

BLA Clinical Review Memorandum

Application Type	BLA
STN	125694/0
CBER Received Date	Oct. 1, 2018
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Division / Office	DCEPT / OTAT
Priority Review (Yes/No)	Yes
Reviewer Name(s)	Mike Singer, MD, PhD
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Review Completion Date / Stamped Date	May 23, 2019
Supervisory Concurrence	Lei Xu, MD, PhD Tejashri Purohit-Sheth, MD
Applicant	AveXis, Inc.
Established Name	onasemnogene abeparvovec-xioi
(Proposed) Trade Name	Zolgensma
Pharmacologic Class	Adeno-associated virus gene therapy vector
Formulation(s), including Adjuvants, etc.	Suspension with a nominal concentration of 2.0×10^{13} vg/mL and excipients 20 mM Tris (pH 8.0), 1 mM magnesium chloride (MgCl_2), 200 mM sodium chloride (NaCl) and 0.005% poloxamer 188
Dosage Form(s) and Route(s) of Administration	Recommended dose is 1.1×10^{14} vg/kg, administered by intravenous infusion
Dosing Regimen	Single-dose
Indication(s) and Intended Population(s)	For the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the <i>survival motor neuron 1 (SMN1)</i> gene
Orphan Designated (Yes/No)	Yes

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GLOSSARY

AAV	adeno-associated virus
AAV9	adeno-associated virus serotype 9
Ab	antibody
ACTIVE-mini	Ability Captured Through Interactive Video Evaluation–mini
AESI	adverse event of special interest
ALT	alanine aminotransferase
anti-AAV9	antibodies directed against adeno-associated virus serotype 9
(b) (4)	
AST	aspartate aminotransferase
AVXS-101	earlier name for Zolgensma (onasemnogene abeparvovec-xioi)
AVXS-101-CL-101	Trial #1 (Study CL-101)
AVXS-101-CL-303	Trial #2 (Study CL-303)
Bayley-III	Bayley Scales of Infant and Toddler Development, 3 rd edition
BiPAP	Bilevel Positive Airway Pressure respiratory support
BLA	Biologics License Application
BIMO	Bioresearch Monitoring
CFR	Code of Federal Regulations
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CL-101	Trial #1
CL-303	Trial #2
CMAP	compound motor action potential
CRF	case report form
ECG	electrocardiogram
ECHO	echocardiogram
EIM	electrical impedance myography
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot assay
EMA	European Medicines Agency
ET	early termination
GCP	Good Clinical Practice ethical and scientific quality standards
GGT	gamma-glutamyl-transpeptidase
Hgb	hemoglobin
anti-hSMN	antibodies against the human survival motor neuron protein
HIV	human immunodeficiency virus
ID	identification
IND	Investigational New Drug application
INR	international normalized ratio
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MUNE	motor unit number estimation
NIV	non-invasive ventilation
PDUFA	Prescription Drug User Fee Act
(b) (4)	
PI	Prescribing Information
PK	pharmacokinetics
PLI	pre-license inspection

PMC	postmarketing commitment
PMDA	Pharmaceuticals and Medical Devices Agency
PMR	postmarketing requirement
PNCR	Pediatric Neuromuscular Clinical Research database
PREA	Pediatric Research Equity Act
(b) (4)	
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SEM	standard error of the mean
SFC	spot-forming cells
SMA	spinal muscular atrophy
SMN1	<i>survival motor neuron 1</i> gene
SMN2	<i>survival motor neuron 2</i> gene
SMN	survival motor neuron protein
snRNPs	small nuclear ribonucleoproteins
PBMC	peripheral blood mononuclear cell
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VAI	voluntary action indicated
vg	vector genomes
vg/kg	vector genomes per kilogram of body weight
WHO	World Health Organization

1. EXECUTIVE SUMMARY

Onasemnogene abeparvovec-xioi (proprietary name: Zolgensma) is a recombinant adeno-associated virus serotype 9-based gene therapy designed to deliver a gene encoding the human survival motor neuron (SMN) protein.

The proposed indication for onasemnogene abeparvovec-xioi is for treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the *survival motor neuron 1 (SMN1)* gene.

SMA is an autosomal recessive disease caused by mutation of *SMN1*, which results in a paucity of SMN protein in motor neurons of the brainstem and spinal cord. The phenotype is influenced by the nearby gene *SMN2*: additional copies of *SMN2*, and the c.859G>C modification in exon 7 of *SMN2*, correlate with reduced severity of disease. Pediatric patients less than 2 years of age with SMA most commonly have two copies of *SMN2*. Such infants may appear normal at birth, but within 6 months typically develop severe flaccid paralysis; they do not achieve developmental milestones such as the ability to sit independently, and generally die of respiratory failure by age 2 years.

The efficacy of onasemnogene abeparvovec-xioi in pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the *SMN1* gene has been evaluated in an ongoing Phase 3 clinical trial (Study CL-303) and a completed Phase 1 clinical trial (Study CL-101). Analysis of data from the Phase 3 trial (as of the March 8, 2019 data cutoff) provided the primary evidence of effectiveness; results from the Phase 1 trial support effectiveness.

All subjects enrolled in these trials experienced onset of clinical symptoms consistent with SMA before age 6 months (i.e., “infantile-onset SMA”). All subjects had genetically-confirmed bi-allelic deletions of *SMN1*; two copies of *SMN2*; and lacked the c.859G>C modification in exon 7 of *SMN2*. In both trials, onasemnogene abeparvovec-xioi was delivered as a single-dose intravenous infusion; subjects also received a course of oral corticosteroid to suppress potential immune reactions to the product.

The ongoing Phase 3 trial is an open-label, single-arm study using available natural history data as the control. The trial was designed to evaluate efficacy and safety of onasemnogene abeparvovec-xioi in pediatric subjects with infantile-onset SMA, and has two primary efficacy endpoints: survival at 14 months of age; and the proportion of subjects able to sit independently for ≥ 30 seconds by 18 months of age. Survival was defined as avoidance of either death or permanent ventilation (tracheostomy or the requirement of ≥ 16 hours of respiratory assistance per day via non-invasive ventilatory support for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation). Sitting independently was defined according to the Bayley Scales of Infant and Toddler Development, 3rd edition. The trial enrolled 21 subjects with infantile-onset SMA from 16 sites in the United States. At baseline, none of the subjects required non-invasive ventilatory (NIV) support. All received onasemnogene abeparvovec-xioi at a dose of 1.1×10^{14} vector genomes per kilogram of body weight (vg/kg). The mean age at infusion was 3.9 months (range 0.5 to 5.9 months).

As of the data cutoff, 13 subjects had reached the time point of age 14 months, and 1 subject had reached the time point of age 18 months.

One of the 21 subjects had died at age 7.8 months due to disease progression; one subject withdrew from the study at age 11.9 months; and the remaining 19 subjects were alive without permanent ventilation. The 19 surviving subjects (16 of whom had not required daily NIV support) ranged from 9.4 to 18.5 months of age.

Ten of the 21 subjects in the trial (48%) had achieved the ability to sit independently for ≥ 30 seconds by 18 months of age (mean age 12.1 months when achieving sitting independence; range 9.2 to 16.9 months).

Based on the natural history of the disease, no patients meeting the study entry criteria would be expected to attain the ability to sit without support, and only approximately 25% would be expected to remain alive without permanent ventilation beyond 14 months of age.

The completed Phase 1 trial was an open-label, single-arm, dose-escalation study in a total of 15 pediatric subjects with infantile-onset SMA. The trial was designed to evaluate safety and preliminary efficacy of onasemnogene abeparvovec-xioi. Two dose cohorts were compared: a low-dose cohort (3 subjects) and a high-dose cohort (12 subjects).

The dose administered to subjects in the low-dose cohort was one-third of the dose administered to subjects in the high-dose cohort. However, the precise doses of onasemnogene abeparvovec-xioi administered to subjects in this completed clinical trial are unclear, due to a change in the method of measuring onasemnogene abeparvovec-xioi concentration, and to decreases in the concentration of stored onasemnogene abeparvovec-xioi over time. These issues became apparent after completion of the trial. The retrospectively-estimated dosage range in the high-dose cohort is approximately 1.1×10^{14} to 1.4×10^{14} vg/kg, with substantial uncertainty.

The mean age of subjects at the time of treatment was 6.3 months (5.9 to 7.2 months) in the low-dose cohort and 3.4 months (0.9 to 7.9 months) in the high-dose cohort.

By the conclusion of the study 24 months after infusion, one of the 3 subjects in the low-dose cohort required permanent ventilation, whereas all 12 subjects in the high-dose cohort were alive without permanent ventilation. In the low-dose cohort, none of the subjects achieved developmental motor milestones such as sitting independently or walking; in the high-dose cohort, 9 of the 12 subjects (75%) were able to sit independently for ≥ 30 seconds, and 2 subjects (17%) were able to walk without assistance. Comparison of these outcomes to natural-history controls supports the effectiveness of onasemnogene abeparvovec-xioi; comparison of the results of the high-dose cohort to those of the low-dose cohort provides further support.

The safety database primarily consists of 42 pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the *SMN1* gene who received intravenous infusion of onasemnogene abeparvovec-xioi, all in open-label clinical trials (the completed Phase 1 trial, with some subjects continuing in an ongoing observational long-term follow-up study; the ongoing US Phase 3 trial; and one ongoing Phase 3 trial conducted outside the United States). Also contributing to the safety database is information from 46 US patients with infantile-onset SMA who received onasemnogene abeparvovec-xioi from the applicant under the FDA expanded access program for investigational drugs

(compassionate use); in all cases, the product was administered by intravenous infusion.

Of the 42 clinical trial subjects, 39 received onasemnogene abeparvovec-xioi at or above the recommended dose, and 3 received a lower dose. In the expanded access program, all 46 patients received the recommended dose. The total safety population ranged in age from 0.4 months to 16 months at the time of infusion.

There have been two deaths: one in the ongoing US Phase 3 clinical trial, and one in an ongoing non-US clinical trial. The US subject died 170 days after infusion; the cause of death was respiratory failure secondary to disease progression. The non-US subject died 52 days after infusion; the subject initially presented with respiratory insufficiency 12 days after infusion, developed seizures and was found to have leukoencephalopathy about 30 days after infusion, and ultimately died following withdrawal of life support.

There have been three serious adverse reactions: acute serious liver injury in one patient who received the product through the expanded access program; and elevation of aminotransferases to above 20 x upper limit of normal (ULN) (up to 48 x ULN) in two US clinical trial subjects. The most frequent adverse reactions (incidence $\geq 5\%$) observed in the US clinical trials were elevated aminotransferases and vomiting.

All the clinical trials enrolled only subjects with baseline anti-AAV9 antibody titers of $\leq 1:50$, measured using an enzyme-linked immunosorbent assay (ELISA). The safety and efficacy of onasemnogene abeparvovec-xioi in subjects with anti-AAV9 antibody titers above 1:50 have not been evaluated. Following onasemnogene abeparvovec-xioi infusion, increases from baseline in anti-AAV9 antibody titers occurred in all subjects. In the completed Phase 1 clinical trial, anti-AAV9 antibody titers reached at least 1:102,400 in every patient, and titers exceeded 1:819,200 in most patients. High anti-AAV9 antibody titers following the initial infusion are expected to preclude the possibility of re-administration of onasemnogene abeparvovec-xioi or any other AAV9 vector-based gene therapy.

The reviewed safety data do not warrant a Risk Evaluation and Mitigation Strategies (REMS), a safety postmarketing requirement (PMR) study, or a safety postmarketing commitment (PMC) study. The postmarketing risk mitigation plans include product labeling; a registry study; as well as ongoing and planned long-term follow-up of subjects in current clinical trials.

In conclusion, SMA in pediatric patients less than 2 years of age with bi-allelic mutations in the *SMN1* gene is a serious and life-threatening genetic disorder and represents an unmet medical need. The submitted data from adequate and well-controlled trials provide substantial evidence of effectiveness for treatment of pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the *SMN1* gene. Efficacy was based on improvement in survival, and achievement of developmental motor milestones such as sitting without support. The more serious risks associated with intravenous infusion of onasemnogene abeparvovec-xioi include acute serious liver injury, and substantial elevation of aminotransferases. These risks can be mitigated by routine medical management, adequate Prescribing Information (PI), and the postmarketing plan proposed by the applicant. The efficacy and safety data in the BLA support a favorable benefit-risk profile for pediatric patients less than 2 years of age with SMA with bi-allelic

mutations in the *SMN1* gene. Therefore, the Clinical Reviewer recommends regular approval of onasemnogene abeparvovec-xioi with a recommended one-time dose of 1.1×10^{14} vg/kg, administered by intravenous infusion.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Demographic information for the 21 subjects in the ongoing Phase 3 trial (Trial #2, CL-303) is shown in Table 1.

The small number of subjects constrains any subgroup analyses by age, sex, race, or ethnicity. In addition, some of the subjects have not yet reached the ages at which assessment of the efficacy endpoints are conducted.

Table 1. Demographic and baseline characteristics for Trial #2 (CL-303)

Characteristic	Efficacy Subjects (n = 21)
Age at treatment (months)	
Mean	3.9
Median	3.6
Minimum, Maximum	0.5, 5.9
Sex	
Male	10 (52%)
Female	11 (48%)
Race	
White	10 (48%)
Black or African American	3 (12%)
Asian	2 (9%)
Other	6 (29%)
Ethnicity	
Non-Hispanic or Latino	17 (81%)
Hispanic or Latino	4 (19%)
Weight at baseline (kg)	
Mean	5.9
Minimum, Maximum	3.9, 7.5
Reported swallowing thin liquid	21
Reported required feeding support	0
Reported required ventilatory support	0

The table only contains information from the 21 subjects who were symptomatic at baseline. A total of 22 subjects were involved in the study, one of whom (Subject (b) (6)) was designated as presymptomatic at baseline.

(Source: Modified from Table 1.2 of Applicant's Efficacy Update of Study CL-303, submitted on 4/30/2019)

1.2 Patient Experience Data

Patient experience data in the form of natural history results were used as an external control (Table 2). Natural history data were obtained from the Pediatric Neuromuscular Clinical Research database and the NeuroNEXT database (Finkel et al., 2014; Kolb et al., 2016; Kolb et al., 2017).

Table 2. Patient Experience Data Relevant to this Application

<input type="checkbox"/>	The patient experience data that were submitted as part of the application include:	Section where discussed, if applicable
<input type="checkbox"/>	Clinical outcome assessment (COA) data, such as	
<input type="checkbox"/>	Patient reported outcome (PRO)	
<input type="checkbox"/>	Observer reported outcome (ObsRO)	
<input type="checkbox"/>	Clinician reported outcome (ClinRO)	
<input type="checkbox"/>	Performance outcome (PerfO)	
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input checked="" type="checkbox"/>	Natural history studies	Section 2.1, Disease or Health-Related Condition(s) Studied
<input type="checkbox"/>	Patient preference studies (e.g., submitted studies or scientific publications)	
<input type="checkbox"/>	Other: (Please specify)	
<input type="checkbox"/>	Patient experience data that were not submitted in the application, but were considered in this review	
<input type="checkbox"/>	Input informed from participation in meetings with patient stakeholders	
<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Other: (Please specify)	
<input type="checkbox"/>	Patient experience data was not submitted as part of this application.	

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Overview

Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disorder caused by mutation of the *SMN1* gene, resulting in deficiency of the survival motor neuron (SMN) protein in motor neurons of the brainstem and spinal cord. SMA is the most common monogenic cause of infant mortality, with an incidence of 4-10 per 100,000 live births (Bodamer 2019).

Although clinical presentations demonstrate a continuum of manifestations, SMA historically has been divided into five subtypes based on age of onset and severity (Table 3) (Butchbach 2016).

Table 3. Historical clinical classification of spinal muscular atrophy

Type	Age of onset	Requires respiratory support at birth	Able to sit	Able to stand	Able to walk	Life expectancy	Predicted SMN2 copy number
0	Prenatal	Yes	No	No	No	<6 months	1
1	<6 months	No	No	No	No	<2 years	2
2	6-18 months	No	Yes	No	No	Adulthood	3
3	>18 months	No	Yes	Yes	Assisted	Adulthood	3-4
4	>10 years	No	Yes	Yes	Yes	Adulthood	>4

(Sources: Modified from Butchbach 2016 and Castro and Iannaccone 2014)

Types 0 and 4 are uncommon, with limited information available regarding incidence. In general, patients with SMA type 1 account for about 50% of cases, type 2 about 20%, and type 3 about 30% (Bodamer 2019, D'Amico et al., 2011)

Phenotype is now known to be influenced primarily by the nearby gene *SMN2*: additional copies of *SMN2*, and the c.859G>C modification in exon 7 of *SMN2*, correlate with reduced severity of disease. Exceptions occur infrequently; their underlying cause remains unclear.

A patient's phenotype thus may be more, or less, severe than predicted by genotype. Patients are confirmed as belonging to an SMA subtype retrospectively, based on whether they achieve the ability to sit, stand, or walk.

Reviewer Comment

For decisions regarding administration of gene therapy, the historic subtype classification can be problematic: early treatment may be critical, yet only genetic information and initial clinical findings, or genetic information alone, may be available.

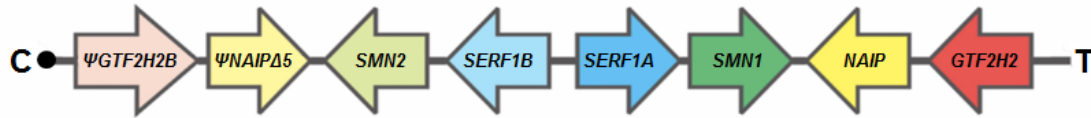
This review therefore generally will refer to the broader category of "infantile-onset SMA" or "pediatric patients < 2 years of age with SMA," consisting of patients exhibiting clinical manifestations consistent with SMA prior to age 6 months, or likely to exhibit clinical manifestations prior to age 6 months based on genetic information. (Of note, all the clinical trials described in this review enrolled primarily patients with infantile-onset SMA with both genetic and clinical features.)

This category encompasses SMA type 1, while including different possible genotypes and avoiding the inherent delay of retrospective classification based on motor milestones. This review will, however, refer to SMA subtypes in reference to scientific or medical findings based on the historical classification.

Scientific Background

Both the *SMN1* and *SMN2* genes are located on the long arm of chromosome 5. That region (5q13) is highly prone to rearrangements and gene conversion (Wirth 2006). Importantly, the region contains a large inverted duplication, unique to humans, giving rise to the centromerically-located paralog *SMN2* (Campbell et al., 1997; Butchbach 2016) (Figure 1).

Figure 1. Organization of the inverted duplication locus on chromosomal region 5q13



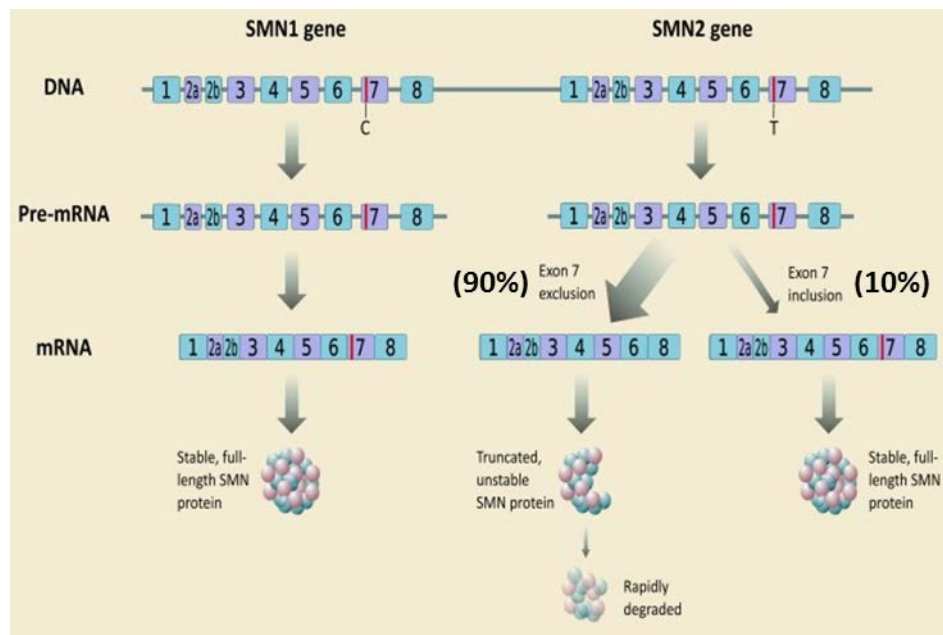
Four protein-coding genes are present within the approximately 500-kilobase inverted duplication in chromosomal region 5q13: *general transcription factor IIH* (*GTF2H2*), *neuronal apoptosis inhibitory protein* (*NAIP*), *survival motor neuron 1* (*SMN1*), and *small EDRK-rich factor 1A* (*SERF1A*). The duplicated genes are *ΨGTF2H2B* (*GTF2H2* pseudogene), *ΨNAIPΔ15* (*NAIP* pseudogene with loss of exon 5), *SMN2*, and *SERF1B*. C, chromosome centromeric end; T, chromosome telomeric end. (Source: Modified from Butchbach 2016).

SMN1 and *SMN2* are nearly identical. Both contain nine exons; the stop codon occurs in exon 7, and exon 8 is not translated (Figure 2) (Bürglen 1996).

SMN2 characteristically differs from *SMN1* by five nucleotide alterations: one nucleotide is exchanged in exon 7 and exon 8, one in intron 6, and two in intron 7. Other variations have been identified, though are not specific to either gene (Wirth et al., 2006).

Notably, the C-to-T transition in exon 7 of *SMN2* is translationally silent, but disrupts an exonic splice enhancer site and creates a new exonic splice silencer. About 90% of *SMN2* pre-mRNA transcripts therefore are alternatively spliced, resulting in production of a shortened, unstable protein. About 10% of *SMN2* transcripts are full-length, and yield functional SMN protein (Figure 2) (Farrar et al., 2017; Wirth et al., 2006; Butchbach 2016). This process enables survival of individuals with *SMN1* mutations, and accounts for the correlation of increased *SMN2* copy number (and the *SMN2* modifier mutation) with milder phenotypes.

Figure 2. Comparison of *SMN1* and *SMN2* genes, transcripts, and protein products

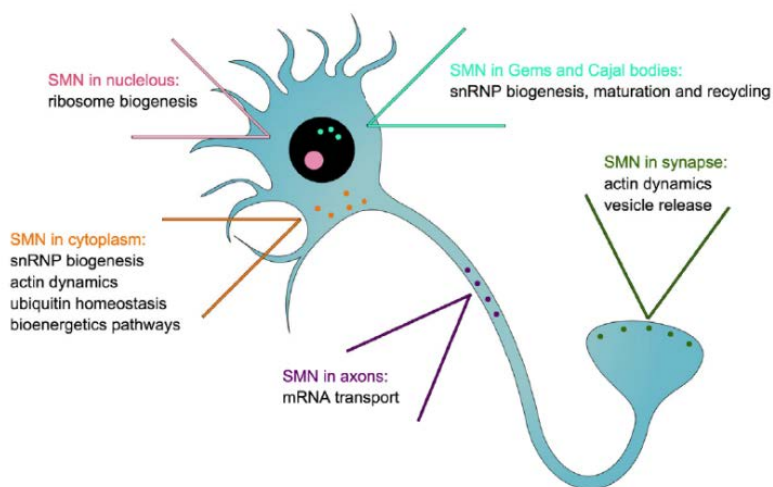


(Source: Modified from Farrar et al., 2017)

Considerable genetic variability has been observed in the number of *SMN2*-containing repeat units per chromosome, ranging from zero to four or more copies. In the general population, most healthy individuals have a total of two copies of *SMN1* and one or two copies of *SMN2* (Wirth 2006).

SMN1 protein is ubiquitously expressed, and has been localized to the cytoplasm, neuronal growth cones, neuronal extensions, nucleolus, and nucleus (Figure 3) (Bowerman et al., 2017). Mutation or deletion in any species carrying a single functional copy of *SMN1* results in early embryonic lethality (Wirth et al., 2006). The protein appears to have multiple roles, including in small nuclear ribonucleoproteins (snRNPs), mRNA transport, cytoskeletal dynamics, ubiquitin-related processes, bioenergetics, and release of synaptic vesicles. The function responsible for the motor neuron pathophysiology seen in SMA, however, remains unknown (Bowerman et al., 2017).

Figure 3. SMN protein localization and functions



(Source: Bowerman et al., 2017)

Clinical Background

SMA type 1 (also known as Werdnig-Hoffman disease) is the most common monogenic cause of infant mortality (Darras 2017), with an estimated incidence of 1 in 10,000 live births and prevalence of about 1–2 per 100,000 (Verhaart, et al., 2017).

SMA type 1 typically presents between birth and 4-6 months, with a median age of symptom onset of 1.2 months (Finkel et al., 2014; Kolb 2016; Arnold et al., 2015). Cognition and eye movement are not affected, and infants often appear alert and attentive (Darras 2017; Kolb and Kissel 2015). Patients develop progressive muscle weakness and atrophy, due to degeneration of motor nuclei in the lower brainstem, and of anterior horn cells in the spinal cord. Physical examination demonstrates weak cry, poor suck and swallow, pooling of secretions in the oropharynx, and severe symmetric flaccid paralysis. Characteristically, SMA type 1 patients are unable to sit without support. Increasing weakness of the respiratory muscles leads to respiratory failure and historically, death before age 2 years. Improvements in care, including ventilatory support and feeding via gastrostomy tube, more recently have enabled prolonged survival (Darras 2017; Kolb and Kissel 2015); mortality now is about 30% at age 2 years,

with approximately half of those survivors fully reliant on noninvasive ventilation (Oskoui et al., 2007).

Two recent natural history studies have provided detailed characterization of SMA type 1 infants with two copies of *SMN2*, which provides historical control data for the present clinical trials (Finkel et al., 2014; Kolb et al., 2016; Kolb et al., 2017).

The median age at death or need for permanent ventilation (at least 16 hours per day for at least 14 consecutive days) was 8 months (95% confidence interval 6-17 months) (Kolb et al., 2016).

Motor testing was performed using the Children's Hospital of Philadelphia Infant Test for Neuromuscular Disorders (CHOP-INTEND). This instrument is a 16-item, 64-point scale, in which higher scores indicate better motor function. CHOP-INTEND was shown to be both reliable as well as sensitive to change over time for patients with SMA type 1 (Glanzman et al., 2010; Glanzman et al., 2011). SMA type 1 patients do not achieve major motor milestones, and experience decline in motor ability. In one natural history study, only one of 34 patients achieved a CHOP-INTEND score of 40 after reaching age 6 months (Finkel et al., 2014). The second study observed that from ages 6 to 12 months, CHOP-INTEND scores decreased by a mean of 10.7 points (Kolb et al., 2016).

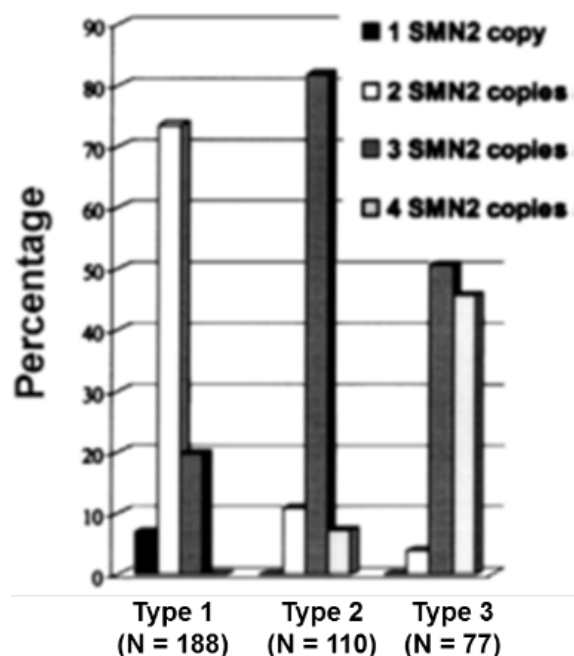
Genotype-Phenotype Discordance

Patients with SMA type 1 most commonly have two copies of *SMN2*. A small proportion of patients with a genotype most likely to result in SMA type 1 nevertheless develop milder disease. The reasons for this discrepancy remain unclear. Patients with milder clinical manifestations may be able to sit or walk, achievements which would result in the phenotypic based designation of SMA type 2 or SMA type 3, respectively.

Reviewer Comment

In the clinical trials discussed in this review, any contribution of genotype-phenotype discordance to the efficacy observed for onasemnogene abeparvovec-xioi cannot be determined.

Figure 4. Frequency of SMA type 1, type 2, and type 3 with *SMN2* copy number



(Source: Feldkotter et al., 2002)

Feldkotter et al. examined the correlation of *SMN2* copy number and phenotypic classification according to historical subtypes (Figure 4). Based on their analysis, they determined the posterior probability of a child with homozygous absence of *SMN1* developing SMA type 1, type 2, or type 3, is conditional on the number of *SMN2* copies. They estimated that a child with one copy of *SMN2* has a risk of >99% of developing SMA type 1, and that a child with two copies of *SMN2* carries a risk of 97% of developing SMA type 1 (Feldkotter et al., 2002).

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

The only FDA-approved treatment currently available for SMA is nusinersen, which received approval for use in children and adults with SMA in December 23, 2016.

Nusinersen is an antisense oligonucleotide, and is delivered via intrathecal injections. Treatment is initiated with 4 loading doses: the first 3 loading doses are administered at 14-day intervals, and the 4th loading dose is then administered 30 days after the 3rd loading dose. A maintenance dose is then administered once every 4 months (Finkel et al., 2017).

The efficacy of nusinersen was demonstrated in a randomized, double-blind, sham-procedure controlled trial involving 121 subjects with infantile-onset SMA with clinical manifestations. The trial was terminated early based on results of a prespecified interim analysis performed after approximately 80 subjects had been enrolled for at least 6 months. The results showed that 39% of subjects in the nusinersen group reached the endpoint of death or permanent assisted ventilation, compared to 68% in the sham-procedure control group. Moreover, in the nusinersen group 8% of subjects

were able to sit independently, and 1% were able to stand; no subjects in the control group reached these developmental motor milestones (Finkel et al., 2017).

Reviewer Comment

The clinical trial demonstrating efficacy of nusinersen for treatment of infantile-onset SMA included a large sample size, and utilized elements such as randomization, double-blind design, and a concurrent sham-procedure control to minimize bias. The enrolled study population was not identical to that of Studies CL-303 or CL-101, and the follow-up duration of the nusinersen trial under the prespecified interim analysis was shorter than that of Studies CL-101 and CL-303. Therefore, this reviewer does not feel that a clear comparison can be made between the results of the nusinersen trial and the results of Studies CL-303 or CL-101.

2.3 Safety and Efficacy of Pharmacologically Related Products

There are no pharmacologically-related products currently available.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

The product is not approved in any country. A Phase 3 clinical trial (CL-302) is ongoing in Europe; a global Phase 3 clinical trial (CL-304) is also ongoing. Death of a subject enrolled in CL-302 has been reported (please see Section 8.4 for details).

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

Major regulatory milestones for the Biologics License Application (BLA) are summarized in Table 4.

Table 4. Major Regulatory Milestones

Date	Milestone
12/20/2011	Pre-IND meeting
8/8/2013	IND submitted
9/27/2013	Fast Track designation granted
9/30/2014	Orphan Drug designation granted
11/6/2015	Transfer of IND sponsorship to AveXis, Inc.
7/15/2016	Breakthrough Therapy designation granted
9/30/2016	Post-Breakthrough Therapy designation Type B meeting to discuss design of Phase 3 clinical trial
5/1/2017	Type B meeting to discuss Phase 3 CMC plans
12/5/2017	Type B End-of-Phase 1 meeting
6/14/2018	Pre-BLA meeting
8/22/2018	Rare Pediatric Disease designation granted
10/1/2018	BLA 125694 submitted
11/28/2018	BLA filed, Priority Review
2/6/2019	BLA 120-day Safety and Efficacy Update received
4/30/2019	Additional safety and efficacy update of ongoing Phase 3 trial (CL-303) received
6/1/2019	PDUFA Action Due Date

BLA, Biologics License Application; CMC, Chemistry, Manufacturing, and Controls; IND, Investigational New Drug application; PDUFA, Prescription Drug User Fee Act.

(Source: FDA clinical review and BLA submission)

Post-Breakthrough Therapy designation Comprehensive Type B meeting to discuss design of Phase 3 trial (9/30/2016)

1. FDA acknowledged applicant's rationale for conducting an open-label, single-arm Phase 3 trial in subjects with infantile-onset SMA. The proposed comparison group was natural history data from the Finkel et al. (Finkel et al., 2014) and NeuroNEXT studies (Kolb et al., 2016; Kolb et al., 2017).
2. FDA recommended the following co-primary endpoint for the proposed Phase 3 clinical trial: (a) the proportion of subjects who survive (i.e., alive without permanent ventilation), and (b) the proportion of subjects who meet the motor milestone of sitting independently.

Pre-BLA Meeting (6/14/2018)

1. FDA agreed that the applicant has demonstrated analytical comparability between the investigational product lots used in the Phase 1 clinical trial (CL-101) and those used in the Phase 3 clinical trial (CL-303).
2. FDA agreed that the applicant may submit BLA based on clinical data from the completed Phase 1 trial and the ongoing Phase 3 trial.
3. The sponsor agreed to provide an updated efficacy dataset from the ongoing Phase 3 clinical trial with the required 4-month safety update following BLA submission.

2.6 Other Relevant Background Information

The product is also undergoing review by the European Medicines Agency (EMA) for approval in Europe, and in Japan by the Pharmaceuticals and Medical Devices Agency (PMDA).

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The BLA submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty. The BLA was filed on November 28, 2018; no filing issues were identified by any of the review disciplines.

3.2 Compliance With Good Clinical Practices and Submission Integrity

All the US studies were conducted under an Investigational New Drug application (IND), in accordance with the regulations specified in 21 CFR 312, and were compliant with Good Clinical Practice (GCP) international ethical and scientific quality standards for the design, conduct, recording, and reporting of clinical trials involving human subjects. The clinical trials included provisions for informed consent by parents or guardians of all study subjects, and for ethical treatment of study subjects.

During the BLA review, routine Bioresearch Monitoring (BIMO) inspections were conducted at four clinical investigator sites that participated in Studies CL-101, CL-303, or LT-001 (Table 5). The inspections did not reveal any significant problems that impact the integrity of the data submitted in the BLA.

Table 5. BIMO Inspection

Site ID	Study Inspected	Study Site	Location	483 Issued	Final Inspection Classification
001	CL-101 CL-303 LT-001	Nationwide Children's Hospital	Columbus, OH	No	No Action Indicated
005	CL-303	Boston Children's Hospital	Boston, MA	No	No Action Indicated
008	CL-303	Stanford Neuroscience Health Center	Palo Alto, CA	No	No Action Indicated
010	CL-303	Nemours Children's Hospital	Orlando, FL	No	No Action Indicated

(Source: FDA BIMO review)

3.3 Financial Disclosures

No significant issues with financial disclosures were identified that could lead to undue bias in the data submitted in support of this BLA.

Covered clinical study (name and/or number):		
<ul style="list-style-type: none"> • AVXS-101-CL-101 • AVXS-101-CL-303 • AVXS-101-LT-001 		
Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: 107		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 5 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Onasemnogene abeparvovec-xioi is a suspension of an AAV vector-based gene therapy. The active ingredient is a recombinant self-complementary vector, in which the double-stranded DNA vector genome is (b) (4) consisting of (b) (4) AAV capsid proteins. The vector DNA (b) (4) instead, the vector DNA contains a transgene encoding the human SMN protein, under control of a cytomegalovirus enhancer/chicken- β -actin hybrid promoter.

Onasemnogene abeparvovec-xioi is formulated in a (b) (4) containing 20 mM Tris, 1 mM magnesium chloride, and 200 mM sodium chloride containing 0.005% poloxamer 188 and sterile-filtered (b) (4) vials.

The completed Phase 1 clinical trial used a single lot of onasemnogene abeparvovec-xioi drug product, manufactured by the initial process (Process A) and administered to both cohorts of subjects. The doses administered in this trial were originally reported to be 6.7×10^{13} vg/kg and 2.0×10^{14} vg/kg, but the assay originally used to determine the concentration of this initial drug product lot was inaccurate and imprecise. The vector genome concentration was revised 44 months after manufacture of this initial drug product lot, following measurement with an accurate and precise assay. Based on the revised concentration of the initial drug product lot, the doses in the Phase 1 trial were retrospectively restated as 3.7×10^{13} vg/kg and 1.1×10^{14} vg/kg.

Stability data submitted late in the review cycle indicate that the product is unstable during long-term frozen storage. Because of the uncertainty about the rate of decay of the initial drug product lot, the Agency is unable to accurately determine the doses that were administered to subjects in the Phase 1 trial. The Agency estimates that the doses administered to the low-dose cohort of the Phase 1 trial may have ranged from approximately 4.3×10^{13} to 4.6×10^{13} vg/kg, and the doses administered to the high-dose cohort may have ranged from approximately 1.1×10^{14} to 1.4×10^{14} vg/kg. The clinical implications of this dose uncertainty is discussed in Section 6.1.4 of this review.

After the Phase 1 clinical trial using the initial clinical lot, the manufacturing process was changed considerably. The current manufacturing process (Process B) produces drug product with critical quality attributes that are comparable to those of the initial clinical lot. Drug product manufactured using the current manufacturing process has a comparable ratio of potency to vector genomes when compared directly to the initial clinical lot, including comparable ability to enhance survival in a mouse model of SMA. Drug product manufactured using the current manufacturing process has better purity (b) (4)

Newly-manufactured lots of drug product were used in all ongoing clinical trials with onasemnogene abeparvovec-xioi, and the vector genome concentrations of these lots were determined using an accurate and precise assay. The 1.1×10^{14} vg/kg dose used in ongoing clinical trials is accurate.

CBER conducted a pre-license inspection (PLI) of two AveXis, Inc. facilities (b) (4) for manufacturing onasemnogene abeparvovec-xioi drug substance. At the conclusion of this inspection, a Form FDA 483 was issued for the (b) (4) site. AveXis responded to the observations, and their corrective actions were found to be adequate. This inspection was classified as voluntary action indicated (VAI).

The applicant and FDA reached agreements on the following CMC Postmarketing Commitments:

1. AveXis, Inc. commits to develop and qualify a suitable method for quantifying (b) (4) and to subsequently provide the method, the method qualification report and an additional process validation report for (b) (4)
2. AveXis, Inc. commits to validate the robustness of the (b) (4) assay by carrying out the study in Protocol REC-2566, and to provide the supplemental validation reports.
3. AveXis, Inc. commits to update the (b) (4) assay to include an assay validity criterion for the reference standard, and to provide a supplemental validation report evaluating the robustness of the (b) (4) assay.

Please refer to the CMC review for further details.

4.2 Assay Validation

Please see the CMC review for details.

4.3 Nonclinical Pharmacology/Toxicology

In vivo pharmacology studies of onasemnogene abeparvovec-xioi were conducted in SMNdelta7 mice, a murine model of SMA. A single intravenous (IV) administration of onasemnogene abeparvovec-xioi at dose levels ranging from 1.2×10^{13} to 1.1×10^{14} vg/kg in neonatal SMNdelta7 mice resulted in dose-dependent improvement in survival. Additional studies in SMNdelta7 mice conducted using early nonclinical vector lots demonstrated improvement in motor function, as well as in neuromuscular transmission, body-weight gain, and cardiac function. Improvement in survival and body-weight gain was highest in mice dosed at postnatal day 1 or 2.

In single-dose toxicology studies conducted in neonatal FVB mice, IV administration of onasemnogene abeparvovec-xioi at dose levels of 7.9×10^{13} vg/kg and higher resulted in dose-dependent minimal to mild microscopic degeneration/regeneration of the myocardium. At dose levels 1.5×10^{14} vg/kg and higher, dose-dependent increases were observed in the incidence and severity of adverse cardiac findings including minimal to moderate atrial thrombosis and slight to marked atrial dilation, fibroplasia, myocardial degeneration, and inflammation. Additional findings in the ventricles included minimal to slight inflammation, edema, and fibrosis. These findings were sometimes associated with increased heart weight and macroscopic changes such as enlargement of the heart, abnormal shape, and/or large atria. Adverse findings in the liver included minimal to moderate hepatocyte degeneration/necrosis, and minimal to slight hepatocellular hypertrophy, perinuclear vacuolation, and increased Kupffer cells. Additionally, at dose levels of 2.4×10^{14} vg/kg and higher, minimal to slight perivascular and chronic inflammation were observed in the lung. Onasemnogene abeparvovec-xioi-related

mortality was observed at dose levels of 2.4×10^{14} vg/kg and higher, associated with the cardiac and liver toxicities described. The cause of death was most frequently attributed to atrial thrombosis, and was associated with atrial dilation, fibroplasia, myocardial degeneration, mononuclear cell infiltration, and hepatocellular degeneration/regeneration.

The biodistribution (BD) and SMN transgene expression profile of onasemnogene abeparvovec-xioi were evaluated in neonatal FVB mice through 12 weeks. Following IV administration of 1.5×10^{14} vg/kg onasemnogene abeparvovec-xioi, the highest vector DNA concentration was detected in the heart, followed by the lung, liver, lumbar spinal cord, quadriceps muscle, brain, ovary, spleen, and testis. The human SMN mRNA transcripts had a similar BD profile with highest levels in the heart, followed by quadriceps muscle, liver, lung, brain, and lumbar spinal cord. Low levels of SMN mRNA were detected in the spleen and gonadal tissues. SMN mRNA transcript levels generally declined over time.

Studies were not conducted to evaluate the safety pharmacology, developmental and reproductive toxicity, genotoxicity, and carcinogenicity/tumorigenicity of onasemnogene abeparvovec-xioi. This decision is acceptable based on the product characteristics, results of the toxicology studies, and target patient population.

Please see the Nonclinical Pharmacology/Toxicology review for further details.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Onasemnogene abeparvovec-xioi is a recombinant AAV9-based gene therapy designed to deliver a gene encoding the SMN protein to pediatric patients less than 2 years of age with SMA caused by bi-allelic mutations in the *SMN1* gene. Intravenous infusion of onasemnogene abeparvovec-xioi results in cell transduction and expression of SMN protein.

4.4.2 Human Pharmacodynamics (PD)

There are no clinically-relevant pharmacodynamics data for onasemnogene abeparvovec-xioi.

4.4.3 Human Pharmacokinetics (PK)

Biodistribution

Biodistribution evaluation of onasemnogene abeparvovec-xioi was performed in postmortem tissue from two subjects: one female subject (Subject (b) (6)), also designated (b) (6) in the ongoing US Phase 3 clinical trial (CL-303), and one male subject (Subject (b) (6)) in an ongoing non-US clinical trial (CL-302).

1. Subject (b) (6) died 170 days after infusion; the cause of death was respiratory failure secondary to disease progression.

The highest levels of vector DNA were found in the liver, followed by spleen, inguinal lymph node, and heart. Lower levels were detected in skeletal muscle, peripheral nerves, kidney, pancreas, lung, spinal cord, brain, and thymus.

Messenger RNA transcripts encoding SMN protein were not detected in the dorsal root, which had low RNA yields, but were detected in all other examined tissues containing recoverable RNA (liver, spleen, inguinal lymph node, heart, skeletal muscle, intestine, stomach, kidney, pancreas, lung, spinal cord, brain, and thymus).

(b) (4) for SMN protein showed generalized SMN expression in spinal motor neurons, neuronal and glial cells of the brain, and in the heart, liver, skeletal muscles, and other tissues evaluated.

2. Subject (b) (6) died 52 days after infusion; he initially presented with respiratory insufficiency 12 days after infusion, developed seizures and was found to have leukoencephalopathy about 30 days after infusion, and ultimately died following withdrawal of life support.

The highest levels of vector DNA were found in the liver, followed by pancreas, spleen, diaphragm, and intercostal muscle. Lower levels were detected in heart, lung, other skeletal muscles, kidney, intestine, lymph node, dorsal root ganglia, and spinal cord. No results were reported for brain, peripheral nerves, or thymus.

RNA analysis was not performed, because the 5-day delay in autopsy and organ collection at the site was thought likely to have compromised the quality of RNA in the tissues.

(b) (4) for SMN protein showed generalized SMN expression in spinal motor neurons and glial cells. SMN expression was also detected in the heart, liver, and skeletal muscles (diaphragm and psoas). No results were reported for the brain.

4.5 Statistical

The Statistics review team confirmed the results of safety and efficacy endpoints. Please see the statistical review for details.

4.6 Pharmacovigilance

The applicant will conduct long-term follow-up studies to collect safety and efficacy information on patients who participated in Phase 1 and Phase 3 clinical trials under IND 15699. Safety monitoring will be conducted for 15 years post-treatment with in-person annual visits for the first 5 years and then annual phone contact for 10 years. In addition, the applicant proposes the following postmarketing measures:

- (1) routine pharmacovigilance activities, including targeted follow-up questionnaires for important identified and potential risks;
- (2) adequate Prescribing Information, including Boxed Warning information for risk of acute serious liver injury;
- (3) a prospective, multi-center, multi-national, observational long-term registry of patients with a diagnosis of SMA (all types). The voluntary registry study will assess effectiveness of treatments for SMA, the long-term safety of patients treated with ZOLGENSMA, and the overall survival of patients with SMA. The sponsor will enroll at least 500 patients and follow-up will be for 15 years or until death, whichever is sooner.

Based on review of available data, the safety concerns from the Phase 1 and Phase 3 clinical trials can be monitored through routine medical practice, adequate Prescribing Information, and the voluntary postmarketing plans proposed by the applicant. The reviewed safety data do not substantiate the need for a Risk Evaluation and Mitigation Strategy (REMS), a safety postmarketing requirement (PMR) study, or a safety postmarketing commitment (PMC) study.

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

5.1 Review Strategy

The sources for this review are: (1) the licensing application, which includes data from the completed Phase 1 clinical trial (Study CL-101) and an ongoing Phase 3 trial (Study CL-303); (2) safety data from an ongoing clinical trial (Study CL-302) conducted outside the United States; (3) sources external to the application, such as safety data from US patients treated under the FDA expanded access program for investigational drugs (compassionate use); and (4) publications submitted by the applicant.

For evaluation of efficacy, this reviewer focused on data from the ongoing Phase 3 trial to provide primary evidence of effectiveness, which is using the intended commercial product (manufactured by Process B), at the recommended dose. The results of the Phase 3 trial were compared to available natural history data. Efficacy data from the completed Phase 1 trial are supportive; however, because of uncertainty arising after completion of the trial regarding the doses that had been used (please see discussion in Section 4.1), those results were not considered satisfactory to provide primary evidence of effectiveness. The dose uncertainty also precludes integrated consideration of efficacy. As the trial sample sizes were small, individual subject-level data was also evaluated.

Reviewer Comment

Absence of study design elements such as randomization, blinding, or placebo controls in the completed Phase 1 and ongoing Phase 3 clinical trials results in a number of limitations in interpreting the results, including attribution of adverse events. Some observed adverse events occur as part of the natural history of SMA, while others are associated with common diseases of infancy. Without a concurrent control group, any additional contribution by the product cannot be clearly determined.

The trials reviewed here include a number of clinical endpoints; those measures provide insight into various aspects of the treatment results, but also have limitations. For example, the CHOP-INTEND score is a sensitive measure of motor strength in infants with SMA, but does not directly reflect how a patient survives, feels, or functions. In accordance with these key determinants of clinical effectiveness, this review focuses on the outcomes considered most significant with regard to SMA: survival (including need for permanent ventilation) and developmental motor milestones (including head control, sitting without support, and walking). Other major outcomes considered include NIV use and the ability to feed orally.

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

5.3 Table of Studies/Clinical Trials

Sources considered in this review are described in Table 6. In all cases, onasemnogene abeparvovec-xioi was administered one-time via intravenous infusion.

The review focuses on two clinical trials: an ongoing Phase 3 clinical trial (Trial #2; Study CL-303), and a completed Phase 1 clinical trial (Trial #1; Study CL-101). Analysis of data from Study CL-303 as of the March 8, 2019 data cutoff provides primary evidence of effectiveness; results of Study CL-101 support effectiveness.

Safety data is considered from both of these trials, as well as from the following sources: ongoing US observational study LT-001; ongoing non-US Phase 3 clinical trial CL-302; and information from 46 patients who received onasemnogene abeparvovec-xioi from the applicant under the FDA expanded access to investigational drugs program (compassionate use).

Table 6. Summary of clinical trials and data sources evaluated in BLA

Trial/Source	Synopsis	Sample Size (n)	Data Contribution to BLA
Trial #1 CL-101 (US) <i>Completed</i> – Process A product [dose uncertain]	Phase 1 single-center (Nationwide Children's Hospital, Columbus, OH) nonrandomized, open-label, dose-escalating clinical trial using natural-history controls. <ul style="list-style-type: none"> • Infantile-onset SMA • Clinical manifestations consistent with SMA • <i>SMN1</i> bi-allelic deletion, and 2 copies of <i>SMN2</i>; absence of <i>SMN2</i> modifier mutation (c.859G>C) predicting milder disease • Age ≤ 9 months at treatment* 	15 3 low-dose 12 high-dose	<ul style="list-style-type: none"> • Efficacy • Safety
LT-001 (US) <i>Ongoing</i>	Single center (Nationwide Children's Hospital, Columbus, OH) long-term observational follow-up study of patients from CL-101. <ul style="list-style-type: none"> • No additional gene therapy treatment • Subjects may receive nusinersen concurrently 	13 3 low-dose 10 high-dose	<ul style="list-style-type: none"> • Safety
Trial #2 CL-303 (US) <i>Ongoing</i> – Process B product [1.1 × 10 ¹⁴ vg/kg]	Phase 3 multicenter, single-arm, open-label clinical trial using natural-history controls. <ul style="list-style-type: none"> • Infantile-onset SMA • <i>SMN1</i> bi-allelic deletion, and 2 copies of <i>SMN2</i>; absence of <i>SMN2</i> modifier mutation (c.859G>C) predicting milder disease • Age ≤ 6 months at treatment 	22 1 presymptomatic 21 symptomatic	<ul style="list-style-type: none"> • Efficacy • Safety
CL-302 (Europe) <i>Ongoing</i> – Process B product [1.1 × 10 ¹⁴ vg/kg]	Phase 3 multicenter, single-arm, open-label clinical trial using natural-history controls. <ul style="list-style-type: none"> • Infantile-onset SMA • Clinical manifestations consistent with SMA • <i>SMN1</i> bi-allelic mutation or deletion, and 1 or 2 copies of <i>SMN2</i>; may include <i>SMN2</i> modifier mutation (c.859G>C) predicting milder disease • Age < 6 months at treatment 	5	<ul style="list-style-type: none"> • Safety
Expanded Access Program (US) <i>Ongoing</i> – Process B product [1.1 × 10 ¹⁴ vg/kg]	FDA expanded access to investigational drugs (compassionate use) program for individual patients not meeting criteria for participation in clinical trials. <ul style="list-style-type: none"> • Patients may receive nusinersen concurrently 	46	<ul style="list-style-type: none"> • Safety

* The age was modified to ≤ 6 months during the conduct of the trial.
 (Source: Modified from Applicant's 120-Day Safety Update)

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

No Advisory Committee meeting was held because initial review of information submitted in the BLA did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

5.4.2 External Consults/Collaborations

Consultation was kindly provided by Dr. Rainer Paine and Dr. Teresa Buracchio of the Division of Neurology Products, Center for Drug Evaluation and Research (January 31, 2019). The questions posed, and a summary of the responses, were:

1. What indication do you consider more appropriate for onasemnogene abeparvovec-xioi: SMA type 1, or infantile-onset SMA?

Drs. Paine and Buracchio recommended the indication “infantile-onset SMA,” rather than a historical SMA type. Their rationale was that patients with the same SMN2 copy number can manifest with different clinical phenotypes, and thus be classified into different traditional SMA types. A positive outcome likely depends on early treatment, before irreversible motor neuron loss. Therefore, patients with infantile-onset disease should not be excluded from treatment based on historical SMA type or SMN2 copy number.

2. The applicant suggests a weight range to limit patients who may be treated. We do not favor this approach; we recognize, however, that older subjects with advanced disease (for example, demonstrating quadriplegia and complete ventilator dependence), are unlikely to have sufficient remaining lower motor neurons to benefit. Would you consider satisfactory a limitation such as “patients [with SMA type1/infantile-onset SMA] who, in the judgment of the treating physician, are likely to have a sufficient number of remaining lower motor neurons”?

Drs. Paine and Buracchio recommended that the decision to provide gene therapy to heavier or older patients should be left to the clinical judgment of the treating physician, in consultation with the patient’s family.

5.5 Literature Reviewed (if applicable)

During review of the BLA, this reviewer consulted FDA regulatory guidance documents, as well as academic literature, for background and context regarding the targeted disease and the mechanism of action of the product. The literature consulted is listed in References.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1 (Completed Phase 1 Trial, CL-101)

Study Title: Phase 1 Gene Transfer Clinical Trial for Spinal Muscular Atrophy Type 1 Delivering AVXS-101

6.1.1 Objectives (Primary, Secondary, etc.)

Primary:

- Safety

Secondary:

- Survival [defined as time from birth to either death or use of invasive ventilation (tracheostomy) or respiratory assistance for ≥16 hours per day (including noninvasive

ventilatory support) continuously for ≥ 14 days in the absence of an acute reversible illness, excluding perioperative ventilation]

- Improvement in motor strength and function, determined using measures such as score on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) and assessment of motor milestones

6.1.2 Design Overview

Study CL-101 was a single-center, non-randomized, open-label, dose-escalation clinical trial assessing safety and preliminary efficacy of onasemnogene abeparvovec-xioi in pediatric subjects with infantile-onset SMA.

Cohorts were compared based on the dose of onasemnogene abeparvovec-xioi administered. In addition, subjects were compared to natural history data from the Pediatric Neuromuscular Clinical Research database and the NeuroNEXT database (Finkel et al., 2014; Kolb et al., 2016; Kolb et al., 2017).

Safety was assessed over the 24-month period following infusion with the product.

Efficacy analyses were conducted at 3 different time points:

1. The primary efficacy data cutoff time point was the date at which all subjects had completed a study visit after reaching 13.6 months of age (January 20, 2017).
2. The time point at which the last enrolled patient had a study visit after reaching 20 months of age (August 7, 2017).
3. The time point at which all patients had completed 24 months of follow-up after infusion (December 14, 2017).

Reviewer Comment

The applicant's initial plan was to test three doses of the product (lowest, intermediate, and highest), in a total of 15 subjects. The Data Safety Monitoring Board (DSMB) considered the preliminary safety and efficacy results after three subjects had received the lowest dose and three subjects had received the intermediate dose. The DSMB recommended that the study not proceed with the highest dose, and instead expand enrollment of subjects receiving the intermediate dose, to a total of 12 subjects at the intermediate dose. The decision was based on several factors: the observed efficacy in subjects who had received the intermediate dose; potential risk hepatotoxicity at higher doses; and preclinical data showing no improvement in survival at higher doses. FDA agreed with this plan.

This review focuses on efficacy results from the last time point, 24 months after infusion.

6.1.3 Population

The study population was planned for a total of 15 subjects. Sixteen patients were screened; one was excluded from the study based on AAV9 antibody titer of $> 1:50$, measured by enzyme-linked immunosorbent assay (ELISA).

A total of 15 subjects were enrolled and analyzed: 3 subjects in the low-dose cohort, and 12 subjects in the high-dose cohort.

Key enrollment criteria were as follows:

Inclusion Criteria

- Type 1 SMA, defined by bi-allelic mutations (deletion or point mutation) in the *SMN1* gene, and 2 copies of the *SMN2* gene.
- Age 6 months or younger at day of infusion. (The first 9 subjects were enrolled under previous versions of the protocol, which allowed an age range ≤ 9 months of age.)
- Hypotonia on clinical examination, with delay in motor skills, poor head control, rounded shoulder posture, and joint hypermobility.

Exclusion Criteria

- Presence of the c.859G>C modification in exon 7 of *SMN2*.
- Use of invasive ventilatory support (tracheotomy with positive pressure) or pulse oximetry $< 95\%$ saturation at the screening visit. Subjects could be managed using non-invasive ventilatory support (e.g., BiPAP) for < 16 hours/day, at the discretion of the physician or research staff.
- Signs of aspiration (based on a swallowing test), and unwillingness to use an alternative method to oral feeding.
- Anti-AAV9 antibody titer of $> 1:50$, determined by ELISA.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Onasemnogene abeparvovec-xioi was infused intravenously.

The dose of onasemnogene abeparvovec-xioi was defined based on the total quantity of vector genomes per kilogram weight of the subject (vg/kg). Two dose levels were originally reported as:

- Cohort 1 (lowest dose; 3 subjects): 6.7×10^{13} vg/kg
- Cohort 2 (intermediate dose; 12 subjects): 2.0×10^{14} vg/kg

Subjects received prophylactic prednisolone (1 mg/kg/day) 24 hours prior to the treatment, to dampen the immune response to the AAV-based therapy. (The first subject was not pretreated with prednisolone.) Prednisolone was continued for a total of 30 days, after which the dose was tapered before being discontinued.

Reviewer Comment

As discussed in Section 4.1, the precise doses received by subjects in this trial are not clear.

Stability data submitted late in the review cycle indicate that the product is unstable during long-term frozen storage. Because of uncertainty about the rate of decay of the initial drug product lot, FDA is unable to determine the doses that were administered to subjects in the Phase 1 trial. FDA estimates that the doses administered to the low-dose cohort of the Phase 1 trial may have ranged from approximately 4.3×10^{13} to 4.6×10^{13} vg/kg, and the doses administered to the high-dose cohort may have ranged from approximately 1.1×10^{14} to 1.4×10^{14} vg/kg.

This new information raised concerns regarding the optimal dose for the patient population, which is a very important dimension for gene therapy given that these patients will have only one chance to receive the product, due to concerns associated with immunogenicity reflected by the production of antibodies and T-cell immune

responses to the product. So, we considered a post-marketing requirement (PMR) for an additional study to identify optimal dosing in the context of safety evaluations. Given that we do not really have specific safety questions that need to be evaluated in a PMR, as hepatotoxicity and cardiotoxicity are adequately addressed in the package insert, we then considered a PMC. However, based on preclinical data, we would not be able to study a dose that is 50-100% higher than the recommended dose in the package insert, since the maximum tolerated dose that preclinical data could support evaluation would be 27% higher than the recommended dose. It is unclear if we would be able to identify any meaningful differences in efficacy given confounding variables, especially as a 27% difference in dose did not seem to identify impactful changes in outcomes based on preclinical data.

Note: Throughout this review, Cohort 1 is referred to as the “low-dose cohort” and Cohort 2 is referred to as the “high-dose cohort.”

6.1.5 Directions for Use

Onasemnogene abeparvovec-xioi is supplied in (b) (4) vials as a frozen liquid at $\leq -60^{\circ}\text{C}$. The product must be stored at 2°C to 8°C . It must be thawed prior to clinical administration. It is administered over about 60 minutes as a single intravenous infusion, through a venous catheter inserted into a peripheral limb vein.

6.1.6 Sites and Centers

Study CL-101 was conducted at a single site (Nationwide Children’s Hospital, Columbus, OH).

6.1.7 Surveillance/Monitoring

Please see Table 7 for the Study CL-101 monitoring schedule.

Assessment of motor milestones was determined by the study physical therapist, and confirmed by an independent central video reviewer. Criteria were based on the Bayley Scales of Infant and Toddler Development, 3rd edition (Bayley-III).

Table 7. Schedule of assessments for Study CL-101

Study Interval						Follow-up Year 1										Follow -up Year 2	
	Screenin	Inpatient					Outpatient										Q3 ^g Month
Visit	1	2					3	4	5	6	7	8	Monthly	Every 3 Months	Every 6 months		
Days in Study ^a	-30 ± 7 days	-1	0	1	2	7	14	21	30	60	90	Up to 12 Months			13-24 Months +/- 21 days		
Informed Consent	X																
Chest X-Ray	X																
Medical History	X																
Physical Exam &	X	X ^c	X ^d	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pulmonary	X			X		X	X	X	X	X	X	X	X	X	X	X	
Photograph Infusion	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Swallowing Test	X														X	X	
Pulse Oximetry ^d	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Capillary Blood Gas	X	X	X	X	X												
Safety Labs (Blood)	X	X		X	X	X	X	X	X	X	X		X	X	X	X	
Coagulation Studies (Prothrombin)											X		X	X	X	X	
Safety Labs	X	X		X	X	X	X		X		X		X	X	X	X	
Immunology (Anti-AAV9/SMN Ab and T-Cells)	X					X	X	X	X	X	X		X	X	X	X	
Research Blood ^e	X							X	X	X	X		X	X	X	X	
CHOP-INTEND ^f (with video)	X	X							X	X	X	X	X	X	X	X	
Bayley Scales ^b	X	X							X	X	X	X ^b	X ^b	X ^b	X	X	
ACTIVE-mini	X	X				X	X	X	X	X	X	X	X	X	X	X	
CMAP/MUNE/EIM	X								X		X		X	X	X	X	
Research Urine	X			X	X	X	X	X	X	X	X	X	X	X	X	X	
Research Saliva/Stool	X			X	X	X	X	X	X	X	X	X	X	X	X	X	
Development Milestones/ Gross Motor Skills Checklist (with video)	X								X					X	X	X	
ECHO/ECG	X								X					X		X	
Prednisolone Dosing		X	X	X	X	X	X	X	X								
Gene Transfer			X														
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications	To be collected from 2 weeks before study dose until final study visit; recorded on separate CRF																

Ab, antibody; ACTIVE-mini, Ability Captured Through Interactive Video Evaluation-mini; anti-AAV9, antibodies directed against AAV serotype 9; (b) (4) CMAP, compound motor action potential; CRF, case report form; ECHO/ECG, echocardiogram/electrocardiogram; EIM, electrical impedance myography; INR, international normalized ratio; MUNE, motor unit number estimation; PI, Principal Investigator (b) (4)

^a Visits on Study Days 7, 14 and 21 allowed a window of ±2 days; all monthly visits following allow a window of ±7 days.

^b The Bayley Fine and Gross Motor subtests were to be administered monthly through the time point that the subject reached 15 months of age or 12 months post-infusion (whichever was later) if a subject reached or exceeded a score of 60 out of 64 on the CHOP-INTEND. The Language and Cognition subtests were to be administered every 3 months if a patient reached or exceeded a score of 60 out of 64 on the CHOP-INTEND. The CHOP-INTEND assessment was to be discontinued and only the Bayley assessment was to be administered for subjects who achieved 2 consecutive scores of ≥ 62.

^c Vital signs were recorded every 4 hours during inpatient hospitalization.

^d Continuous monitoring during gene transfer procedure. Axillary temperature was to be captured pre- and post-infusion.

^e Research blood sample was to be used to perform baseline exon 7 modification testing and could also be used to re-confirm SMA type 1 diagnosis, SMN2 copy number, and exon-7 modification testing through a third-party laboratory.

^f Subjects who achieved 2 consecutive scores of ≥ 62 could have ceased further CHOP-INTEND assessments, as per PI, physical therapist, and sponsor decision.

^g Quarterly visits in Year 2 were to have a ±21-day window. Missed visits were to be made up within the allowed window; the time between study visits was not to exceed 6 months.

(Source: Applicant Clinical Study Report for AVXS-101-CL-101)

6.1.8 Endpoints and Criteria for Study Success

Primary

- Safety (assessed based on factors including adverse events; vital signs; physical examination; and laboratory studies).

Secondary

- Survival, defined as time from birth to either death or use of invasive ventilation (tracheostomy or respiratory assistance for ≥ 16 hours per day [including noninvasive ventilatory support] continuously for ≥ 14 days in the absence of an acute reversible illness, excluding perioperative ventilation).
- Change from baseline in CHOP-INTEND score.
- Demonstration of improved motor function and muscle strength, indicated by achievement of significant development motor milestones including the ability to roll over unassisted and to sit independently.

Exploratory

Prior to data analysis, the following exploratory efficacy analyses were added:

- Achievement of the developmental motor milestone of functional independent sitting (sitting for ≥ 30 seconds without assistance); and milestones of sitting unassisted for 15 seconds, 10 seconds, and 5 seconds, respectively, for subjects who did not achieve functional independent sitting.
- The proportion of patients who were independent of ventilatory support (defined as requiring no daily ventilator support in the absence of acute reversible illness, and excluding perioperative ventilation).
- The proportion of patients not requiring non-oral nutrition prior to therapy who maintained the ability to thrive (defined as able to tolerate thin liquids, demonstrated through a formal swallowing test; not receiving nutrition through mechanical support such as a feeding tube; and maintaining weight $>3^{\text{rd}}$ percentile for age and sex, based on WHO Clinical Growth Standards [WHO 2006]).

Reviewer Comment

For this review, the following efficacy endpoints were emphasized:

- Survival, defined as above (referred to in this review as Efficacy Endpoint #1).
- Achievement of developmental motor milestones, including head control; sitting independently for ≥ 30 seconds; and walking unassisted.

6.1.9 Statistical Considerations & Statistical Analysis Plan

All analyses were considered descriptive, and were performed without a statistical analysis plan (SAP). Study results were compared to natural history data from the Pediatric Neuromuscular Clinical Research database and the NeuroNEXT database (Finkel et al., 2014; Kolb et al., 2016; Kolb et al., 2017).

Reviewer Comment

This review also emphasized comparison of results from the low-dose and high-dose cohorts in Study CL-101, which demonstrated a dose-response relationship.

6.1.10 Study Population and Disposition

All subjects had onset of clinical symptoms consistent with SMA and had confirmed bi-allelic mutations in the *SMN1* gene; two copies of the *SMN2* gene; and lacked the *SMN2* modifier mutation c.859G>C.

6.1.10.1 Populations Enrolled/Analyzed

Analyses of efficacy and safety included all 15 subjects in Study CL-101 who received the product.

6.1.10.1.1 Demographics

Key demographic information for both the low-dose cohort and the high-dose cohort is summarized in Table 8. There were more female subjects than male subjects. Most subjects were white and not of Hispanic or Latino ethnicity. The mean age at infusion for subjects in the low-dose cohort was older than for those in the high-dose cohort.

Table 8. Demographic and baseline characteristics for Study CL-101

Characteristic	Low-Dose Cohort (n = 3)	High-Dose Cohort (n =12)	Total (n = 15)
Age at treatment (months)			
Mean	6.3	3.4	4.0
Median	5.9	3.1	4.1
Minimum, Maximum	5.9, 7.2	0.9, 7.9	0.9, 7.9
Sex			
Male	1	5	6
Female	2	7	9
Race			
White	3	11	14
Other	0	1	1
Ethnicity			
Non-Hispanic or Latino	3	10	13
Hispanic or Latino	0	2	2
Weight at baseline (kg)			
Mean	6.6	5.7	5.9
Minimum, Maximum	6, 7.1	3.6, 8.4	
Reported swallowing thin liquid	0	4	4
Reported required feeding support	3	5	8
Reported required ventilatory support	3	1	4

(Source: Applicant's BLA submission Table 14.1.2-24, with modifications)

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Please see Table 9 below for a summary of the medical characteristics of the 15 subjects.

Table 9. Medical characterization of subjects in Study CL-101

Subject ID/ Age at Infusion (months)	Cohort	Age at Symptom Onset (months)	Family History of SMA	Baseline SMA Symptoms				
				Hypotonia	Limb Weakness	Pneumonia/ Respiratory Symptoms	Swallowing/ Feeding Difficulties	Tongue Fasciculations*
(b) (6) 5.9	Low	3	Yes	X	X	X		
5.9	Low	1	No	X	X			
7.2	Low	1	No	X			X	
5.6	High	3	Unknown	X	X			
4.2	High	1	No	X	X			
1.9	High	1	Yes	X	X			
3.6	High	1	No	X	X		X	
7.9	High	2	No	X	X		X	
4.9	High	3	No	X	X		X	
0.9	High	0	No	X				
2.3	High	1	No	X	X			
2.6	High	2	Yes	X	X			
0.9	High	0	Yes	X	X			
4.1	High	2	No	X	X		X	
2.1	High	1	No	X	X		X	

*No subjects in Study CL-101 had tongue fasciculations.

(Source: AVXS-101-CL-101 Study Report Listing 16.2.4.2-14, with minor adaptations)

Reviewer Comment

Study CL-101 was conducted prior to FDA approval of nusinersen (please see Section 2.2). None of the subjects in the trial was using nusinersen, or had a history of nusinersen use. This trial does not provide insight into potential benefits or drawbacks of using onasemnogene abeparvovec-xioi in combination with nusinersen for treatment of infantile-onset SMA.

6.1.10.1.3 Subject Disposition

Fifteen subjects were enrolled and received infusion of onasemnogene abeparvovec-xioi: 3 subjects in the low-dose cohort, and 12 subjects in the high-dose cohort.

All 15 subjects completed the 24-month follow-up period.

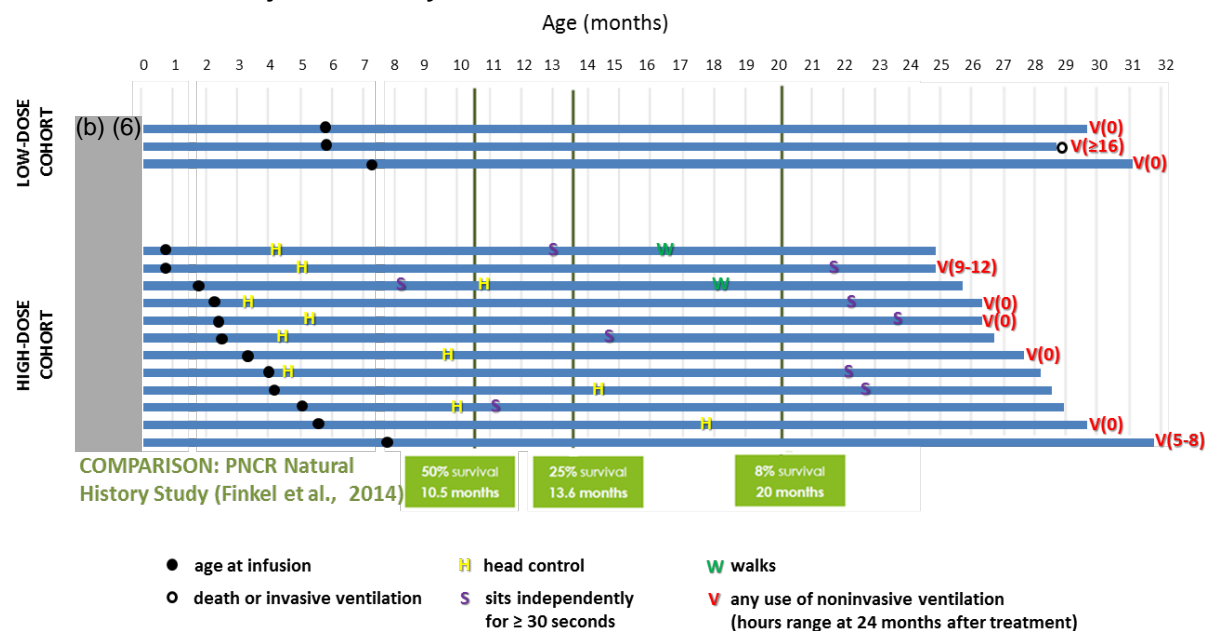
6.1.11 Efficacy Analyses

6.1.11.1 Analysis of Efficacy Endpoint #1

Survival (alive without permanent ventilation)

As shown in Figure 5, by 24 months following infusion, 1 subject in the low-dose cohort required tracheostomy (i.e., permanent ventilation), and thus did not reach the survival efficacy endpoint. All subjects in the high-dose cohort were alive without permanent ventilation, thereby meeting the survival efficacy endpoint.

Figure 5. Swimmer illustration of survival, motor milestone achievement, and ventilation use for subjects in Study CL-101 at 24 months after infusion



Subject ID in black indicates male; red indicates female
(Source: Adapted from FDA statistical review; Mendell et al., 2017; and Applicant's Clinical Information Amendment submitted 5/8/2019)

6.1.11.2 Analyses of Other Endpoints

Developmental Motor Milestones

Developmental motor milestone achievement for all subjects by 24 months after infusion is shown in Figure 5.

In the low-dose cohort, none of the 3 subjects achieved any developmental motor milestones, including head control, sitting independently, or walking without assistance.

In the high-dose cohort, 11 of the 12 subjects (92%) were able to hold their head erect for ≥ 3 seconds, 9 subjects (75%) were able to sit independently for ≥ 30 seconds, and 2 subjects (17%) were able to stand and walk without assistance.

For the 9 subjects who were able to sit independently for ≥ 30 seconds, the mean age at achieving that milestone was 16.6 months (range 8.2 to 23.6 months); 4 of the 12 subjects (33%) in the high-dose cohort achieved that milestone before 18 months of age.

Reviewer Comment

Motor milestone data in Study CL-101 were not rigorously collected from the start of the study. The date of milestone achievement was conservatively assessed by the applicant based on the date of video documentation definitively confirmed by external review; the actual date of milestone achievement may have been earlier. Therefore, this data may not be suitable for comparison to motor milestone results from Study CL-303.

For the 2 subjects who were able to stand and walk without support at approximately 20 months of age, both were the youngest subjects in the study to receive the treatment.

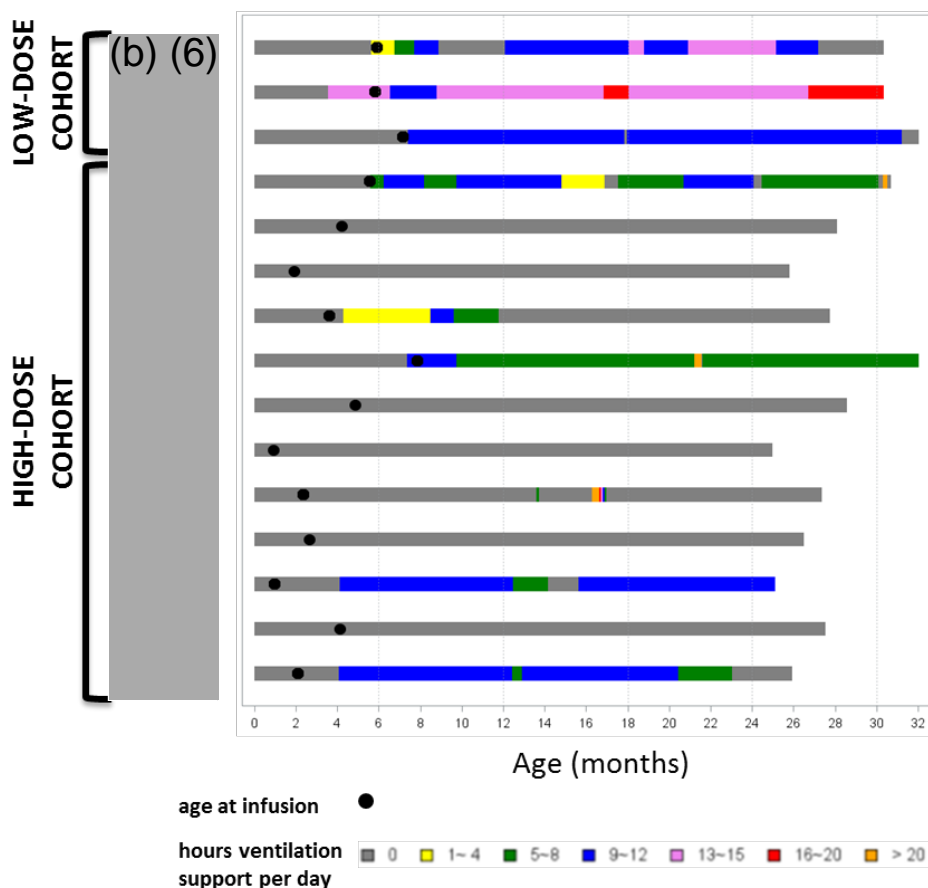
Reviewer Comment

These findings suggest that early treatment with the product may prevent more motor neurons from degenerating, and thus enable patients to achieve more motor milestones. Age at dosing appears to be one factor but does not seem to be the only factor. Two subjects in the high dose cohort were treated at about the same age as two in the low-dose cohort, but still achieved motor milestones (Figure 5), suggesting that the dose is also an important factor.

Pulmonary

Ventilator-use results for all subjects throughout the study are shown in Figure 5, and in greater detail in Figure 6.

Figure 6. Swimmer plot of ventilation-support hours for each subject in Study CL-101



Subject ID in black indicates male; red indicates female
(Source: Modified from FDA Statistical review)

In the low-dose cohort, all 3 subjects required daily use of non-invasive ventilation (NIV) both at baseline and after infusion. In one subject (b) (6), the need for ventilatory support increased, leading to tracheostomy within the 24-month follow-up period after infusion.

In the high-dose cohort, 10 of the 12 subjects did not require NIV at baseline. Both of the 2 subjects who used NIV prior to infusion continued to require daily NIV use at 24 months following infusion. Of the 10 subjects who did not require NIV at baseline, 7 remained free of daily NIV use at 24 months following infusion.

Nutritional

In the low-dose cohort, all 3 subjects required non-oral nutrition at baseline and after infusion. None of these subjects was able to feed orally.

Nutritional status for subjects in the high-dose cohort is summarized in Table 10. At baseline, 7 of the 12 subjects did not require non-oral nutrition (i.e., were able to exclusively feed orally). At 24 months following infusion, 5 of those 7 subjects still could exclusively feed orally.

Of the 5 subjects from the high-dose cohort who at baseline required non-oral nutrition, 4 were able to also feed orally at 24 months after infusion.

Table 10. Nutritional status of subjects in the high-dose cohort in Study CL-101

Subject ID	Age at Infusion (months)	Enteral Feeding at Baseline	Enteral Feeding Added During Study	Able to Feed Orally at End of Study	Able to Feed Exclusively Orally at End of Study
(b) (6)	5.6		X	X	
	4.2			X	
	1.9			X	X
	3.6	X		X	
	7.9	X			
	4.9			X	X
	0.9			X	X
	2.3	X		X	
	2.6			X	X
	0.9	X		X	X
	4.1			X	X
	2.1	X		X	

(Source: Applicant's Clinical Information Amendment 77, received 5/8/2019.)

CHOP-INTEND Score

CHOP-INTEND is an assessment of neuromuscular strength designed to quantify motor abilities in infants and young children with infantile-onset SMA. The scale contains 16 items, each scored from 0 to 4. The maximum score of 64 reflects the level of neuromuscular function of a healthy baby by 3-6 months of age. Scores of 30-40 points or less indicate significant neuromuscular impairment. Untreated children ages 6 months or older with infantile-onset SMA typically do not achieve a score of more than 40 points.

For the low-dose cohort, the mean CHOP-INTEND score at baseline was 16 (range 6 to 23). At 6 months after infusion, the mean score was 20.7 (range 9 to 34), and at 12 months after infusion was 19.5 (range 8 to 31). No CHOP-INTEND score was available beyond 19 months after infusion.

For the high-dose cohort, the mean CHOP-INTEND score at baseline was 28.2 (range 12 to 50). At 6 months after infusion, the mean CHOP-INTEND score was 49.7 (range

11 to 64), at 12 months after infusion was 50.8 (range 16 to 64), and at 24 months after infusion was 52.8 (range 16 to 64). Eleven of the 12 subjects in the high-dose cohort achieved a score of 50 points or more by 24 months after infusion.

6.1.11.3 Subpopulation Analyses

For a trial such as Study CL-101 with a small number of subjects, subgroup analysis by age, sex, race, or ethnicity is unlikely to be meaningful. Moreover, of the 15 total subjects, 14 were white, and 13 were of non-Hispanic/Latino ethnicity.

6.1.11.4 Dropouts and/or Discontinuations

There were no dropouts or discontinuations.

6.1.12 Safety Analyses

6.1.12.1 Methods

All 15 subjects are included in the Safety Population, which was used to conduct the safety analyses.

All 15 subjects experienced at least one treatment-emergent adverse event (TEAE). There were no statistically significant differences between the low-dose cohort and the high-dose cohort with regard to occurrence of any specific TEAE. The most frequent TEAEs among the 15 subjects were upper respiratory tract infection (73%), pyrexia (53%), vomiting (53%), constipation (47%), pneumonia (47%), gastroesophageal reflux disease (40%), and nasal congestion (40%).

Reviewer Comment

These events are common in infancy, as well as in the natural history of infantile-onset SMA. Without a concurrent placebo arm, any increased susceptibility to these TEAEs due to onasemnogene abeparvovec-xioi cannot be determined.

6.1.12.3 Deaths

No subjects in Study CL-101 died.

By 24 months following infusion, one subject (b) (6) in the low-dose cohort required tracheostomy (i.e., permanent ventilation); although she remained alive, she did not reach the defined survival efficacy endpoint.

6.1.12.4 Nonfatal Serious Adverse Events

Of the 15 total subjects, 13 were reported to experience at least one serious adverse event (SAE): all 3 subjects in the low-dose cohort, and 10 of the 12 subjects in the high-dose cohort.

The most frequent treatment-emergent SAEs overall were pneumonia (47%), parainfluenza virus infection (20%), pneumonia respiratory syncytial viral (20%), respiratory syncytial virus bronchiolitis (20%), and upper respiratory tract infection requiring hospitalization (20%).

Two SAEs (elevated aminotransferases) were considered definitely related to treatment with onasemnogene abeparvovec-xioi. These SAEs are discussed further in Section 6.1.12.5.

Reviewer Comment

Pulmonary infections are a common occurrence in the natural history of infantile-onset SMA. As noted above with regard to overall adverse events in Study CL-101, in the absence of a concurrent placebo arm, any increased susceptibility to these SAEs due to onasemnogene abeparvovec-xioi cannot be determined.

6.1.12.5 Adverse Events of Special Interest (AESI)

The following three adverse events were considered of special interest: elevated aminotransferases; elevated troponin-I; and decreased platelet counts/thrombocytopenia.

- Concerns regarding aminotransferases and troponin-I arose from nonclinical toxicology studies. Dose-dependent hepatic and cardiac toxicities were observed following intravenous administration of onasemnogene abeparvovec-xioi (please see Nonclinical Pharmacology/Toxicology review for full details).

Liver findings included hepatocellular hypertrophy, Kupffer cell activation, perinuclear vacuolation, and scattered hepatocellular necrosis.

Myocardial abnormalities were present in the myocardium of neonatal mice receiving doses of 7.9×10^{13} vg/kg and higher. Findings included slight to mild mononuclear cell inflammation accompanied by edema, slight to mild fibrosis, and scattered myocardial cell degeneration/regeneration. At doses of 1.5×10^{14} vg/kg and higher, atrial thrombosis and dilation was also present.

Target-organ toxicity in the heart and liver was associated with mortality at dose levels of 2.4×10^{14} vg/kg (about 2.2-fold higher than the recommended clinical dose) and higher.

- Concerns regarding possible thrombocytopenia were prompted by clinical findings of decreased platelet levels following treatment with onasemnogene abeparvovec-xioi.

Elevated Aminotransferases

Of the 15 total subjects, 4 subjects experienced a total of 5 treatment-emergent adverse events (TEAEs) of elevated serum aminotransferases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) (Table 11). Two of these events were SAEs. All are considered definitely related to treatment with onasemnogene abeparvovec-xioi.

Table 11. Subjects in Study CL-101 experiencing elevated aminotransferases

Subject	Cohort	AE	SAE	Study Day Onset	Study Day End
(b) (6)	Low-dose	Aminotransferases increased	Yes	27	90
	High-dose	Aminotransferases increased	No	27	127
	High-dose	AST increased	No	9	27
		Aminotransferases increased	No	64	279
	High-dose	Aminotransferases increased	Yes	34	111

AST, aspartate aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities
(Source: modified from BLA Submission, Study AVXS-101-CL-101—Study Report, Table 46, page 112)

All 5 TEAEs occurred without clinical findings of jaundice or other symptoms of hepatic impairment, and all resolved during the observation period. None met both criteria for “Hy’s Law,” the commonly-used rubric for predicting severe drug-related hepatotoxicity: (1) elevation of transaminases over 3 x ULN; and (2) increased bilirubin, to at least 2 x ULN. These two findings must occur in the absence of another cause of hepatotoxicity, such as an illness or known toxin (Temple 2006).

One subject in each cohort experienced elevation of aminotransferases to the level of an SAE:

- Low-dose cohort: Subject (b) (6), the first subject in the study, had ALT of 31 x ULN, and AST of 14 x ULN. Her alkaline phosphatase and total and indirect bilirubin were unremarkable, and no clinical symptoms were evident. These abnormalities were attenuated by treatment with prednisolone.

All subsequent subjects in the study were prophylactically administered prednisolone before and after infusion of onasemnogene abeparvovec-xioi. (Please see section 6.1.4 for details.)

- High-dose cohort: Subject (b) (6) had ALT of 35 x ULN and AST of 37 x ULN, with total bilirubin reaching 1.9 x ULN. She required additional prednisolone for resolution of the event.

Reviewer Comment

AAV vector administration in humans has been observed to stimulate activation of capsid-specific CD8⁺ T cells, resulting in increased liver enzymes. T cell-mediated immune responses appear to occur in a dose-dependent fashion (Collela et al., 2018). A course of corticosteroid appears to mitigate this response; the optimal regimen of corticosteroid, however, remains unclear. The recommended corticosteroid dosing regimen in the package insert was used for most subjects in CL101 and CL-303.

Elevated Troponin-I

One subject in the low-dose cohort and 7 in the high-dose cohort had elevations of cardiac troponin-I levels that met the pre-specified protocol criterion for potential clinical significance (> 0.05 µg/L). Of these 8 total subjects, 2 had increased troponin-I levels at baseline. None of the elevations observed during the study was considered clinically significant by the investigator. The highest value observed was 0.176 µg/L, in Subject

(b) (6) in the high-dose cohort. By study end, all values had decreased either to within the normal range or to below 0.05 µg/L.

The clinical significance of these findings is unknown, as there were no other clinical sequelae.

Decreased Platelet Levels/Thrombocytopenia

No cases of thrombocytopenia were observed in Study CL-101. Decreases from baseline in mean platelet count were observed at multiple time points, but without clinical changes. Platelet counts did not fall below the lower limit of normal (normal range, $140 \times 10^9/L$ to $440 \times 10^9/L$) for any subject at any visit.

Reviewer Comment

A dose-response relationship for hepatotoxicity is evident in subjects from Study CL-101: despite receiving prophylactic treatment with prednisolone, three subjects from the high-dose cohort developed elevated aminotransferases (with one SAE), compared to one subject in the low-dose cohort (SAE) who did not receive prophylaxis. Prednisolone treatment seems effective in ameliorating hepatotoxicity.

A dose-response relationship was also present with regard to elevated troponin-I.

6.1.12.6 Clinical Test Results

Anti-AAV9 Antibody Levels

All subjects had anti-AAV9 titers < 1:50 at baseline, per study entrance criteria. Following infusion of onasemnogene abeparvovec-xioi, increases from baseline in anti-AAV9 antibody titers over time occurred in all subjects. Some subjects had anti-AAV9 titers >1:819,200 at different time points after product administration (Table 12).

Table 12. Anti-AAV9 Antibody Titers in Study CL-101

Anti-AAV9 titers	Total subjects (low-dose cohort + high-dose cohort)				
	≤ 1:50	>1:50 - <1:800	1:800 – <1:51200	1:51200 – <1:819,200	>1:819,200
Baseline	15 (3+12)				
Week 1	5 (1+4)	4 (2+2)	5 (0+5)		
Week 2		1 (0+1)	10 (2+8)	1 (0+1)	
Month 1			12 (2+10)	3 (1+2)	
Month 3			1 (0+1)	12 (3+9)	2 (0+2)
Month 6				10 (2+8)	5 (1+4)
Month 12				11 (3+8)	3 (0+3)
Month 24			3 (0+3)	8 (1+7)	1 (1+0)

(Source: Adapted from BLA submission, Study CL-101 Table 14.3.4.1.6-24)

Reviewer Comment

High anti-AAV9 antibody titers after onasemnogene abeparvovec-xioi infusion are expected to preclude the possibility of re-administration of the product.

T-cell Responses to AAV9

Interferon (IFN)- γ Enzyme-Linked ImmunoSpot (ELISpot) was used to detect T-cell responses to AAV9. The test measures the number of spot-forming cells (SFC) per 1×10^6 peripheral blood mononuclear cells (PBMCs).

Four subjects in Study CL-101 experienced elevated aminotransferases:

- For 3 subjects (b) (6) the elevation of aminotransferase levels appeared to correlate with a greater T-cell response to AAV9, as indicated by the increased number of SFCs per 1×10^6 PBMCs.
- In 1 subject (b) (6), the elevation of aminotransferase levels was not associated with a greater T-cell response to AAV9.

For subjects who did not experience elevation of aminotransferases, increased T-cell responses to AAV9 were observed in some cases.

Reviewer Comment

Responses measured from T cells in the blood may not be well-correlated with T cell responses in the liver.

Anti-SMN Antibody Levels

All subjects had an anti-hSMN titer of $<1:12.5$ at baseline, and all subjects had anti-hSMN titers of $<1:50$ at all time points after infusion. These observations, however, may reflect differences in technical aspects of the assay: a minimum titer of $1:12.5$ was used at screening (using frozen serum samples), whereas a minimum titer of $1:50$ was used at all subsequent time points (using plasma).

Reviewer Comment

Because SMN is an endogenous protein that is normally expressed at some level by patients with SMA, a humoral immune reaction to the SMN protein is unlikely following infusion with onasemnogene abeparvovec-xioi.

T-cell Response to SMN

The T-cell response to SMN fluctuated over time in the low-dose cohort, increasing modestly from baseline. The clinical significance is unclear.

Reviewer Comment

Because SMN is an endogenous protein that is normally expressed at some level by patients with SMA, a clinically important T-cell response would not be expected.

6.1.13 Study Summary and Conclusions

For all subjects in Study CL-101, onasemnogene abeparvovec-xioi demonstrated a clear benefit with regard to survival. Based on the natural history of infantile-onset SMA, only about 8% of patients would be expected to survive past age 20 months (Finkel et al., 2014). In Study CL-101, only one subject in the low-dose cohort did not reach the survival endpoint (alive without permanent ventilation); all of the 12 subjects in the high-dose cohort met that endpoint.

The product also demonstrated benefit with regard to achievement of developmental motor milestones. No subjects in the low-dose cohort achieved any such milestones. In the high-dose cohort, however, at the 24-month time point after infusion, nearly all (11)

of the 12 subjects demonstrated head control, most (9) were able to sit independently for ≥ 30 seconds, and some (2) were able to walk without assistance. The most serious risk of onasemnogene abeparvovec-xioi evident from Study CL-101 was elevation of aminotransferases.

Reviewer Comment

Factors other than onasemnogene abeparvovec-xioi may have contributed to these outcomes:

- As discussed above in Section 2.1, a small fraction of patients with the same genotype as the subjects in Study CL-101 may develop a milder-than-expected phenotype. The reasons for those relatively rare discrepancies are unclear.
- In addition, Study CL-101 involved a small sample size, and open-label studies such as Study CL-101 are more susceptible to bias than are studies with a randomized, double-blind, and placebo-controlled design.

While factors such as genotype-phenotype discordance, random effects in a small sample, and/or bias may have influenced the observed results, overall the likelihood appears remote that such factors could account all or a substantial part of the difference observed between the results of Study CL-101 and the expected natural history outcome for these subjects. This conclusion is supported by the dose-effect efficacy relationship observed in the trial: all subjects who received the higher dose of onasemnogene abeparvovec-xioi met the survival endpoint, and only subjects in the high-dose cohort achieved any developmental motor milestones.

6.2 Trial #2 (Ongoing Phase 3 Trial, Study CL-303)

Study CL-303 is ongoing as of this review. Enrollment was completed June 8, 2018.

Study Title: Phase 3, Open-Label, Single-Arm, Single-Dose Gene Replacement Therapy Clinical Trial for Patients with Spinal Muscular Atrophy Type 1 with 1 or 2 *SMN2* Copies Delivering AVXS-101 by Intravenous Infusion

6.2.1 Objectives (Primary, Secondary)

Co-primary Efficacy Objectives:

- Achievement of the developmental motor milestone of sitting independently for ≥ 30 seconds by the age 18 months study visit.
- Survival at age 14 months. Survival is defined as avoidance of the combined endpoint of either death or permanent ventilation (defined as tracheostomy or the requirement of ≥ 16 hours of respiratory assistance per day via non-invasive ventilatory support for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation).

Co-secondary Efficacy Objectives:

- Independence of ventilatory support (defined as requiring no daily ventilator support at age 18 months, excluding acute reversible illness and perioperative ventilation).
- Maintenance of the ability to thrive (defined as achieving all of the following at age 18 months: does not receive nutrition through mechanical support, such as a feeding tube or other non-oral method; able to tolerate thin liquids, as demonstrated in a formal swallowing test; and maintains weight $> 3^{\text{rd}}$ percentile for age and sex, based on WHO Clinical Growth Standards [WHO 2006]).

6.2.2 Design Overview

Study CL-303 is a US multicenter, open-label, single-arm, single-dose study of the efficacy and safety of onasemnogene abeparvovec-xioi. The main comparator group for Study CL-303 is the natural-history controls from the PNCr study (Finkel et al., 2014), which also served as a control for Study CL-101. Study CL-303 enrolled a total of 22 subjects; one subject (b) (6) was considered presymptomatic at baseline; therefore, for this review only efficacy data from the other 21 subjects is evaluated.

Reviewer Comment

A preferable design for Study CL-303 would have included a concurrent control with appropriate blinding. Nusinersen was approved by FDA at the time Study CL-303 was being planned. Based on discussion between FDA and the applicant, recruitment of subjects for trial involving a placebo control would not have been feasible, after publication of results of Study CL-101 (Mendell et al., 2017) and availability of nusinersen. FDA recommended considering use of nusinersen as an active control; however, FDA acknowledged that this approach would likely be difficult, considering the need for repeated invasive delivery procedures involving sedation, and the cost. Use of external historical controls, while not ideal, appears reasonable in this case, because an unmet medical need remain present for treatment of this fatal condition; the natural history of infantile-onset SMA is well-documented and follows a relatively predictable course that can be objectively measured and verified; and the results of Study CL-101 indicated that the expected treatment effect is large, readily ascertained, and shows close temporal association with the intervention.

6.2.3 Population

The study population was planned to consist of up to 20 subjects who met the eligibility criteria. Twenty-five patients were screened; three were excluded from the study (two did not meet eligibility criteria, and one experienced an unspecified adverse event).

A total of 22 subjects were enrolled; of those, 21 had a clinical diagnosis consistent with SMA before 6 months of age and are included in the efficacy ITT analysis for this review.

Key enrollment criteria were as follows:

Inclusion Criteria

- Diagnosis of SMA based on gene mutation analysis with bi-allelic *SMN1* mutations (deletion or point mutations) and 1 or 2 copies of *SMN2*, inclusive of the known *SMN2* gene modifier mutation c.859G>C
- Age < 6 months at the time of infusion
- Undergo swallowing evaluation prior to infusion
- Up-to-date on childhood vaccinations

Exclusion Criteria

- Gestational age at birth younger than 35 weeks (245 days)
- Pulse oximetry < 96% saturation at screening while the patient is awake or asleep without any supplemental oxygen or respiratory support
- Tracheostomy, or current use of non-invasive ventilatory support averaging ≥ 6 hours/day
- Inability to tolerate non-thickened liquids on a formal swallowing test

- Weight-for-age below the 3rd percentile based on WHO Child Growth Standards (WHO 2006)
- Active viral infection (including HIV or positive serology for Zika virus or hepatitis B or C)
- Serious non-respiratory tract illness within 2 weeks prior to screening
- Upper or lower respiratory infection within 4 weeks prior to screening
- Other recent severe infection or concomitant illness
- Known allergy/hypersensitivity to prednisolone, other glucocorticoids, or their excipients
- Concomitant use of drugs for immunomodulation; treatment of myopathy, neuropathy, diabetes mellitus; or recent immunosuppressive therapy
- Anti-AAV9 antibody titer > 1:50, determined by ELISA
- Clinically significant abnormal laboratory values (GGT, ALT, and AST > 3 × ULN, bilirubin ≥ 3.0 mg/dL, creatinine ≥ 1.0 mg/dL, hemoglobin < 8 or > 18 g/dL; white blood cell count > 20,000 per cm³)
- Participation in a recent SMA treatment clinical study
- Expectation of major surgical procedures during the study assessment period

Reviewer Comment

The enrollment criteria for Study CL-303 allowed participation of subjects with backgrounds different from those in Study CL-101 and the natural history studies: presymptomatic subjects; subjects with infantile-onset SMA and only 1 copy of the *SMN2* gene; and subjects harboring the *SMN2* modifier mutation c.859G>C. Enrolling up to 20 subjects under these broader enrollment criteria was projected to enable enrollment of at least 15 subjects that met the intent-to-treat population (ITT) criteria defined below (please see Section 6.2.9). Nevertheless, 21 of the 22 subjects ultimately enrolled in Study CL-303 had clinical manifestations consistent with SMA before 6 months of age; *SMN1* bi-allelic gene deletions; 2 copies of *SMN2*; and none carried the *SMN2* modifier mutation c.859G>C. The CL-303 study population therefore can be compared to the PNCR and NeuroNEXT natural history datasets.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Each subject received a single intravenous infusion at the recommended dose of 1.1×10^{14} vg/kg.

6.2.5 Directions for Use

Same as for the high-dose cohort in Trial #1 C(CL-101) (Please see Section 6.1.5.)

6.2.6 Sites and Centers

Study CL-303 is being conducted at the locations listed in Table 13.

Table 13. Sites for Study CL-303

ID	Location
001	Nationwide Children's Hospital, Columbus, OH
002	University of California, Los Angeles Medical Center
003	St. Louis Children's Hospital/Washington University Medical Center
004	Children's Medical Center Dallas/University of Texas Southwestern Medical Center
005	Boston Children's Hospital
006	Lurie Children's Hospital of Chicago/Northwestern University
007	University of Utah, Salt Lake City, UT
008	Stanford University, Palo Alto, CA
009	Johns Hopkins University, Baltimore, MD
010	Nemours Children's Hospital, Orlando, FL
011	Children's Hospital Colorado, Aurora, CO
012	Duke University, Durham, NC
013	Oregon Health & Science University, Portland, OR
014	Columbia University Irving Medical Center, New York, NY
015	University of Wisconsin, Madison, WI
016	Children's Hospital of Philadelphia

(Source: Adapted from BLA submission)

6.2.7 Surveillance/Monitoring

The monitoring schedule for Study CL-303 is detailed in Table 14.

Table 14. Schedule of assessments for Study CL-303

Study Period	Screening	Treatment (Inpatient)				Follow-up (Outpatient)					End of Study ^a
Visit	1	2				3	4	5	6	7+	Age 18 Months or ET
Days in Study	-30 to -2	-1	1 _b	2	3	7	14	21	30	Monthly ^c	Age 18 Months or ET
Visit Window (days)						±2 days				±7 days (0-14 days at age 14 months)	0-14 days
Informed Consent	X										
Prophylactic Prednisolone		X ^q	X	X	X	X	X	X	X ^q		
Infusion			X								
Bayley Scales/Developmental Milestones ^d (with video) ^e	X								X ^f	X ^f	X
CHOP-INTEND ^g (with video) ^e	X	X ^s				X	X	X	X	X	X
CMAP	X									X ^j	X
Demographic/Medical History	X										
Physical Exam	X		X	X	X	X	X	X	X	X	X
Vital Signs ^h /Weight and Length	X	X	X ⁱ	X	X	X	X	X	X	X	X
12-Lead ECG	X	X	X	X						X ^j	X
12-Lead Holter Monitoring ^k		X	X	X	X						
Echocardiogram	X									X	X
Pulmonary Exam	X	X		X	X	X	X	X	X	X	X
Swallowing Test	X									X ^j	X
Photograph of Infusion Site			X	X	X	X	X	X	X		
Hematology/Chemistry/Urinalysis	X	X ^o		X		X	X	X	X	X	X
CK-MB	X					X			X	X ^r	X
Virus Serology	X										
Capillary Blood Gas		X		X							
ELISA anti-AAV9/SMN Ab	X					X	X	X	X ⁱ		
Immunology Testing (ELISpot)						X			X ⁱ		
Anti-AAV9 Ab Screen in Mother	X										
Blood for Diagnostic Confirmation Testing	X										
Saliva, Urine, and Stool Sample (for viral shedding analysis) ^p	X			X ^m	X ^m	X	X	X	X		
Adverse Events ⁿ	X	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant Medications	Collected from 2 weeks before infusion until End of Study visit										

Ab, antibody; CMAP, compound motor action potential; ECG, electrocardiogram; ELISA, enzyme-linked immunosorbent assay; ELISpot, enzyme-linked immunosorbent assay; ET, early termination; WHO, World Health Organization

^a The End of Study visit must occur within 0 to 14 days after the date on which the patient reaches age 18 months or early termination of the study.

^b Study Day 1 assessments will be performed prior to the start of gene replacement therapy infusion.

^c The age 14 months visit must occur within 0 to 14 days after the date on which the patient reaches age 14 months.

^d Developmental milestones will be assessed as defined by Bayley Scales of Infant and Toddler Development, 3rd edition. Independent sitting also will be assessed as defined by the WHO Multicentre Growth Reference Study (WHO 2006).

^e Videos may be submitted for review by a central reader.

^f The full Bayley-III test will be administered every 6 months, starting at Month 6; the Bayley Fine Motor and Gross Motor subtests will be administered at each monthly visit.

^g Subjects achieving 3 consecutive CHOP-INTEND scores ≥ 58 will not continue to undergo CHOP-INTEND assessments.

^h Vital signs include blood pressure, respiratory rate, pulse, axillary temperature, and pulse oximetry.

ⁱ Vital signs will be continuously monitored throughout the infusion, and recorded every 15 minutes for the first 4 hours (+/- 5 minutes) after the start of infusion, then every hour (+/- 15 minutes) until 24 hours after the start of infusion. Axillary temperature will be recorded before and after infusion.

^j Completed every 6 months, starting at Study Month 6.

^k Serial ECG data will be obtained in triplicate from the Holter monitor at the following time points: pre-infusion (within 24 hours); and 2 hours, 4 hours, 6 hours, 8 hours, 12 hours, 24 hours, 36 hours, and 48 hours post-infusion.

^l Additional sampling may be performed at subsequent time points if ELISpot value(s) continue to be elevated, based on discussion with the Principal Investigator and Medical Monitor.

^m Collected at 24 and 48 hours post-infusion.

ⁿ Serious Adverse Event data will be collected from signing of the informed consent through the last study visit. All adverse events occurring from the start of infusion through the last study visit will be collected.

^o Laboratory samples collected on Study Day -1 will be processed locally, prior to dosing.

^p Sites participating in the viral shedding sub-study will collect 24-hour full-volume samples for urine and feces at 24 and 48 hours. All other sites will collect singular urine and feces samples within 24 hours and 48 hours of dosing.

^q Prednisolone will be given 24 hours prior to scheduled infusion, and continued as per protocol Section 9.2.1.

^r CK-MB will be performed at Study Day 60, and Study Month 6, 9, 12, 15 months of age, 18 months of age/study end.

^s If CHOP-INTEND assessment is not completed, a CHOP-INTEND assessment should be completed on Study Day 1 prior to infusion.

(Source: Study Protocol for AVXS-101-CL-303, version 3.0/21 December 2017)

6.2.8 Endpoints and Criteria for Study Success

Co-Primary Endpoints:

1. Proportion of subjects achieving functional independent sitting for ≥ 30 seconds (defined by Bayley-III criteria) by the age 18 months study visit.
2. Survival at age 14 months. Survival is defined by avoidance of the combined endpoint of either death or use of permanent ventilation (tracheostomy or respiratory assistance for ≥ 16 hours per day [including noninvasive ventilatory support] continuously for ≥ 14 days in the absence of an acute reversible illness, excluding perioperative ventilation).

Co-Secondary Endpoints:

1. Proportion of subjects independent of ventilatory support at age 18 months (defined as requiring no daily ventilator support, excluding acute reversible illness and perioperative ventilation). Ventilator use is determined by usage data captured from the (b) (4) BiPAP device.
2. Proportion of subjects maintaining the ability to thrive at age 18 months (defined as not receiving nutrition through mechanical support, such as a feeding tube or other non-oral method; able to tolerate thin liquids, as demonstrated in a formal swallowing test; and maintaining weight $> 3^{\text{rd}}$ percentile for age and sex, based on WHO Clinical Growth Standards [WHO 2006]).

Exploratory Endpoints:

1. Change of CHOP-INTEND score from baseline
2. Proportion of subjects achieving other motor milestones by 18 months of age, such as head control, rolling from back to sides, standing, and walking.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Key features of the Statistical Analysis Plan for Study CL-303 are as follows:

The intent-to-treat (ITT) population consists of subjects with clinical manifestations consistent with SMA prior to 6 months of age; bi-allelic deletion of *SMN1*; 2 copies of *SMN2*; and absence of the *SMN2* gene modifier mutation c.859G>C. The ITT population comprises the primary population for evaluation of the primary and secondary endpoints. Study power is based upon efficacy analysis of the ITT population.

- Co-primary endpoint #1: Sitting without support for ≥ 30 seconds at 18 months of age
 - Response rate of the historical control is zero (or as low as 0.1%).
 - Assumed response rate of the ITT population is 30% - 40%, based on Study CL-101.
 - A sample size of 15 subjects that meet ITT criteria will be enrolled, and assuming approximately 30% of subjects are excluded from analysis, would yield an ITT population that would provide power of $> 90\%$ to detect a significant difference from 0.1% with $\alpha = 0.025$ using a 1-sided exact test for a binomial proportion
- Co-primary endpoint #2: Survival at 14 months of age
 - Historical control: 25% survival rate.

- Assumption that 80% of patients in the ITT population are expected to survive through 14 months of age.
- An enrolled sample size of 15 subjects that meet ITT criteria (assuming 30% of subjects are excluded from the analysis) would yield an ITT population that would provide power of > 80% to detect a significant difference from the historical control with $\alpha = 0.05$ using a 2-sided Fisher's exact test.

For details, please see FDA statistical review.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

A total of 22 subjects enrolled. All received intravenous infusion of onasemnogene abeparvovec-xioi prior to age 6 months.

The efficacy ITT population consists of 21 subjects who had clinical findings consistent with SMA before age 6 months; carry bi-allelic deletion mutations of *SMN1* (exon 7/8 common homozygous deletions) and 2 copies of *SMN2*; and do not harbor the *SMN2* gene modifier mutation c.859G>C.

One subject (b) (6) was presymptomatic and therefore is not included in the efficacy ITT population. She is white, and of non-Hispanic or Latino ethnicity. She did not have any clinical findings associated with SMA, but does have the same characteristic genetic features described above. She was treated at age 1.1 months.

6.2.10.1.1 Demographics

Demographic information for the Study CL-303 efficacy ITT population is in Table 1.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The medical characterization of the Study CL-303 efficacy ITT population is summarized in Table 15 below.

Table 15. Medical characterization of ITT population in Study CL-303

Subject ID/ Age at Infusion (months)	Age at Symptom Onset (months)	Family History of SMA	Baseline SMA Symptoms				
			Hypotonia	Limb Weakness	Pneumonia/ Respiratory Symptoms	Swallowing/ Feeding Difficulties	Tongue Fasciculations
(b) (6)	2.1	No	X	X	X		X
	4.3	No	X	X			
	5	No	X			X	X
	2.7	Yes	X	X	X		
	3.1	Yes	X	X			
	2.7	No	X	X			X
	5.3	No	X	X			X
	2.6	No	X	X			X
	3.4	No	X	X			
	1.9	Yes	X	X	X		X
	3.6	No	X	X	X		X
	5.3	No	X	X	X		X
	2.9	Yes	X	X	X		X
	5.9	Unknown	X				X
	5.7	Unknown	X	X			
	3.8	No	X	X	X		X
	5.8	Yes	X	X	X		X
	5.9	No	X	X	X		X
	5.1	No	X	X			X
	0.5	Unknown	X	X			
	3.4	Unknown	X	X	X	X	X

(Source: Adapted from AVXS-101-CL-303 Study Report Listing 16.2.4.2.2)

6.2.10.1.3 Subject Disposition

Subject disposition as of the March 8, 2019 data cutoff:

- One subject (b) (6) died. She was 7.8 months old (Study Day 171) at the time of death. The cause of death was respiratory arrest, attributed to progression of SMA.
- One subject (b) (6) discontinued the study early due to withdrawal of consent. She was alive (age 11.9 months) at the time of withdrawal. She was 6 months post infusion of onasemnogene abeparvovec-xioi.
- The remaining 19 subjects were alive without permanent ventilation and continuing in the trial.

6.2.11 Efficacy Analyses

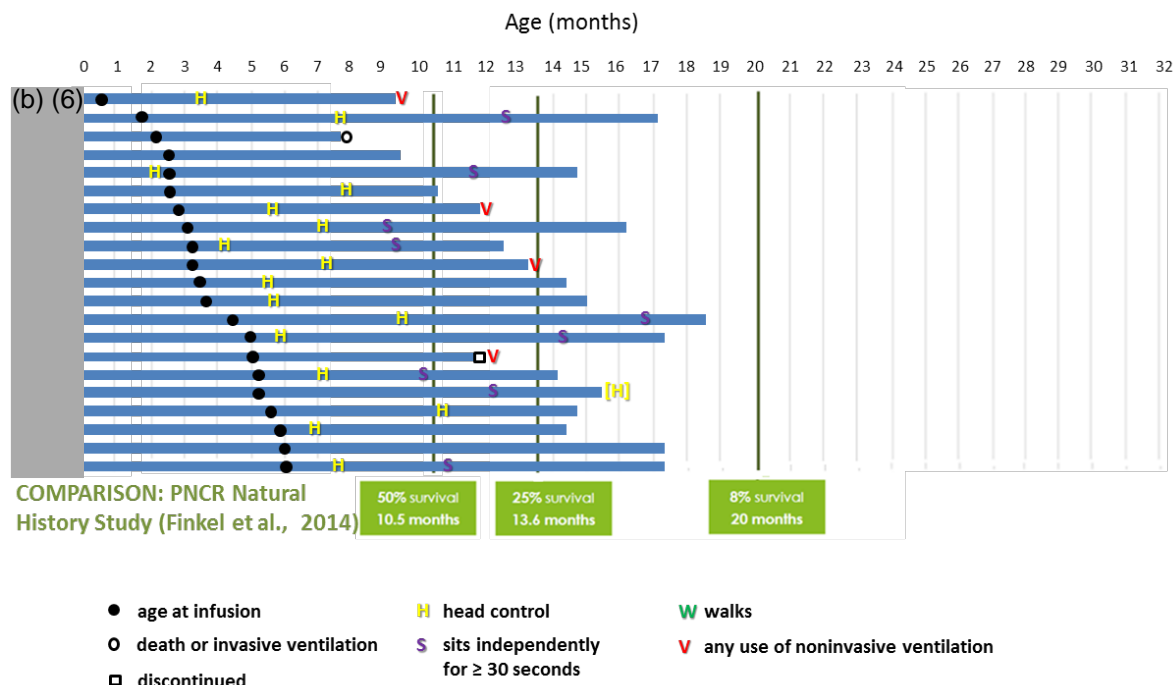
6.2.11.1 Analyses of Primary Endpoint(s)

Co-Primary Endpoint #1

Co-Primary Endpoint #1 is the proportion of subjects achieving functional independent sitting for at least 30 seconds (i.e., sitting up straight unassisted, with head erect) at the age 18 months study visit.

As shown in Figure 7, by the March 8, 2019 data cutoff only one subject had reached 18 months of age. Of the 21 subjects, however, 10 already met the endpoint of functional independent sitting for ≥ 30 seconds. The mean age of those subjects when achieving the milestone was 12.1 months (range 9.2 to 16.9 months).

Figure 7. Swimmer illustration of survival, motor milestone achievement and ventilation use for subjects in Study CL-303 after infusion (as of March 8, 2019)



Subject ID in black indicates male; red indicates female. For Subject (b) (6), the head control milestone is in brackets to indicate that no reviewed video head-control data are verified, although head control is implied by sitting independently.

(Source: Adapted from Applicant's efficacy and safety update of Study CL-303, received 4/30/2019, with revisions by the clinical reviewer)

Co-Primary Endpoint #2

Co-Primary Endpoint #2 is survival at 14 months of age.

Survival results for Study CL-303 as of the March 8, 2019 data update are also shown in Figure 7. One of the 21 subjects (b) (6) died; she had required BiPAP support, although not to the extent that would meet the definition of permanent ventilation. One subject (b) (6) withdrew consent at age 11.9 months. Of the remaining 21 subjects, 13 had reached age 14 months, and all of them have survived without requiring permanent ventilatory support.

Comparison to Natural-History Controls

As summarized in Table 16, the survival and motor milestone results for subjects in the ongoing Study CL-303 compare favorably with results from the Finkel et al. natural history study (Finkel et al., 2014).

Table 16. Survival and Motor Milestone Achievement in Study CL-303 and Finkel et al. (2014) Natural-History Control

Endpoint	Study CL-303 [N = 21] n (%)	Natural-History Control [N = 23] %
Survival at 14 months of age*	13 (67%)	25% [#]
Sitting without support for ≥ 30 seconds	10 (47%)	0

*Only 13 of the 19 remaining subjects in Study CL-303 had reached 14 months of age by the March 8, 2019 data cutoff.

[#]The patient-level survival rate of this control cohort determined at 13.6 months of age from the Kaplan-Meier curve is approximately 25%;

(Source: Applicant's efficacy and safety update, received 4/30/2019; Applicant's PNCR and NeuroNEXT Database Report, page 14, 6/1/2019)

Reviewer Comment

Sixteen (16) patients in the natural-history control cohort reached the combined endpoint of death or the need for a minimum of 16 hours/day of noninvasive ventilation support for a minimum of 14 continuous days by 13.6 month of age. However, there were no data on the number of patients who reached the combined endpoint by 14 months of age. Therefore, it is more appropriate to use the patient-level survival rate of this control cohort determined at 13.6 months of age from the Kaplan-Meier curve.

6.2.11.2 Analyses of Secondary Endpoints

Secondary Endpoint #1

Secondary Endpoint #1 is the proportion of subjects who are independent of ventilatory support, defined as requiring no daily ventilator support at 18 months of age, excluding acute reversible illness and perioperative ventilation, as defined above through assessment of actual usage data captured from the (b) (4) device.

As of the March 8, 2019 data update, only 1 of the 19 surviving subjects had reached the age of 18 months; she does not require daily ventilator use. (Of the other 18 surviving subjects, thus far 3 have required some daily ventilation use.)

Secondary Endpoint #2

Secondary Endpoint #2 is the proportion of subjects maintaining the ability to thrive (defined as achieving all of the following at age 18 months: not receiving nutrition through mechanical support, such as a feeding tube or other non-oral method; able to tolerate thin liquids, as demonstrated in a formal swallowing test; and maintaining weight > 3rd percentile for age and sex, based on WHO Clinical Growth Standards [WHO 2006]).

As of the March 8, 2019 data update, all 19 surviving subjects remained able to exclusively feed orally; as noted above, however, by the data cutoff only 1 subject had reached age 18 months.

6.2.11.2 Analyses of Exploratory Endpoints

Motor Milestones Other than Sitting Independently

Achievement of additional motor milestones for subjects in Study CL-303 is summarized below in Table 17.

Table 17. Achievement of other developmental motor milestones by subjects in Study CL-303 (as of March 8, 2019)

Motor Milestone	Subjects [n = 21] (%)	Mean Age [months] at Milestone Achievement (range)
Head control*	16 (76%)	6.5 (2.2 - 10.6)
Rolls from back to sides	8 (38%)	10.6 (7.4 - 14.3)

*Subject (b) (6), who is included in this table, demonstrated head control at baseline.
(Source: Adapted from efficacy and safety update of Study CL-303 as of March 8, 2019)

Four of the 21 subjects in Study CL-303 did not achieve any motor milestones by the March 8, 2019 data cutoff. Of these four, Subject (b) (6) died at age 7.8 months; Subject (b) (6) withdrew from the study at 11.9 months of age; Subject (b) (6) was 9.3 months old and Subject (b) (6) was 17.4 months old.

CHOP-INTEND Score

The mean CHOP-INTEND score at baseline (n = 21) was 31 (range 18 to 47). The mean CHOP-INTEND score at 6 months (n = 20) following infusion of onasemnogene abeparvovec-xioi was 46 (range 29 to 58) (Subject (b) (6) died before the month 6 study visit.). In contrast, CHOP-INTEND scores for the natural history comparator group declined over time (Kolb et al., 2016; Kolb et al., 2017).

6.2.11.3 Subpopulation Analyses

Study CL-303 is ongoing, which limits subpopulation analysis. In addition, the small sample size also constrains subgroup analyses by age, sex, gender and ethnicity.

6.2.11.4 Dropouts and/or Discontinuations

One subject (Subject (b) (6)) discontinued the study by withdrawal of consent. 2018. She was 11.9 months of age at the time of withdrawal, and was 6 months post infusion of onasemnogene abeparvovec-xioi.

6.2.11.5 Exploratory and Post Hoc Analyses

6.2.12 Safety Analyses

6.2.12.1 Methods

The safety population consists of all 22 subjects who received the product. (One of the 22 subjects was reported as presymptomatic, and therefore was not included in the efficacy ITT population discussed above in Section 6.2.11).

6.2.12.2 Overview of Adverse Events

As of the efficacy and safety update of March 8, 2018:

- All 22 subjects had experienced at least 1 TEAE. Nine subjects experienced a TEAE considered by the investigator to be related to onasemnogene abeparvovec-xioi. Six subjects had at least 1 SAE.
- One subject (b) (6) died at 7.8 months of age. The cause of death was respiratory arrest, attributed to progression of SMA (see Section 6.2.12.3 for detail).
- One subject (b) (6) discontinued the study early (see Section 6.2.12.7 for detail).

The most frequent TEAEs for Study CL-303 were pyrexia (46%), upper respiratory tract infection (36%), aspartate aminotransferase increased (27%), and alanine aminotransferase increased (23%), and gastroesophageal reflux disease (18%).

Reviewer Comment

Pyrexia, upper respiratory tract infection, and gastroesophageal reflux disease are common in infancy, as well as in the natural history of patients with infantile-onset SMA. Without a concurrent placebo arm, any increased susceptibility to these TEAEs due to onasemnogene abeparvovec-xioi cannot be determined.

6.2.12.3 Deaths

One subject (b) (6) in Trial #2 (CL-303) died at age 7.8 months.

Subject (b) (6) underwent infusion of onasemnogene abeparvovec-xioi on (b) (6), at age 62 days old. There were no reported complications.

Her baseline CHOP-INTEND score was 18. At her last study visit (Month 5 Visit) on (b) (6), her total CHOP-INTEND score was 45.

Subject (b) (6) experienced the following SAEs:

- On (b) (6), she was reported by the investigator as experiencing poor weight gain (“abnormal weight gain”) and “respiratory failure.” On (b) (6), BiPAP, aggressive cough assist, and chest physiotherapy were initiated; in addition, a naso-jejunal (N-J) tube was placed, and N-J feeding begun. She was to continue receiving exclusive enteral nutrition via the N-J tube (100%) for 18 hours per day at home. She was discharged home on (b) (6), with resolution of both SAEs. They were not considered by the investigator as related to the investigational product.
- On (b) (6) (Study Day 171), she experienced respiratory arrest, resulting in her death. Per the SAE report, she was found lifeless in her car seat after an approximately 30-minute car ride. These events were not considered by the investigator to be related to the investigational product.

6.2.12.4 Nonfatal Serious Adverse Events

As of the March 8, 2019 update, the following nonfatal treatment-related SAEs were reported in a total of 3 subjects in Study CL-303 (Table 18).

Table 18. Nonfatal SAEs in Study CL-303 (as of March 8, 2019)

SAE Classification	Number of Subjects
AST increased	1
ALT increased	1
Aminotransferases increased	1
Hydrocephalus	1

(Source: Study CL-303 Efficacy and Safety Update Report, Table 14.3.1.3-1.)

6.2.12.5 Adverse Events of Special Interest (AESI)

Elevated Aminotransferases

Seven subjects in Study CL-303 experienced TEAEs of elevated aminotransferases (ALT and/or AST). In 1 subject, AST and ALT levels reached approximately 40 X ULN. For 3 subjects, AST and ALT levels were between 5-10 X ULN. None of the subjects met criteria for Hy's Law (please see Section 6.1.12.5; Temple 2006).

Decreased Platelets/Thrombocytopenia

Three subjects in Study CL-303 experienced TEAEs of thrombocytopenia (median time to onset was 10 days; range 7-63 days). Two additional subjects experienced decreased platelet levels, but still within the normal range ($140 \times 10^9/L$ to $440 \times 10^9/L$).

Communicating Hydrocephalus

Subject (b) (6) in Study CL-303 is a black male infant who developed communicating hydrocephalus at age 6.5 months.

He was diagnosed with SMA at age 5 weeks. He received intravenous infusion of onasemnogene abeparvovec-xioi on (b) (6), at age 2.6 months. He had not achieved any developmental motor milestones.

On (b) (6) (Study Day 131), he developed irritability and vomiting. He was noted to have accelerated increase in head size, impaired upgaze, and left sixth nerve palsy. Head ultrasound demonstrated ventriculomegaly affecting the lateral and third ventricles, consistent with communicating hydrocephalus. He was hospitalized in the pediatric ICU. No evidence of infection was present.

On (b) (6), he underwent endoscopic third ventriculostomy. No significant change was noted subsequently in ventricular dilatation, and intracranial pressure remained elevated. On (b) (6), he underwent placement of a right ventricular peritoneal shunt. He was discharged from the hospital on (b) (6). The SAE of communicating hydrocephalus was considered resolved.

Reviewer Comment

Possible relationship of the product to the occurrence of communicating hydrocephalus is unknown. Please see further discussion in Section 8.4.8.

6.2.12.6 Clinical Test Results

Anti-AAV9 Antibody Levels

All subjects had anti-AAV9 titers < 1:50 at baseline, per study entrance criteria. Following infusion of onasemnogene abeparvovec-xioi, increases from baseline in anti-AAV9 antibody titers occurred in all subjects. At 4 weeks after product administration,

the titers ranged from 1:800 to 1:1,600. One subject (b) (6) had blood taken on Day 98 for unknown reason and the titer was 1:102,400.

Reviewer Comment

Per Study CL-303 protocol, anti-AAV9 titer will be measured during the first month after product infusion.

Based on data from Study CL-101, the anti-AAV9 titer will likely continue trending up during the second and third month after product infusion.

T-cell Responses to AAV9

No subjects appear to have had elevated T-cell responses to AAV9.

Reviewer Comment

Samples were not collected as frequently in CL-303 as in CL-101; consequently, these findings are difficult to interpret.

Anti-SMN Antibody Levels

All subjects had anti-SMN titers of <1:12.5 prior to administration of the product. As in Study CL-101, development of antibodies to SMN protein was not observed.

T-cell Response to SMN

The T-cell response to SMN for subjects in Study CL-303 was similar to that observed in Study CL-101.

6.2.12.7 Dropouts and/or Discontinuations

One subject (Subject (b) (6)) discontinued the study early due to withdrawal of consent. She was 11.9 months of age at the time of withdrawal, and was 6 months post infusion of onasemnogene abeparvovec-xioi.

She experienced onset of SMA symptoms at age 2 months. Other than SMA type 1, she had no other clinically-significant medical history. Physical examination at her screening visit demonstrated hypotonia, limb weakness, tongue fasciculations, and developmental delay. She had a functional swallow, and did not require any ventilatory support. Her baseline CHOP-INTEND score was 24 (Study Day -1).

She underwent infusion at the age of 154 days old. She did not achieve any developmental motor milestones. Her highest CHOP-INTEND score was 32, achieved on Study Day 28. Her CHOP-INTEND score was 29 on Day 122, and her CHOP-INTEND score reported at discontinuation was 22.

She experienced multiple SAEs, including thrombocytopenia, severe dysphagia, and respiratory-related events. Only thrombocytopenia (began on Study Day 10 and resolved on Study Day 17) was considered related to onasemnogene abeparvovec-xioi.

6.2.13 Study Summary and Conclusions

Results from the ongoing Study CL-303 are consistent with those of Study CL-101, and provide primary evidence of effectiveness of onasemnogene abeparvovec-xioi:

- As of the March 8, 2019 data cutoff, 18 subjects in Study CL-303 reached age 10.5 months and had survived without permanent ventilation, compared to 50% in the PNCR natural history study (Finkel et al., 2014). Thirteen subjects in Study CL-303 who reached age 13.6 months had survived without permanent ventilation, compared to 25% in the PNCR natural history study.
- Although only 1 of the 21 subjects has reached the time point of age 18 months, 10 subjects in Study CL-303 have already achieved the ability to sit independently for ≥ 30 seconds. Based on the natural history of the disease, no patients meeting the study entry criteria would be expected to attain that developmental motor milestone.

The more serious risks of onasemnogene abeparvovec-xioi include elevation of aminotransferases, as well as thrombocytopenia. These abnormalities resolved after the subjects were treated with prednisolone. The occurrence of communicating hydrocephalus in one subject is noteworthy, but the association with the product is unclear.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

An Integrated Overview of Efficacy (i.e., an analysis using pooled data from all subjects treated with intravenous infusion of onasemnogene abeparvovec-xioi) was not performed, for the following reasons:

- As discussed in Section 4.1, the doses that subjects in Study CL-101 received are unclear. Those dose uncertainties preclude direct comparison of the efficacy outcomes of Study CL-101 with those of Study CL-303, in which all subjects were treated with 1.1×10^{14} vg/kg of the product.
- The primary evidence of effectiveness for onasemnogene abeparvovec-xioi is provided by analysis of results (as of the March 8, 2019 data cutoff) of Study CL-303, which is ongoing and therefore incomplete.
- Other potential sources of efficacy data (long-term observational study LT-101; non-US clinical trial CL-302; and the expanded access program) are also ongoing and therefore incomplete. In addition, interpretation of results of these sources may be confounded by factors such as differences in *SMN2* copy number; presence of the *SMN2* gene modifier mutation c.859G>C; inclusion of presymptomatic patients; and (in Study LT-101 and the expanded access program) concurrent use of nusinersen.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The Integrated Overview of Safety is based on pooled data from subjects treated with intravenous infusion of onasemnogene abeparvovec-xioi.

The data was assembled from available clinical trial results, an ongoing observational study, as well as information from patients receiving the product through the expanded

access program. Important limitations in interpreting the pooled data are detailed below in Section 8.3.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

As of December 30, 2018, a total of 42 subjects had received onasemnogene abeparvovec-xioi intravenously as part of clinical trials summarized in Table 6. Of these subjects, 27 received the recommended dose of 1.1×10^{14} vg/kg; the dose administered to the 15 subjects in Study CL-101 is uncertain (please see Section 4.1 for details).

In addition, a total of 46 patients have received onasemnogene abeparvovec-xioi from the applicant under the FDA expanded access to investigational drugs program (compassionate use). All were administered the product intravenously at the recommended dose of 1.1×10^{14} vg/kg.

Study CL-101

All 15 subjects in the completed Study CL-101 had clinical manifestations consistent with SMA prior to treatment with onasemnogene abeparvovec-xioi. All were confirmed to have bi-allelic *SMN1* deletions; 2 copies of the *SMN2* gene; and absence of the *SMN2* modifier mutation c.859G>C. All 15 subjects completed the study.

Study LT-001

Study LT-001 is an observational long-term follow-up study which enrolled 13 of the 15 subjects who received onasemnogene abeparvovec-xioi in Study CL-101. (High-dose cohort subjects (b) (6) are not participating in Study LT-001). Subjects have not received any further infusion of the product, and are permitted to receive nusinersen. Safety information is being collected only for SAEs and the following AESIs: liver function enzyme elevations; new occurrences of a malignancy or hematologic disorder; and new occurrences or exacerbations of existing neurologic or autoimmune disorders. As of September 27, 2018, subjects in Study LT-001 had been followed for a mean of 42 months (maximum 53.3 months) after infusion of onasemnogene abeparvovec-xioi in Study CL-101. At 1-year follow-up visit, 3 subjects were taking nusinersen.

Study CL-303

Twenty-one of the 22 subjects enrolled in Study CL-303 had clinical manifestations consistent with SMA prior to treatment with onasemnogene abeparvovec-xioi; one subject was designated as presymptomatic. All 22 subjects had the same genetic features as the subjects described above in Study CL-101 (i.e., bi-allelic *SMN1* deletions; 2 copies of *SMN2*; and absence of the *SMN2* modifier mutation c.859G>C). As of the March 8, 2019 data cutoff, 1 subject discontinued from the study due to withdrawal of consent, and 1 subject died of respiratory failure due to progression of SMA.

Study CL-302

The 5 subjects enrolled in the non-US Study CL-302 had clinical and genetic features matching those of the subjects in Study CL-101. As of the September 27, 2019 data cutoff, Study CL-302 subjects had been followed for a mean of 0.51 months (maximum 1 month) after treatment with onasemnogene abeparvovec-xioi, to a maximum of 1 month.

Expanded Access

The FDA expanded access program enrolls individual patients not meeting criteria for participation in clinical trials. The age of the 46 patients ranged from 2 weeks to 15 months. Thirty-two of the 46 patients also received nusinersen. 8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The overall demographic characteristics for the safety population is summarized below in **Error! Reference source not found.**

Table 19. Demographic information for safety population

Characteristic	CL-101 Low-Dose (n=3)	CL-101 High-Dose (n=12)	LT-001 Low-Dose (n=3)	LT-001 High-Dose (n=10)	CL-302 (n=5)	CL-303 (n=22)	Expanded Access ^a (n=46)
Age at treatment (months)							
Mean	5.3	3.4	5.3	2.9	3.2	3.7	5.1
Median	5.9	3.1	5.9	2.6	2.7	3.5	5
Min, Max	5.9, 7.2	0.9, 7.9	5.9, 7.2	1, 6	2.2, 5.6	0.5, 5.9	0.5, 15
Sex							
Male	1	5	1	5	3	10	21
Female	2	7	2	5	2	12	25
Race							
White	3	11	3	9	*	11	
Black/African American	0	0	0	0	*	3	
Asian	0	0	0	0	*	2	
Am Ind/Alaskan Native	0	0	0	0	*	0	
Other/Multiple	0	1	0	1	*	6	
Ethnicity							
Non-Hispanic/Latino	3	10	3	8	*	18	
Hispanic or Latino	0	2	0	2	*	4	
Weight at baseline (kg)							
Mean	6.6	5.7	13.2	12	6.1	5.8	
Min, Max			12.0, 14.7	9.9, 14.6	4.7, 8.4	3.9, 7.5	
Baseline swallowed thin liquids	0	4	0	10	5	22	
Baseline required feeding support	3	5	3	5	2	0	
Baseline required ventilatory support	3	1	3	6	2	0	

*missing data

^aInformation such as race, ethnicity, weight at dosing, and baseline functional status are incomplete. (Sources: Applicant's 120-Day Safety Update; Applicant's Clinical Information Amendment submitted 5/8/2019; and FDA clinical reviewer's analysis of information from expanded access investigators.)

8.2.3 Categorization of Adverse Events

All AEs analyzed in the safety database were treatment-emergent adverse events.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Several important factors must be considered in assessing the pooled safety population:

- The doses received by all 15 subjects in Study CL-101 are uncertain (please see Section 4.1 for details). In addition, Study CL-101 was composed of two dose cohorts: a low-dose cohort (3 subjects) and a high-dose cohort (12 subjects).
- Safety information is limited from Studies LT-001, CL-303, and CL-302, all of which are ongoing.

- Some patients in the safety population have received nusinersen: 3 subjects in Study LT-001, the sponsor's long-term observational study; and 32 patients in the expanded access program.
- The safety population includes at least one subject (from Study CL-303) who was presymptomatic.
- Detailed demographic and other background information is not available for the 46 patients in the expanded access program.
- Some demographic information (race and ethnicity) is not available from the non-US trial (CL-302).

8.4 Safety Results

8.4.1 Deaths

Two deaths have occurred within the safety population:

1. One subject in Study CL-303: Subject (b) (6) underwent infusion of onasemnogene abeparvovec-xioi at age 62 days old. She died at age 7.8 months (Study Day 171), after experiencing respiratory arrest, which is likely due to disease progression (Please see Section 6.2.12.3 for details.).
2. One subject in Study CL-302: Subject (b) (6) underwent infusion of onasemnogene abeparvovec-xioi at age 5 months. He died at age 6.7 months (Study Day 52). The relationship of his death to the investigational product is not clear.

Subject (b) (6) had bi-allelic deletion of the *SMN1* gene, 2 copies of *SMN2*, and did not harbor the *SMN2* modifier c.859G>C. At baseline, he had swallowing difficulties, and was completely dependent on nasogastric tube for feeding. He also had a history of possible aspiration pneumonia. His weight was 5.8 kg.

He received onasemnogene abeparvovec-xioi on (b) (6) (Study Day 0).

On Study Day 12, he presented with increased respiratory secretions, which progressed to respiratory distress. He was admitted to a local hospital on Study Day 14 and was intubated.

By Study Day 27, his condition had further deteriorated, with hypotensive episodes requiring inotropes. He developed focal seizures, and on Study Day 32 was transferred to a tertiary-care center. On Study Day 46, he experienced respiratory arrest due to accumulation of secretions, and required re-intubation. His evaluation on Study Day 50 demonstrated significant CNS impairment.

MRI scan of the brain showed leukoencephalopathy. Testing of respiratory secretions was positive for respiratory syncytial virus and parainfluenza virus.

On Study Day 52, repeated attempts at extubation and placement on non-invasive ventilation were unsuccessful. Life support was withdrawn; he was transferred to palliative care, and died on Study Day 52.

Reviewer Comment

It is unclear whether the seizures and leukodystrophy were due to product administration, or to the hypotensive episodes or another cause. The final autopsy report is pending.

8.4.2 Nonfatal Serious Adverse Events

Acute Serious Liver Injury

A patient with infantile-onset SMA in the expanded access program developed acute serious liver injury after receiving onasemnogene abeparvovec-xioi. At baseline, she had elevated AST and ALT of unknown etiology; other indicators of liver function (gamma-glutamyl transferase, total bilirubin, and prothrombin time) were normal.

Approximately 7 weeks after onasemnogene abeparvovec-xioi infusion, the patient developed jaundice. Laboratory testing was consistent with acute liver failure: AST was approximately 80 × ULN, ALT was approximately 45 × ULN, total serum bilirubin was approximately 4 × ULN, and plasma prothrombin time was approximately 4 × ULN. Liver biopsy showed acute massive degeneration of hepatocytes, and massive mixed inflammatory infiltrate (primarily CD8-positive T lymphocytes).

She recovered to baseline with prednisolone treatment.

Elevated Aminotransferases

Three subjects in clinical trials experienced SAEs of elevated aminotransferases: two subjects in Study CL-101 (one in the low-dose cohort and one in the high-dose cohort), and one in Study CL-303.

Thrombocytopenia/Decreased Platelets

Three subjects, all in Study CL-303, experienced thrombocytopenia.

Elevated Troponin-I

In Study CL-101, 8 subjects (1 subject in the low-dose cohort and 7 in the high-dose cohort) had elevations in cardiac troponin-I levels that met the pre-specified protocol criterion for potential clinical significance (>0.05 µg/L).

Communicating Hydrocephalus

A subject in Study CL-303 developed communicating hydrocephalus at age 6.5 months (please see Section 6.2.12.5 for details).

8.4.3 Study Dropouts/Discontinuations

There has been one dropout from the clinical trials: Subject (b) (6) from Study CL-303. (Please see Section 6.2.12.7 for details.)

8.4.4 Common Adverse Events

The most common treatment-related, treatment-emergent adverse events seen in clinical trial subjects were elevated aminotransferase levels above the upper limit of

normal (12 subjects), and vomiting (3 subjects). Elevated aminotransferases include elevation of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST).

8.4.8 Adverse Events of Special Interest

Six adverse events of special interest were noted (Table 20): acute serious liver injury; elevated aminotransferases; thrombocytopenia; elevated troponin-I; seizures and leukoencephalopathy; and communicating hydrocephalus.

Table 20. Adverse events of special interest in the pooled safety population

Adverse Events of Special Interest	CL-101 (n = 15)	LT-001 (n = 13)	CL-302 (n = 5)	CL-303 (n = 22)	Exp Access (n = 46)	Total
Acute serious liver injury					1	1
Elevated aminotransferases (ALT and/or AST)	5 ^a		1	7 ^b	1	14
Thrombocytopenia			1	3		4
Elevated troponin-I	8					8
Seizures and leukoencephalopathy			1			1
Communicating hydrocephalus				1		1

^a Includes 2 SAEs

^b Includes 1 SAE

(Source: FDA clinical reviewer's analysis)

Acute Serious Liver Injury

A patient in the expanded access program developed acute severe hepatic injury after receiving onasemnogene abeparvovec-xioi (please see Section 8.4.2 for further details).

Elevated Aminotransferases

In Study CL-101, 4 subjects experienced a total of 5 TEAEs of elevated serum aminotransferases. All 5 TEAEs occurred without clinical findings of jaundice or other symptoms of hepatic impairment, and all resolved during the observation period. Two of these events were SAEs:

- One subject in the low-dose cohort developed ALT of 31 x ULN, and AST of 14 x ULN. Other indicators of liver function (alkaline phosphatase and total and indirect bilirubin) were unremarkable, and no clinical symptoms were evident. These abnormalities were attenuated by treatment with prednisolone. She was the first subject in Study CL-101; afterwards, the protocol was amended to include prophylaxis with prednisolone.
- One subject in the high-dose cohort had ALT of 35 x ULN and AST of 37 x ULN, with total bilirubin reaching 1.9 x ULN. She required additional prednisolone for resolution of the event.

In Study CL-303, 7 subjects experienced TEAEs of elevated aminotransferases. One subject had increased AST and ALT levels to approximately 40 x ULN after infusion of onasemnogene abeparvovec-xioi, despite concurrent treatment with prednisolone. Total

bilirubin was normal. The subject was asymptomatic, and the abnormalities resolved with prednisolone treatment.

One subject in Study CL-302 and one patient in the expanded access program were noted to have elevated aminotransferases; in the latter case, values were elevated at baseline (ALT and AST 4 x ULN), and rose substantially after infusion (maximum ALT 45 x ULN; maximum AST 74 x ULN).

Reviewer Comment

Because of the potential serious risks associated with hepatotoxicity, a Boxed Warning is included in the package insert for onasemnogene abeparvovec-xioi to alert prescribers to the possibility of acute serious liver injury and elevated aminotransferases.

Thrombocytopenia

Three subjects in Study CL-303 experienced thrombocytopenia (median time to onset was 10 days, range 7-63 days).

Three additional subjects (two in CL-303 and one in CL-302) experienced decreased platelet counts (median onset 8 days, range 6-9 days) which did not reach the threshold for thrombocytopenia.

In Study CL-101, decreases from baseline in mean platelet counts were observed at multiple time points, but without falling below the lower limit of normal for any subject at any visit.

Elevated Troponin-I

In Study CL-101, one subject in the low-dose cohort and 7 in the high-dose cohort had elevations in cardiac troponin-I levels that met the pre-specified protocol criterion for potential clinical significance (>0.05 $\mu\text{g/L}$). Of these 8 total subjects, 2 had increased troponin-I levels at baseline. By study end, all values had decreased either to within the normal range or below 0.05 $\mu\text{g/L}$.

Seizures and Leukoencephalopathy

One subject in Study CL-302 experienced respiratory distress and hypotension, after which he developed focal seizures and was found to have leukoencephalopathy. He subsequently died. (Please see Section 8.4.1 for details.)

Communicating Hydrocephalus

One subject in Study CL-303 developed communicating hydrocephalus at age 6.5 months (Study Day 131). This event was considered to be possibly related to the investigational product. (Please see Section 6.2.12.5 for details.)

Reviewer Comment

The overall prevalence of infantile hydrocephalus is estimated as 1.1 per 1,000 infants (Tully and Dobyns 2014; Munch et al., 2012; Munch et al., 2014). Hydrocephalus is not typically part of the natural history of SMA.

Of note, 5 cases of communicating hydrocephalus not associated with bleeding or meningitis have been reported in SMA patients treated with nusinersen; that medication is dosed intrathecally via lumbar puncture.

It is unknown whether combination therapy with nusinersen and onasemnogene abeparvovec-xioi may increase the likelihood of the adverse event of communicating hydrocephalus. Careful clinical monitoring is warranted.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

Overall dose dependency of onasemnogene abeparvovec-xioi for adverse events could not be clearly determined, because the precise doses received by subjects in Study CL-101 (and therefore the subjects continuing in the long-term follow-up trial LT-101) are unclear. All other subjects treated with onasemnogene abeparvovec-xioi via intravenous administration received a dose of 1.1×10^{14} vg/kg.

Dose-response relationships could be discerned from Study CL-101 for hepatotoxicity and elevated troponin-I:

- Despite receiving prophylactic treatment with prednisolone, 3 subjects from the high-dose cohort developed elevated transaminases (with one SAE), compared to one subject in the low-dose cohort (SAE) who did not receive prophylaxis. Prednisolone treatment was effective in ameliorating hepatotoxicity.
- One subject in the low-dose cohort and 7 in the high-dose cohort had elevations in cardiac troponin-I levels that met the pre-specified protocol criterion for potential clinical significance (>0.05 µg/L). Of these 8 total subjects, 2 had increased troponin-I levels at baseline.

8.5.2 Time Dependency for Adverse Events

Variability in time of onset was observed for the development of thrombocytopenia or decreased platelet counts (not meeting the threshold for thrombocytopenia). Three subjects in Study CL-303 experienced SAEs of thrombocytopenia, with a median time to onset of 10 days (range 7-63 days). Three additional subjects (two in Study CL-303 and one in Study CL-302) experienced decreased platelet counts, with median onset of 8 days (range 6-9 days).

8.5.3 Product-Demographic Interactions

No clear evidence is discernable to indicate increased product-demographic interactions related to treatment with onasemnogene abeparvovec-xioi.

8.5.5 Product-Product Interactions

Three subjects in the long-term observational follow-up Study LT-101, as well as 32 patients in the expanded access program, have received onasemnogene abeparvovec-xioi and nusinersen for treatment of infantile-onset SMA.

- Thrombocytopenia has been observed with both onasemnogene abeparvovec-xioi and nusinersen.
- Communicating hydrocephalus has been observed with both onasemnogene abeparvovec-xioi (1 case) and nusinersen (5 cases).

Any potential increased risk with receipt of both products is unknown.

8.5.6 Human Carcinogenicity

No animal studies have been performed to evaluate the effects of onasemnogene abeparvovec-xioi on carcinogenesis, mutagenesis or impairment of fertility, as based on characteristics of the product and preclinical data, this was not warranted.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

8.5.8 Immunogenicity (Safety)

In clinical trials of onasemnogene abeparvovec-xioi, subjects were required to have baseline anti-AAV9 antibody titers of $\leq 1:50$, measured using ELISA. Evidence of prior exposure to AAV9 was uncommon. The safety and efficacy of onasemnogene abeparvovec-xioi in subjects with anti-AAV9 antibody titers above 1:50 have not been evaluated.

Following infusion of onasemnogene abeparvovec-xioi, increases from baseline in anti-AAV9 antibody titers occurred in all subjects; in some of these cases, anti-AAV9 antibody titers exceeded 1:819,200. High anti-AAV9 antibody titers resulting from the initial ZOLGENSMA infusion are expected to preclude the possibility of re-administration of AAV9 vector-based gene therapy.

8.5.9 Person-to-Person Transmission, Shedding

Vector shedding after infusion with onasemnogene abeparvovec-xioi was investigated at multiple time points during Study CL-101. Samples of saliva, urine and stool were collected the day after infusion, weekly through Day 30, and then monthly through Month 12 and every 3 months thereafter. Samples from 5 subjects were used for onasemnogene abeparvovec-xioi vector DNA shedding analysis through the Month 18 visit.

Vector DNA was shed in saliva, urine and stool after infusion of onasemnogene abeparvovec-xioi, with much higher concentrations of vector DNA found in stool than in saliva or urine. The vector DNA concentration in saliva was low on Day 1 after infusion, and declined to undetectable levels within 3 weeks. In urine, vector DNA concentration was very low on Day 1 after infusion, and declined to undetectable levels within 1 to 2 weeks. In stool, vector DNA concentration was higher than in saliva or urine for 1 to 2 weeks after infusion, and declined to undetectable levels by 1 to 2 months after infusion.

Reviewer Comment

Temporary vector shedding of the product may occur, primarily through stool. Caregivers should be instructed on the proper handling of patient feces, e.g., sealing disposable diapers in disposable trash bags and then discarding into regular trash. Caregivers and families should be instructed regarding proper hand hygiene when coming into direct contact with patient body waste. These precautions should be followed for one month after product infusion.

8.6 Safety Conclusions

The most serious risk clearly associated with intravenous infusion of onasemnogene abeparvovec-xioi is hepatotoxicity, including substantial elevation of aminotransferases

and acute serious liver injury. Individuals with hepatic abnormalities at baseline may be at increased risk. The uncertainty regarding the doses used in the Phase 1 trial in turn prompts uncertainty as to the dose(s) of onasemnogene abeparvovec-xioi associated with the occurrences of hepatotoxicity.

High anti-AAV9 antibody titers occurred following infusion of onasemnogene abeparvovec-xioi in all subjects. High anti-AAV9 antibody titers are expected to preclude the possibility of re-administration of onasemnogene abeparvovec-xioi because of both potential safety and efficacy concerns.

Thrombocytopenia is also a potential additional risk.

Any relationship between onasemnogene abeparvovec-xioi and the development of seizures and leukoencephalopathy in one subject, and communicating hydrocephalus in one subject, remains unclear.

The potential for clinical cardiotoxicity, similar to that observed in neonatal mice treated with onasemnogene abeparvovec-xioi, also remains uncertain.

In addition, the long-term effects of treatment with onasemnogene abeparvovec-xioi are unknown. Although AAV vectors are nonreplicative and nonintegrating, laboratory studies using AAV vectors suggest that caution is warranted: integration in the host genome has been reported in experimental settings (Deyle and Russell, 2009), and neonatal mice injected with an AAV vector expressing beta-glucuronidase subsequently developed hepatocellular carcinoma (Donsante et al., 2001; Donsante et al., 2007).

Nusinersen has also been associated with thrombocytopenia, as well as with 5 cases of communicating hydrocephalus. The possibility of increased risk from use of onasemnogene abeparvovec-xioi together with nusinersen for treatment of pediatric patient less than 2 years of age with SMA is unknown. The safety concerns are appropriately noted in the package insert.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

Administration of onasemnogene abeparvovec-xioi requires concomitant treatment with corticosteroids to mitigate possible adverse immune responses. Because corticosteroid treatment may adversely affect neurological development of premature neonates, administration of the product to infants before they reach full-term gestational age is not recommended.

9.1.1 Human Reproduction and Pregnancy Data

Onasemnogene abeparvovec-xioi was administered to infant patients. Effects on future reproduction and pregnancy are unknown.

Onasemnogene abeparvovec-xioi can be shed, primarily in feces. Effects on reproduction and pregnancy for caregivers or others exposed to the product via shedding is unknown.

9.1.2 Use During Lactation

Onasemnogene abeparvovec-xioi was not studied in breastfeeding mothers.

9.1.3 Pediatric Use and PREA Considerations

Onasemnogene abeparvovec-xioi is not subject to PREA, since the product received Orphan Drug designation.

9.1.4 Immunocompromised Patients

Onasemnogene abeparvovec-xioi was not studied in immunocompromised patients.

9.1.5 Geriatric Use

Onasemnogene abeparvovec-xioi was not studied in geriatric patients.

10. CONCLUSIONS

The primary evidence of effectiveness is generated by comparing results of multiple clinically meaningful efficacy endpoints (as of the March 8, 2019 data cutoff) in the ongoing Phase 3 clinical trial to available natural history data for patients with infantile-onset SMA.

The safety database included 42 subjects from the completed Phase 1 trial and several ongoing clinical trials. The major risks associated with onasemnogene abeparvovec-xioi infusion include acute serious liver injury, and substantial elevations in aminotransferases. These risks can be mitigated by routine medical management, adequate PI, and the postmarketing plan proposed by the applicant.

Review of the submitted data indicates that onasemnogene abeparvovec-xioi appears safe and effective for the treatment of pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the *SMN1* gene. Onasemnogene abeparvovec-xioi is expected to improve survival, as well as to promote achievement of motor functions that are clinically meaningful in the intended patient population.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and reasons
Analysis of Condition	<ul style="list-style-type: none"> Spinal muscular atrophy (SMA) results from bi-allelic mutations in the <i>SMN1</i> gene, leading to degeneration of lower motor neurons. Patients with infantile-onset SMA (about 45-60% of SMA patients) typically develop severe flaccid paralysis by 6 months of age; they do not achieve the ability to sit independently, and generally die of respiratory failure by age 2 years. 	<ul style="list-style-type: none"> Spinal muscular atrophy is a serious and life-threatening disease.
Unmet Medical Need	<ul style="list-style-type: none"> The only FDA-approved treatment for infantile-onset SMA is nusinersen. Efficacy of nusinersen was demonstrated in a randomized, double-blind, sham-procedure controlled trial of 121 subject with infantile-onset SMA. In a prespecified interim analysis of subjects who had been enrolled at least 6 months, 61% of subjects in the nusinersen group met the survival endpoint (alive without permanent assisted ventilation), compared to 32% in the sham-procedure control group. In the nusinersen group, 8% were able to sit independently, and 1% were able to stand; no subjects in the control group achieved these developmental motor milestones. 	<ul style="list-style-type: none"> Data for survival and achievement of developmental motor milestones indicates that there remains an unmet medical need for treatment of pediatric patient less than 6 months of age with SMA, including infantile-onset SMA.
Clinical Benefit	<ul style="list-style-type: none"> An ongoing open-label, single-arm Phase 3 clinical trial is assessing the efficacy of onasemnogene abeparvovec-xioi in 21 subjects with infantile-onset SMA (using natural history data as an external control). Nineteen of the 21 subjects remain alive without permanent assisted ventilation; of these nineteen subjects, thirteen have reached age 14 months. Based on natural history, only approximately 25% would be expected to remain alive without permanent assisted ventilation by 14 months of age. In addition, 10 of the 21 subjects (48%) have attained the ability to sit independently for ≥ 30 seconds; based on natural history, none would be expected to achieve that developmental motor milestone. A completed open-label, single-arm, dose-escalation Phase 1 clinical trial studied onasemnogene abeparvovec-xioi in 15 subjects with infantile-onset SMA. By 24 months after infusion, 2 of the 3 subjects in the low-dose cohort were alive without permanent assisted ventilation, while all 12 subjects in the high-dose cohort were alive without permanent assisted ventilation. In the low-dose cohort, none of the subjects achieved developmental motor milestones such as sitting independently or standing; in the high-dose cohort, 9 of the 12 subjects (75%) were able to sit independently for ≥ 30 seconds, and 2 subjects (17%) were able to stand and walk without assistance. Of note, the doses used in the trial were later found to be uncertain: subjects in the high-dose cohort likely received a dose ranging from approximately 1.1×10^{14} vg/kg to 1.4×10^{14} vg/kg. 	<ul style="list-style-type: none"> Overall, substantial evidence indicates clinical benefit of onasemnogene abeparvovec-xioi, based on data from the two open-label, single-arm trials. Improvement in survival and achievement of developmental motor milestones are clinically meaningful. Comparison of results (as of the March 8, 2019 data cutoff) of the ongoing Phase 3 clinical trial to available natural history data for patients with infantile-onset SMA provides primary evidence of the effectiveness. Comparison of results for the high-dose cohort to results for the low-dose cohort in the completed Phase 1 trial supports effectiveness. Durability of the clinical benefits is unknown. It is unknown whether a dose higher than that used in the ongoing Phase 3 trial would be more effective. Both trials enrolled only subjects less than 1 year of age with infantile-onset SMA with genetic and clinical findings consistent with SMA.
Risk	<ul style="list-style-type: none"> The most substantial risk is hepatotoxicity, manifesting with elevated aminotransferases, and in one case with acute serious liver injury. Other risks include thrombocytopenia and elevated troponin-I. High anti-AAV9 antibody titers developed after onasemnogene abeparvovec-xioi infusion. 	<ul style="list-style-type: none"> High anti-AAV9 antibody titers are expected to preclude the possibility of re-administration of onasemnogene abeparvovec-xioi even if the clinical benefits diminish over time.
Risk Management	<p>The risk management plan includes:</p> <ul style="list-style-type: none"> 15-year long-term follow-up studies to collect safety and efficacy information on subjects who participated in the Phase 1 or Phase 3 clinical trials (under IND 15699). A prospective, multi-center, multinational, observational long-term registry of patients with a diagnosis of SMA who are treated with onasemnogene abeparvovec-xioi. Adequate information provided in package insert 	<ul style="list-style-type: none"> The risks can be mitigated through routine medical management, adequate PI and the postmarketing plan proposed by the applicant without requiring other regulatory measures such as REMS, PMR, or clinical PMC. <p>The data do not support the need for a risk evaluation and mitigation strategy (REMS).</p>

11.2 Risk-Benefit Summary and Assessment

The overall risk-benefit is sufficiently favorable for administration of onasemnogene abeparvovec-xioi as a single intravenous infusion of 1.1×10^{14} vg/kg to pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the *SMN1* gene.

An unmet medical need exists for treatment of pediatric patients less than 2 years of age with SMA. There is substantial evidence that onasemnogene abeparvovec-xioi provides clinical benefit with regard to survival, as well as achievement of motor milestones such as sitting independently.

Available evidence indicates that the major known risks associated with onasemnogene abeparvovec-xioi, including severe hepatotoxicity, can be prevented or mitigated by management within routine medical practice and suitable prescribing information; the PMR study proposed by the applicant should help clarify those risks.

11.3 Discussion of Regulatory Options

The regulatory options include (1) standard approval; or (2) approval with a Postmarketing Requirement to obtain additional information about risks associated with onasemnogene abeparvovec-xioi administration.

11.4 Recommendations on Regulatory Actions

Based on analyses of the clinical safety and efficacy data contained in the BLA submission, the Clinical Reviewer considers the benefit/risk profile sufficiently favorable in support of standard approval of onasemnogene abeparvovec-xioi for the treatment of pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the *SMN1* gene.

11.5 Labeling Review and Recommendations

FDA made substantial changes to each section of the Prescribing Information (PI), based on available clinical trial data, as well as FDA guidance on product labeling. The Clinical Reviewer considers the revised PI to be acceptable.

The overall content of the PI suitably conveys known information regarding safety and efficacy results demonstrated in clinical studies of onasemnogene abeparvovec-xioi, as well as additional safety information obtained from the expanded access program.

The overall content of the PI contains adequate warnings for medical practitioners, as well as for caregivers, considering onasemnogene abeparvovec-xioi for treatment of pediatric patients.

Reviewer Comment

The two trials that support approval of onasemnogene abeparvovec-xioi enrolled only patients with infantile-onset SMA (i.e., these patients had symptoms consistent with SMA before 6 months of age, mutations in the *SMN1* gene, and 2 copies of the *SMN2* gene). However, the term “infantile-onset” might be construed to imply that a patient must be symptomatic in order to benefit from onasemnogene abeparvovec-xioi. The reviewer expects that increasingly, SMA patients will be first identified through newborn screening; these newborns will be detected based on genetic mutations, but at that time may have minimal or no SMA symptoms. The reviewer expects that patients identified

early in the disease, before onset of symptoms, will benefit from onasemnogene abeparvovec-xioi. Therefore, to avoid the implication that patients must have symptom onset, the indication statement does not include the term “infantile-onset.”

11.6 Recommendations on Postmarketing Actions

Based on review of the safety data, none of the following are required: a REMS, a safety PMR study, or a safety PMC study. The postmarketing risk mitigation plans proposed by the applicant are acceptable, including product labeling, a registry study as well as ongoing and planned long-term follow-up studies for subjects treated in the completed and ongoing clinical trials under IND 15699.

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