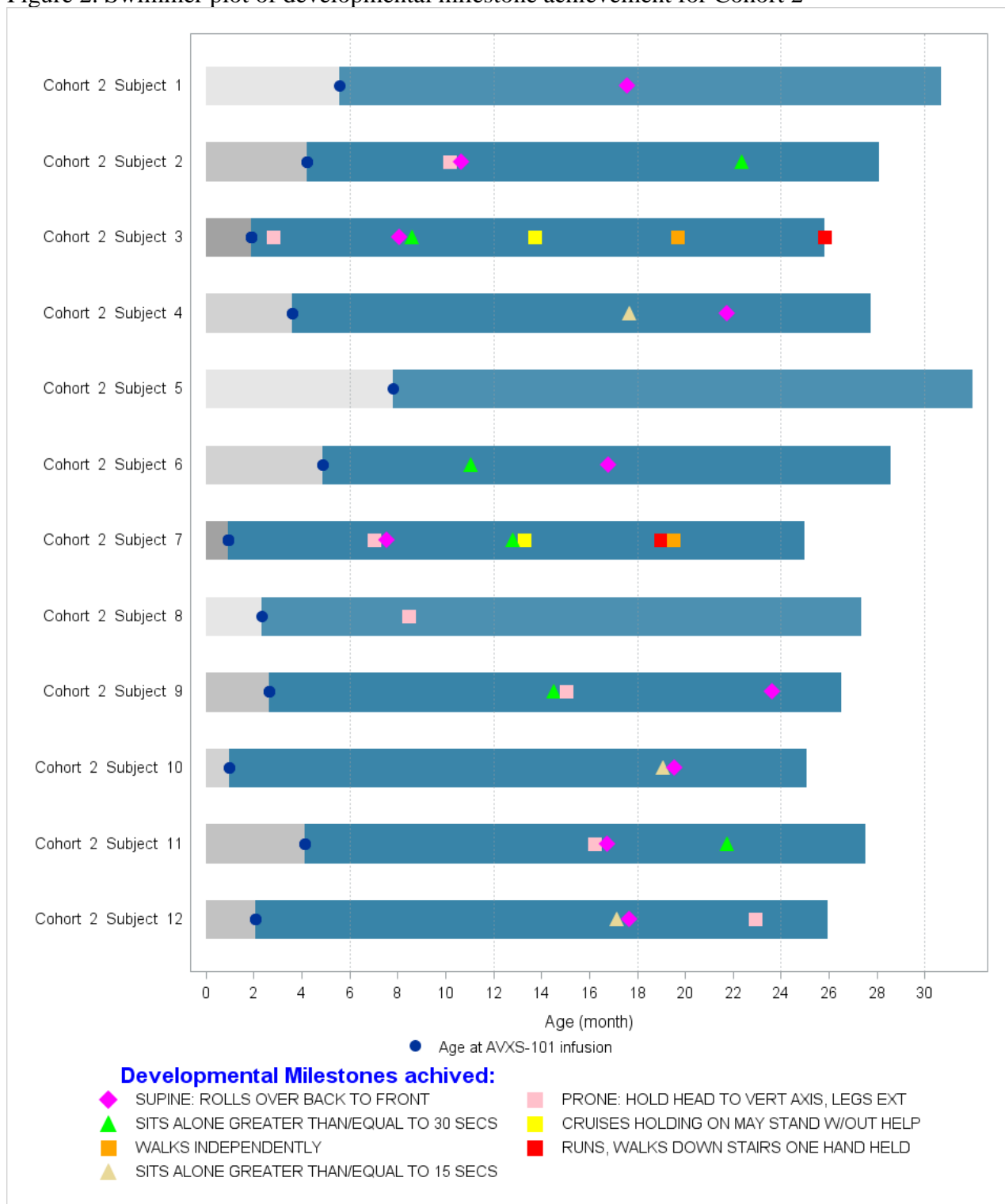
Table 5. Number of Cohort 2 subjects reached developmental milestones

Developmental Milestone	Milestone Achieved in Cohort 2(N=12) n (%)
SUPINE: ROLLS OVER BACK TO FRONT	10 (83%)
PRONE: HOLD HEAD TO VERT AXIS, LEGS EXT	7 (58%)
SITS ALONE GREATER THAN/EQUAL TO 15 SECS	9 (75%)
SITS ALONE GREATER THAN/EQUAL TO 30 SECS	6 (50%)
CRUISES HOLDING ON, MAY STAND W/OUT HELP	2 (17%)
WALKS INDEPENDENTLY	2 (17%)
RUNS, WALKS DOWN STAIRS ONE HAND HELD	2 (17%)

(Source: FDA statistical reviewer's analysis)

Figure 2 shows the timing of each milestone reached for subjects in Cohort 2.

Figure 2. Swimmer plot of developmental milestone achievement for Cohort 2



(Source: FDA statistical reviewer's analysis)

We notice the following discrepancies regarding milestone achievement between our results and the applicant's report:

1. PRONE: HOLD HEAD TO VERT AXIS, LEGS EXT

The applicant's result showed 8 subjects reached this milestone, while our analysis indicated 7 subjects. The applicant explained that one subject (AVXS-101-CL-101-(b) (6)) did not meet this milestone as recorded in *Developmental Milestone* form, however, this subject reached "Lifts head in prone" milestone as recorded in the *Gross Motor Skills Checklist* form, which they considered this subject reached the PRONE: HOLD HEAD TO VERT AXIS, LEGS EXT milestone.

2. SUPINE: ROLLS OVER BACK TO FRONT

The applicant stated that one subject (AVXS-101-CL-101-(b) (6)) has the achievement recorded at an *Unscheduled visit* and did not count by the applicant.

Table 6 summarizes the number and percentage of subjects developed motor function milestone determined by central review. The follow up time was 24 months.

Table 6. The number and percentage of subjects developed motor function milestone determined by central review

Developmental Milestone achieved	Cohort 2 (N=12) n (%)
Hold head erect \geq 3 seconds, unsupported	11 (92%)
Rolling (back to side from both sides)	9 (95%)
Sits alone $<$ 10 seconds	11 (92%)
Sits alone \geq 10 seconds	10 (83%)
Sits alone \geq 15 seconds	9 (75%)
Sits alone \geq 30 seconds	9 (75%)
Stands with assistance	2 (17%)
Stands alone	2 (17%)
Walks with assistance	2 (17%)
Walks alone	2 (17%)

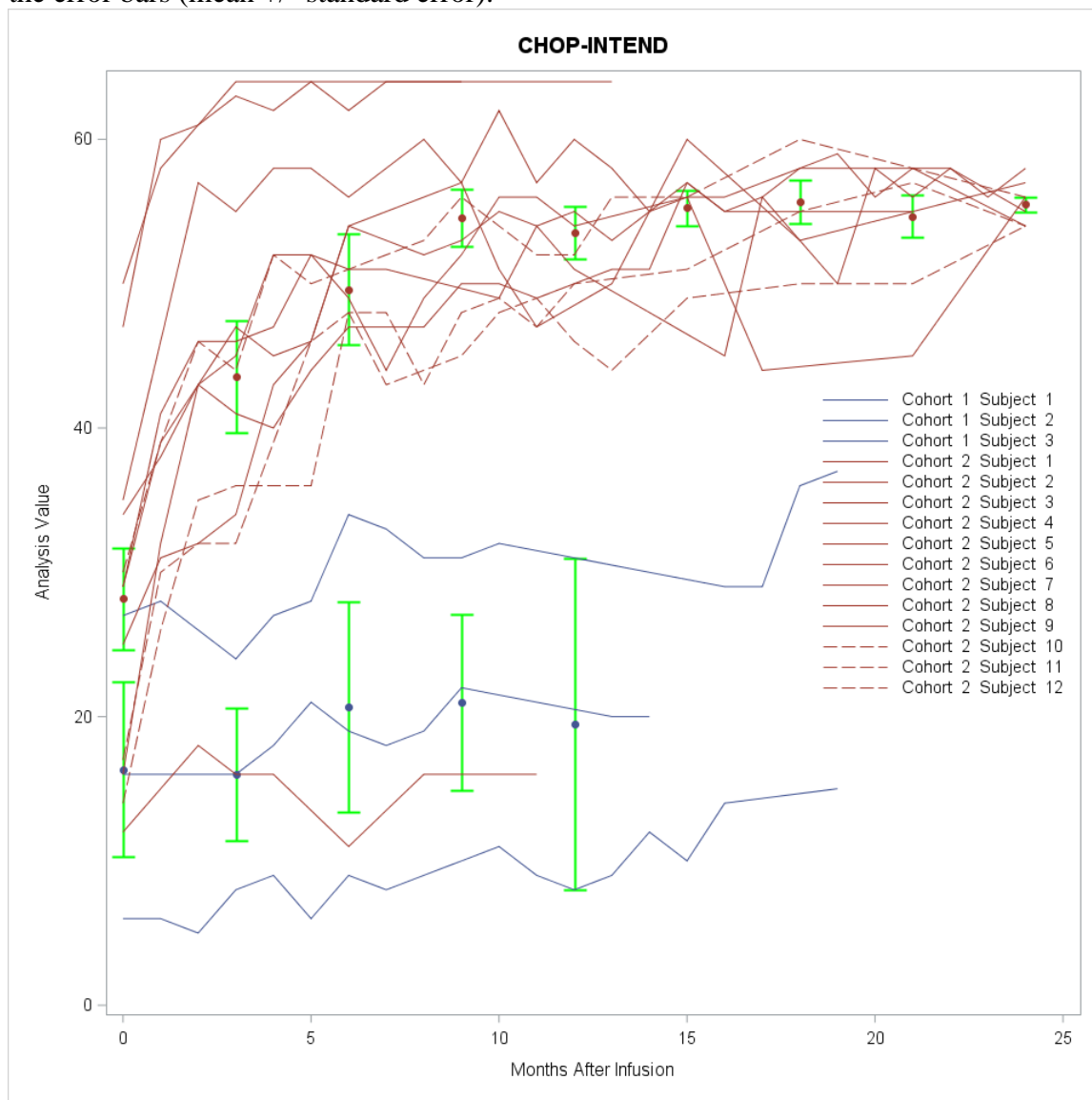
(Source: FDA statistical reviewer's analysis)

Score change in CHOP-INTEND

Figure 3 shows the CHOP-INTEND score at each visit. CHOP-INTEND was developed by Glanzman et. al.³ at the Children's Hospital of Philadelphia to evaluate the motor skills of patients with SMA Type 1. It has 16 items, each item is constructed to capture the movement of one body segment against another or against gravity³. The maximum score is 64. A score \geq 40 is beyond that reported in the literature for maximum function amongst symptomatic patients with SMA Type 1². Furthermore, an average decline of 10.7 points between the ages of 6 and 12 months were reported amongst untreated infants in the natural history study¹.

It appears that subjects' CHOP-INTEND score only changed slightly in Cohort 1. In comparison, subjects' score increased dramatically in Cohort 2 except one subject whose CHOP-INTEND score did not change much. The mean CHOP-INTEND score for Cohort 2 at baseline was 28.2 (standard error=3.5), 49.6 (standard error=3.8) at 6 months, 53.6 (standard error=1.8) at 12 months, and 55.5 (standard error=0.5) at 24 months.

Figure 3. CHOP-INTEND score at each visit for all subjects. The green vertical bars are the error bars (mean \pm standard error).



(Source: FDA statistical reviewer's analysis)

6.1.11.3 Subpopulation Analyses

Cohort 1 did not seem to show efficacy. Cohort 2 showed efficacy across multiple efficacy endpoints and it appears that efficacy results were consistent across age group, gender, race and ethnicity.

For efficacy endpoint of permanent ventilation free survival, none of the Cohort 2 subjects had the endpoint event, thus results were consistent across all subgroups.

For efficacy endpoint of achievement of significant development milestones, as illustrated in Table 7, it appears that subjects treated at a younger age (<3.1 months)

achieved more milestones than subjects treated at an older age (>3.1 months). However, the sample size is too small to make a conclusion.

Table 7 Milestone achieved by age group

Developmental Milestone	Overall N=12	Age Group	
		< 3.1 month (N=6)	>3.1 month (N=6)
SUPINE: ROLLS OVER BACK TO FRONT	10 (83%)	5 (83%)	5 (83%)
PRONE: HOLD HEAD TO VERT AXIS, LEGS EXT	7 (58%)	5 (83%)	2 (33%)
SITS ALONE GREATER THAN/EQUAL TO 15 SECS	9 (75%)	5 (83%)	4 (67%)
SITS ALONE GREATER THAN/EQUAL TO 30 SECS	6 (50%)	3 (50%)	3 (50%)
CRUISES HOLDING ON MAY STAND W/OUT HELP	2 (17%)	2 (33%)	0
WALKS INDEPENDENTLY	2 (17%)	2 (33%)	0
RUNS, WALKS DOWN STAIRS ONE HAND HELD	2 (17%)	2 (33%)	0

(Source: FDA statistical reviewer's analysis)

Table 8 shows that female and male subjects had similar developmental milestone achievement.

Table 8 Milestone achieved by gender

Developmental Milestone	Overall N=12	Gender	
		Female (N=7)	Male (N=5)
SUPINE: ROLLS OVER BACK TO FRONT	10 (83%)	6 (86%)	4 (80%)
PRONE: HOLD HEAD TO VERT AXIS, LEGS EXT	7 (58%)	2 (29%)	5 (100%)
SITS ALONE GREATER THAN/EQUAL TO 15 SECS	9 (75%)	5 (71%)	4 (80%)
SITS ALONE GREATER THAN/EQUAL TO 30 SECS	6 (50%)	3 (43%)	3 (60%)
CRUISES HOLDING ON MAY STAND W/OUT HELP	2 (17%)	1 (14%)	1 (20%)
WALKS INDEPENDENTLY	2 (17%)	1 (14%)	1 (20%)
RUNS, WALKS DOWN STAIRS ONE HAND HELD	2 (17%)	1 (14%)	1 (20%)

(Source: FDA statistical reviewer's analysis)

The majority (92%) of the subjects were White and only 1 (8%) subjects was not White, therefore no meaningful subgroup analysis by race could be conducted.

The majority (83%) of the subjects were non-Hispanic or Latino, and only 2 (17%) subjects were Hispanic or Latino, therefore no meaningful subgroup analysis by ethnicity could be conducted.

For the efficacy endpoint of score change in CHOP-INTEND, all subjects except 1 had CHOP-INTEND score increased dramatically in Cohort 2, thus results were consistent across all subgroups.

6.1.12 Safety Analyses

This section summarizes safety results of Study AVXS-101-CL-101.

6.1.12.1 Methods

Descriptive statistics were used to summarize safety data for study AVXS-101-CL-101. The safety analysis set in this section includes a total of 15 subjects who received AVXS-101, 3 from Cohort 1 and 12 from Cohort 2.

6.1.12.3 Deaths

No deaths occurred during the 24 months follow-up after dosing.

6.1.12.4 Nonfatal Serious Adverse Events

The sponsor reported the following non-fatal serious treatment emergent adverse events (TEAE). All 3 subjects in Cohort 1 (6.7×10^{13} vg/kg) had at least one serious TEAE. Ten (83.3%) subjects in Cohort 2 (2.0×10^{14} vg/kg) had at least one serious TEAE. The most common serious TEAE was infections and infestations (Table 9).

Table 9. Serious TEAE for subject in study AVXS-101-CL-101

Serious Treatment-Emergent Adverse Events by Primary MedDRA System Organ Class and Preferred Term
Safety Analysis Set

System Organ Class/ Preferred Term	6.7 x 10 ¹³ vg/kg (N=3)		2.0 x 10 ¹⁴ vg/kg (N=12)		All Patients (N=15)	
	Events	n (%)	Events	n (%)	Events	n (%)
Any Serious TEAE	7	3 (100.0)	53	10 (83.3)	60	13 (86.7)
Cardiac disorders	0	0	1	1 (8.3)	1	1 (6.7)
Tachycardia	0	0	1	1 (8.3)	1	1 (6.7)
Infections and infestations	5	3 (100.0)	38	9 (75.0)	43	12 (80.0)
Adenovirus infection	0	0	2	2 (16.7)	2	2 (13.3)
Bronchitis	1	1 (33.3)	0	0	1	1 (6.7)
Enterovirus infection	0	0	3	2 (16.7)	3	2 (13.3)
Gastroenteritis	0	0	1	1 (8.3)	1	1 (6.7)
Gastroenteritis viral	0	0	1	1 (8.3)	1	1 (6.7)
Influenza	1	1 (33.3)	0	0	1	1 (6.7)
Lower respiratory tract infection	0	0	2	1 (8.3)	2	1 (6.7)
Parainfluenzae virus infection	1	1 (33.3)	2	2 (16.7)	3	3 (20.0)
Pneumonia	0	0	10	7 (58.3)	10	7 (46.7)
Pneumonia parainfluenzae viral	0	0	1	1 (8.3)	1	1 (6.7)
Pneumonia respiratory syncytial viral	1	1 (33.3)	2	2 (16.7)	3	3 (20.0)
Pneumonia viral	0	0	1	1 (8.3)	1	1 (6.7)
Postoperative wound infection	0	0	2	1 (8.3)	2	1 (6.7)
Respiratory syncytial virus bronchiolitis	1	1 (33.3)	2	2 (16.7)	3	3 (20.0)
Rhinovirus infection	0	0	5	2 (16.7)	5	2 (13.3)
Upper respiratory tract infection	0	0	3	3 (25.0)	3	3 (20.0)
Viral upper respiratory tract infection	0	0	1	1 (8.3)	1	1 (6.7)
Injury, poisoning and procedural complications	0	0	2	2 (16.7)	2	2 (13.3)
Femur fracture	0	0	1	1 (8.3)	1	1 (6.7)
Post procedural haemorrhage	0	0	1	1 (8.3)	1	1 (6.7)
Investigations	1	1 (33.3)	6	4 (33.3)	7	5 (33.3)
Enterovirus test positive	0	0	1	1 (8.3)	1	1 (6.7)
Human rhinovirus test positive	0	0	2	2 (16.7)	2	2 (13.3)
Norovirus test positive	0	0	1	1 (8.3)	1	1 (6.7)
Oxygen saturation decreased	0	0	1	1 (8.3)	1	1 (6.7)
Transaminases increased	1	1 (33.3)	1	1 (8.3)	2	2 (13.3)
Metabolism and nutrition disorders	0	0	1	1 (8.3)	1	1 (6.7)
Dehydration	0	0	1	1 (8.3)	1	1 (6.7)
Respiratory, thoracic and mediastinal disorders	1	1 (33.3)	5	5 (41.7)	6	6 (40.0)
Atelectasis	0	0	1	1 (8.3)	1	1 (6.7)
Pneumonia aspiration	0	0	2	2 (16.7)	2	2 (13.3)
Respiratory distress	0	0	2	2 (16.7)	2	2 (13.3)
Respiratory failure	1	1 (33.3)	0	0	1	1 (6.7)

(Source: AVXS-101-CL-101 study report Table 14.3.16-24)

6.1.12.5 Adverse Events of Special Interest (AESI)

The AESI was Hepatic-Related disorders and the applicant reported no such events occurred.

Insert text here

6.1.12.7 Dropouts and/or Discontinuations

No dropouts or discontinuation occurred during the 24 months follow-up after dosing.

6.2 AVXS-101-CL-001

Study AVXS-101-CL-001 (Study LT-001 for a short form) is an ongoing, observational, long-term, single-center study of patients who were dosed in and have completed Study AVXS-101-CL-101 (Study 101 for a short form). Visits occur annually. As of 31 Dec 2018, 13 of the 15 patients from Study 101 had enrolled in Study LT-001. The applicant provided a brief study report of Study 001 in their 120-day additional efficacy update. These are the major findings:

- All 13 (100%) of the patients who enrolled in Study LT-001 were alive as of 31 Dec 2018. These patients ranged from 39.1 to 62.4 months of age (39.1 to 55.3

months of age for the 10 patients treated at the proposed therapeutic dose). The time since dosing ranged from 37 to 56.5 months (37 to 49.7 months for the 10 patients treated with the proposed therapeutic dose).

- b. Table 10 summarizes the highest developmental motor milestone achievement in Study 101 and Study LT-001 and nusinersen usage for subjects treated at the therapeutic dose.

It appears that compared to the video-confirmed milestones captured at the end of Study 101, there was no evidence of loss of the highest acquired developmental motor milestones.

Of the 10 enrolled patients from Study 101 who received the proposed therapeutic dose, nusinersen usage data are available for all 10 patients at the baseline visit and five patients at the 1-year follow-up visit. Four patients are documented as taking nusinersen. Two patients were taking nusinersen at the baseline visit. Three patients were taking nusinersen at the 1-year follow-up visit. Of the two patients taking nusinersen at the baseline visit, one is documented as taking nusinersen at the 1-year follow-up visit; data are not available for the other patient. Based on this small dataset, there are no clear trends between use of nusinersen and efficacy in Study LT-001.

Table 10. Highest Developmental Motor Milestone Achievement in Study 101 and Study LT-001 and Nusinersen Usage

Patient ID	Highest Milestone Achieved in Study 101 (Video-Confirmed)	Highest Milestone Achieved in Study LT-001	Nusinersen Usage at Baseline in Study LT-001	Nusinersen Usage at Year 1 in Study LT-001
Therapeutic Dose				
(b) (6)	Sits alone >=5 seconds	Sitting without support	No	
	Sits alone >=30 seconds	Data Not Recorded ¹	Yes	
	Walks alone	Walk alone	No	
	Sits alone >=15 seconds	Stand with assistance	Yes	Yes
	None	Not in Study	Not in Study	Not in Study
	Sits alone >=30 seconds	Not in Study	Not in Study	Not in Study
	Walks alone	Walk alone	No	
	Sits alone >=30 seconds	Stand with assistance ²	No	No
	Sits alone >=30 seconds	Sitting without support	No	Yes
	Sits alone >=30 seconds	Sitting without support	No	Yes
	Sits alone >=30 seconds	Sitting without support	No	
	Sits alone >=30 seconds	Sitting without support	No	No

¹ After the 31 Dec 2018 data cutoff date, on 14 Jan 2019 Patient (b) (6) was seen and recorded as sitting without support

² Milestone achievement recorded at study entry but not maintained at 1-year post study entry assessment.

(Source: 120 day ADDITIONAL CLINICAL EFFICACY UPDATE Table 2)

6.3 AVXS-101-CL-303

Study AVXS-101-CL-303 (Study 303 for a short form) is an ongoing, Phase 3, open-label, single-arm, single-dose, multicenter study (conducted in the United States) using

intravenously administered (IV) AVXS-101 for the treatment of patients with SMA Type 1 with 1 or 2 copies of the *SMN2* gene.

The sponsor provided a brief study report of Study 303 in their 120-day additional efficacy update. These are the major findings:

- a. As of 31 Dec 2018, 21 of the 22 patients were alive without permanent ventilation. The surviving patients ranged in age from 8 to 16.3 months and were 6.5 to 14.1 months post-dose. One patient died due to disease progression.
- b. Development milestone achieved is shown in Table 11.

Table 11. Developmental Motor Milestone Achievement in Study 303

Developmental Milestone achieved	n (%) (N=22)
Hold head erect \geq 3 seconds, unsupported	17 (77.3%)
Rolling (back to side from both sides)	7 (31.8%)
Sits independently for greater than 10 seconds*	6 (27.3%)
Sits alone without support for at least 30 seconds	8 (36.4%)
Supports own weight for at least 2 seconds	1 (4.5%)

*The WHO definition of sitting independently differs from the Bayley scale definition for sitting alone without support, thus not all patients who achieve sitting alone without support for 30 seconds by the Bayley definition will achieve sitting independently for 10 seconds by the WHO definition, and vice versa.
(Source: adapted 120 day ADDITIONAL CLINICAL EFFICACY UPDATE Table 1)

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

ZOLGENSMA is a gene therapy. It consists of adeno associated virus (AAV) vector expressing the human Survival Motor Neuron (SMN) gene. This Biologics License Application (BLA) seeks licensure of ZOLGENSMA for the treatment of pediatric patients with infantile-onset spinal muscular atrophy (SMA) with confirmed biallelic mutations in the *SMN1* gene.

The primary source of evidence to support this application is a Phase I, single center, single arm, single dose, dose escalation study (AVXS-101-CL-101). Fifteen (15) subjects were enrolled, and 3 subjects were treated at the low dose of 6.7×10^{13} vg/kg (Cohort 1) and the other 12 were treated at the therapeutic dose of 2.0×10^{14} vg/kg (Cohort 2).

For Cohort 2 (n=12), no subjects died or needed permanent ventilation (defined as at least 16-hour per day of ventilation support for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative use) within 24 months after infusion. In comparison, in a natural history study¹ only 8% of patients were over 24 months of age and permanent ventilation free. Eleven subjects (92%) reached the developmental milestone of holding head erect for at least 3 seconds unsupported, 9 (75%) were able to roll back to side from both sides, 9 (75%) were able to sit alone for at least 30 seconds, 2

subjects were able to stand alone and walk independently. In addition, the mean Chop-INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders) score increased from baseline of 28.2 (standard error=3.5) to 49.6 (standard error=3.8) at 6 months, 53.6 (standard error=1.8) at 12 months, and 55.5 (standard error=0.5) at 24 months. In general clinical practice, untreated SMA Type 1 children 6 months of age or older do not surpass a score of 40 points on the CHOP-INTEND². Furthermore, an average decline of 10.7 points between the ages of 6 and 12 months were reported amongst untreated infants in the natural history study¹.

For Cohort 1 (n=3), one subject needed permanent ventilation. No subject developed any major developmental milestone. Their CHOP-INTEND scores only changed slightly over the course of the trial.

No deaths occurred during the 24 months follow-up after dosing in study AVXS-101-CL-101. All 3 subjects in Cohort 1 (6.7×10^{13} vg/kg) had at least one serious TEAE. Ten (83.3%) subjects in Cohort 2 (2.0×10^{14} vg/kg) had at least one serious TEAE. The most common serious TEAE was infections and infestations. Three (100%) subjects in Cohort 1 and 9 (75%) subjects in Cohort 2 had AEs in this category.

10.2 Conclusions and Recommendations

The statistical analysis results provide evidence to support the applicant's proposed indication for ZOLGENSMA in this BLA.

11. REFERENCES

1. Kolb SJ, Coffey CS, Yankey JW, et al. Natural history of infantile-onset spinal muscular atrophy. *Ann Neurol*. 2017;82(6):883-891.
2. Finkel RS, McDermott MP, Kaufmann P, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. *Neurology*. 2014;83(9):810-817.
3. Glanzman AM, Mazzone E, Main M, et al. The Children's Hospital of Philadelphia Infant TEST of Neuromuscular Disorders (CHOP INTEND): test development and reliability. *Neuromuscul Disord*. 2010 Mar; 20(3): 155–161.