

Summary Basis for Regulatory Action

Date: May 24, 2019

From: Andrew Byrnes, PhD

BLA STN#: 125694/0

Applicant Name: AveXis, Inc

Date of Submission: October 1, 2018

Goal Date: May 31, 2019

Proper Name: onasemnogene abeparvovec-xioi

Proprietary Name: ZOLGENSMA

Indication: 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

Recommended Action: The Review Committee recommends approval.

Office of Tissues and Advanced Therapies Signatory Authority:

Wilson W. Bryan, MD, Director

- I concur with the summary review.
- I concur with the summary review and include a separate review to add further analysis.
- I do not concur with the summary review and include a separate review.

Office of Compliance and Biologics Quality Signatory Authority:

Mary A. Malarkey, Director

- I concur with the summary review.
- I concur with the summary review and include a separate review to add further analysis.
- I do not concur with the summary review and include a separate review.

The table below indicates the material reviewed when developing the SBRA

Document title	Reviewer name
<p>CMC Reviews <i>CMC (OTAT/DCGT and OCBQ/DBSQC)</i></p> <p><i>Facilities review (OCBQ/DMPQ)</i> <i>Establishment Inspection Reports (OCBQ/DMPQ, OTAT/DCGT and Team Biologics)</i></p> <p><i>CMC Consult Review (CDER)</i></p>	<p>Andrew Byrnes, PhD (OTAT/DCGT) Angela Whatley, PhD (OTAT/DCGT) Hyesuk Kong, PhD (OCBQ/DBSQC) Varsha Garnepudi (OCBQ/DBSQC) Wei Wang, PhD (OCBQ/DMPQ) Wei Wang, PhD (OCBQ/DMPQ) Deborah Trout, (OCBQ/DMPQ) Andrew Byrnes, PhD (OTAT/DCGT) Angela Whatley, PhD (OTAT/DCGT) Burnell Henry (OBPO/Team Biologics) Sharadrao Patil, PhD (CDER/OPQ/OTR/DPA) Kang Chen, PhD (CDER/OPQ/OTR/DPA)</p>
<p>Clinical Reviews <i>Clinical (OTAT/DCEPT)</i> <i>Clinical Consult Review (CDER)</i></p> <p><i>Clinical Branch Chief Review</i> <i>Postmarketing safety epidemiological review (OBE/DE)</i> <i>BIMO</i></p>	<p>Mike Singer, MD, PhD (OTAT/DCEPT) Rainer Paine, MD, PhD (CDER/ODEI/DNP) Teresa Buracchio, MD (CDER/ODEI/DNP) Lei Xu, MD, PhD (OTAT/DCEPT) Deborah Thompson, MD, MSPH (OBE/DE)</p> <p>Erin McDowell (OCBQ/BMB)</p>
<p>Statistical Review <i>Clinical data (OBE/DB)</i></p>	<p>Xue Lin, PhD (OBE/DB)</p>
<p>Pharmacology/Toxicology Review <i>Toxicology (OTAT/DCEPT)</i></p>	<p>Feorillo Galivo, MD, PhD (OTAT/DCEPT)</p>
<p>Labeling Review <i>APLB (OCBQ/APLB)</i></p>	<p>Sonny Saini (OCBQ/APLB)</p>
<p>Other Reviews <i>Finding of No Significant Impact (OTAT)</i></p>	<p>Wilson W. Bryan, MD (OTAT)</p>

1. INTRODUCTION

AveXis, Inc. submitted a Biologics License Application (BLA), STN 125694, for licensure of onasemnogene abeparvovec-xioi. Onasemnogene abeparvovec-xioi is an original biologic product, with the proprietary name of ZOLGENSMA. ZOLGENSMA is an adeno-associated virus (AAV) vector-based gene therapy indicated for the 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.

Mutations in the *SMN1* gene lead to survival motor neuron (SMN) protein deficiency that causes motor neuron loss in the brainstem and spinal cord, leading to weakness and muscle atrophy. ZOLGENSMA is designed to deliver a normal copy of the gene encoding the SMN protein in patients with SMA.

This document summarizes the basis for regular approval of ZOLGENSMA. An ongoing Phase 3 clinical trial and a completed Phase 1 clinical trial provide the primary evidence of safety and effectiveness for the treatment of pediatric patients less than 2 years of age with SMA. Data from additional ongoing trials contribute further to the safety database. The recommendation for approval is based on improvement in survival and achievement of developmental motor milestones such as sitting without support, demonstrated in the ongoing Phase 3 clinical trial. The more serious risks of ZOLGENSMA include acute liver injury and elevation of liver enzymes (e.g., alanine aminotransferase [ALT], aspartate aminotransferase [AST]), and decreased platelet counts.

The review team recommends regular approval of this BLA with the Chemistry, Manufacturing, and Control (CMC) Postmarketing Commitments (PMCs).

2. BACKGROUND

Disease Background

Spinal muscular atrophy (SMA) with bi-allelic mutations in the *SMN1* gene is a serious autosomal recessive neurodegenerative disorder. Infantile SMA is the most severe and common form of SMA, with an estimated incidence of 1 in 10,000 live births and prevalence of about 1–2 per 100,000. Infants with SMA have problems with motor function, such as holding their head up, sucking and breathing that may be present at birth or by the age of 6 months. Most patients with infantile-onset SMA do not survive past early childhood due to respiratory failure. It is the most common monogenic cause of infant mortality.

Available Therapies

Nusinersen is the only FDA-approved treatment for SMA. Nusinersen has marketing approval for use in children and adults with SMA. Nusinersen is an antisense oligonucleotide, which inhibits splicing of exon 7 from *SMN2* mRNA transcripts, and thus increases the SMN protein level.

Regulatory History

Key regulatory milestones in the development of ZOLGENSMA are summarized in Table 1.

Table 1. Regulatory Milestones

Date	Milestones
12/20/2011	PreIND meeting
8/8/2013	IND submission
9/27/2013	Fast Track designation granted
9/30/2014	Orphan Drug designation granted
7/15/2016	Breakthrough Therapy designation granted
6/14/2018	Pre-BLA meeting
8/21/2018	Rare Pediatric Disease designation granted
10/1/2018	BLA 125694 submission
11/28/2018	BLA filed, priority review
2/6/2019	120-day safety and efficacy update received
4/30/2019	Additional efficacy and safety update for the ongoing Phase 3 trial received
6/1/2019	PDUFA* Action Due Date

*PDUFA=Prescription Drug User Fee Act

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

a) Product Quality

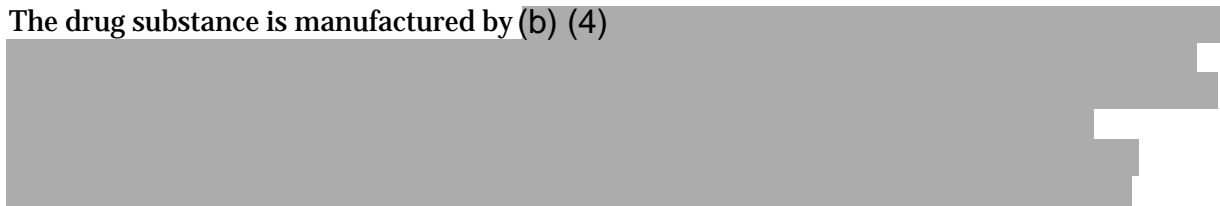
The CMC review team concludes that the manufacturing process for ZOLGENSMA is capable of yielding a product with consistent quality characteristics, and the CMC review team recommends approval.

ZOLGENSMA is a suspension of an adeno-associated viral (AAV) vector-based gene therapy for intravenous infusion. The active ingredient is a recombinant self-complementary vector, where the double-stranded DNA vector genome is enclosed in a capsid that consists of (b) (4) 9 AAV capsid proteins. The vector DNA (b) (4) virus. The vector DNA contains a transgene encoding the human survival motor neuron (SMN) protein, under the control of a cytomegalovirus enhancer and a chicken- β -actin hybrid promoter.

The drug product has a nominal concentration of 2.0×10^{13} vector genomes (vg)/mL. Each 10 mL vial of drug product contains an extractable volume of not less than either 5.5 mL or 8.3 mL and the excipients 20 mM tris (pH 8.0), 1 mM magnesium chloride ($MgCl_2$), 200 mM sodium chloride (NaCl) and 0.005% poloxamer 188. The drug product is sterile and contains no preservative. The secondary packaging is a carton that contains 2-9 vials (depending on the weight of the patient) along with one alcohol wipe per vial. The carton is shipped frozen, and after receipt the carton should be stored in a refrigerator for no more than 14 days.

Manufacturing and quality

The drug substance is manufactured by (b) (4)



(b) (4)

(b) (4)

(b) (4)

(b) (4) drug product are tested for general properties, including appearance, pH, osmolality and the molecular weights of AAV capsid proteins. The strength of (b) (4) drug product is measured by (b) (4), and strength is expressed in units of vg/mL.

The drug product is manufactured by (b) (4) performing a sterile filtration. The drug product manufacturing process does not introduce any process-related impurities, and also does not include any manufacturing steps that further remove impurities. After sterile filtration, drug product is filled aseptically into vials and frozen.

Drug product sampled from final containers is tested for microbial contaminants, identity, purity, strength and potency. Self-complementary AAV vectors such as ZOLGENSMA have (b) (4)

. The drug substance manufacturing process has been validated (b) (4). The drug product specifications control the amounts of the various (b) (4) using an assay that quantifies the (b) (4) of the (b) (4).

The activity and potency of drug product lots are controlled using several assays, including a quantitative assay that measures the ability of the drug product to produce SMN protein in cells; a quantitative assay that measures (b) (4) and a semi-quantitative assay that measures the ability of intravenously-injected drug product to prolong mouse survival in a transgenic mouse model of spinal muscular atrophy.

Testing specifications

The analytical methods and their validations or qualifications reviewed for the ZOLGENSMA drug substance and drug product were found to be adequate for their intended use.

Stability

The drug product is stable for 14 days at refrigerated temperature and 8 hours in syringes at room temperature. The drug product is not light-sensitive.

At the time of BLA submission, drug product stability had not been followed for a sufficient length of time to support the stability of drug product when stored at the long-term frozen storage temperature of $\leq -60^{\circ}\text{C}$. Late in the review cycle, the applicant submitted real-time stability data from (b) (4) lots of drug product that had been evaluated for up to 1 year at the long-term frozen storage temperature. These data demonstrate time-dependent declines in the strength, activity and potency of ZOLGENSMA. When stored frozen at the long-term storage temperature, the strength (vector genome concentration) declines at a rate of approximately (b) (4) over the first year, with significant uncertainty about the rate of decline in subsequent years. As a result, the shelf life of drug product lots stored at the long-term frozen temperature will be limited to 12 months.

The completed Phase 1 clinical trial (NCT02122952) was conducted using a single lot of ZOLGENSMA drug product, administered to two cohorts of subjects. The doses administered in this Phase 1 trial were originally reported to be 6.7×10^{13} vg/kg and 2.0×10^{14} vg/kg, but the assay that was originally used to determine the concentration of this initial drug product lot was inaccurate and imprecise. Forty-four months after manufacture of this initial drug product lot, the vector genome concentration was revised based on 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 ZOLGENSMA is unstable during long-term frozen storage. Because of uncertainty about the rate of decay of the initial drug product lot, the Agency is unable to 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 (b) (4), and the doses administered to the high-dose cohort may have ranged from approximately 1.1×10^{14} to (b) (4).

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

b) CBER Lot Release

The lot release protocol template for ZOLGENSMA was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

Container/ Closure

The container closure system consists of a clear plastic vial, stopper, and an aluminum seal with plastic button cap. The Drug Product is filled into clear 10 mL (b) (4) vials. The (b) (4) cyclic olefin polymer vial is sterile and ready-to-use supplied by (b) (4). The 20 mm (b) (4) chlorobutyl elastomeric stopper is sterile, ready-to-use, and (b) (4) supplied by (b) (4). The

aluminum seal with a lacquered green plastic flip-off top is sterile and ready-to-use supplied by (b) (4). Container-closure integrity was tested by (b) (4) at the AveXis (b) (4) manufacturing facility and all acceptance criteria were met.

c) Facilities review/inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of ZOLGENSMA are listed in the table below. The activities performed, and inspectional histories are noted in the table.

Manufacturing Facilities Table for ZOLGENSMA

Name/Address (Activities)	FEI Number	Inspection/Waiver	Justification/Results
AveXis, Inc. (b) (4) <ul style="list-style-type: none"> • <i>Drug Substance Manufacture,</i> • <i>Drug Product Manufacture,</i> • <i>Drug Product Release Testing,</i> • <i>Primary and Secondary Labeling and Packaging</i> 	(b) (4)	Pre-license Inspection (PLI)	CBER (b) (4) VAI
AveXis, Inc. (b) (4) <ul style="list-style-type: none"> • <i>Drug Product Release Testing</i> 	(b) (4)	PLI	Team Biologics (b) (4) NAI
(b) (4) <ul style="list-style-type: none"> • <i>Drug Product Release Testing</i> 	(b) (4)	Waived	Team Biologics (b) (4) VAI
(b) (4) <ul style="list-style-type: none"> • <i>Drug Product Release Testing</i> 	(b) (4)	Waived	ORA and CDER (b) (4) VAI
(b) (4) <ul style="list-style-type: none"> • <i>Drug Product Release Testing</i> 	(b) (4)	Waived	ORA (b) (4) VAI
(b) (4) <ul style="list-style-type: none"> • <i>Drug Product Release Testing</i> 	(b) (4)	Waived	ORA (b) (4) VAI

CBER conducted a pre-license inspection (PLI) at the (b) (4) manufacturing facility in (b) (4) and a FDA Form 483 was issued at the end of the inspection. All inspectional issues were resolved, and the inspection was classified as Voluntary Action Indicated (VAI).

Team Biologics performed a PLI of the AveXis, Inc. (b) (4) Testing Site in (b) (4). No Form 483 was issued, and the inspection was classified as No Action Indicated (NAI).

Team Biologics performed a surveillance inspection of the (b) (4) facility in (b) (4). All 483 issues were resolved, and the inspection was classified as VAI.

The Office of Regulatory Affairs (ORA) and CDER performed a surveillance inspection of the (b) (4). All 483 issues were resolved, and the inspection was classified as VAI.

ORA performed a surveillance inspection of the (b) (4) facility in (b) (4). All 483 issues were resolved, and the inspection was classified as VAI.

ORA performed a surveillance inspection of the (b) (4) facility in (b) (4). All 483 issues were resolved, and the inspection was classified as VAI.

d) Environmental Assessment

The applicant submitted an environmental assessment (EA) pursuant to 21 CFR part 25. The Agency determined that approval of ZOLGENSMA will not result in any significant environmental impact. A Finding of No Significant Impact (FONSI) memorandum has been prepared.

e) Product Comparability

After the Phase 1 clinical trial using the initial clinical lot, the manufacturing process was changed considerably. The current manufacturing process produces drug product with critical quality attributes that are comparable to those of the initial clinical lot. Although the concentration of drug product declines over time during storage, the ratio of potency to vector genomes is comparable when lots from the current manufacturing process are 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).

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

In vivo pharmacology studies of ZOLGENSMA were conducted in SMNdelta7 mice, a murine model of SMA. A single intravenous administration of ZOLGENSMA 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, neuromuscular transmission, body weight gain, and cardiac function. Improvement in survival and body weight gain were highest in mice dosed at postnatal day 1 or 2.

In single-dose toxicology studies conducted in neonatal FVB mice, intravenous administration of ZOLGENSMA 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, there were dose-dependent increases in the incidence and severity of adverse cardiac findings which included minimal to moderate atrial thrombosis, slight to marked atrial dilation, and minimal to slight 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 weights and macroscopic changes which included enlarged heart, abnormal shape, and/or large atrium. 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 was observed in the lung. ZOLGENSMA-related

mortality was observed at dose levels of 2.4×10^{14} vg/kg and higher, associated with the cardiac and liver toxicities observed. 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 and SMN transgene expression profile of ZOLGENSMA were evaluated in neonatal FVB mice through 12 weeks. Following intravenous administration of 1.5×10^{14} vg/kg ZOLGENSMA, 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 tissue expression 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.

Studies to evaluate the safety pharmacology, developmental and reproductive toxicity, genotoxicity, carcinogenicity/tumorigenicity were not conducted for ZOLGENSMA. These studies were not warranted based on the product characteristics, results from the toxicology studies, and target patient population.

5. CLINICAL PHARMACOLOGY

Vector shedding after infusion with ZOLGENSMA was investigated at multiple time points during the completed clinical study. 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 patients were used for ZOLGENSMA vector DNA shedding analysis through the Month 18 visit.

Vector DNA was shed in saliva, urine and stool after infusion of ZOLGENSMA, 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, the vector DNA concentration was very low on Day 1 after infusion and declined to undetectable levels within 1 to 2 weeks. In stool, the vector DNA concentration was much higher than saliva or urine for 1 to 2 weeks after infusion and declined to undetectable levels by 1 to 2 months after infusion.

Biodistribution was evaluated in two patients who died 5.7 months and 1.7 months after infusion of ZOLGENSMA at the dose of 1.1×10^{14} vg/kg. Both cases showed that the highest levels of vector DNA were found in the liver, followed by the spleen, inguinal lymph node and heart. Vector DNA was also detected in the muscles, peripheral nerves, kidney, pancreas, lung, spinal cord, brain, and thymus. Immunostaining for SMN protein showed generalized SMN expression in spinal motor neurons, neuronal and glial cells of the brain, skeletal muscles, heart, liver, kidney, lung, pancreas, spleen, thymus, stomach, large intestines, small intestines, and inguinal lymph nodes.

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

a) Clinical Program

The ongoing Phase 3 trial and the completed Phase 1 trial form the basis of the review team's recommendation for regular approval of ZOLGENSMA for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the

SMN1 gene. The Phase 3 trial provides the primary evidence of effectiveness, and results of the Phase 1 trial support effectiveness. The Phase 1 and Phase 3 trials, other ongoing trials, as well as patients treated through the expanded access program, contribute to the safety database.

Study Description

The completed Phase 1 trial was an open-label, single-arm, ascending-dose study in a total of 15 infants with SMA. It was designed to evaluate safety and preliminary efficacy. Two doses were compared in the trial. Three patients were enrolled in the low-dose cohort and 12 patients were enrolled in the high-dose cohort. There was a clear dose-response relationship with respect to efficacy. However, the precise dosages of ZOLGENSMA administered to patients in this trial are not clear. Patients in the low-dose cohort may have received from 4.3×10^{13} to 4.6×10^{13} vg/kg, and patients in the high-dose cohort may have received from 1.1×10^{14} to 1.4×10^{14} vg/kg, with considerable uncertainty in the administered dose (please see Section 3 CMC of this document for more details).

The ongoing Phase 3 trial is an open-label, single-arm study using available natural history data as control. This study was designed to evaluate the efficacy and safety of ZOLGENSMA in patients with infantile-onset SMA. The trial enrolled 21 patients with infantile-onset SMA. All patients received the 1.1×10^{14} vg/kg dose.

All patients enrolled in these two trials experienced onset of clinical symptoms consistent with SMA before 6 months of age. All patients had genetically confirmed bi-allelic *SMN1* deletions and 2 copies of *SMN2*, and absence of the c.859G>C modification in exon 7 of *SMN2* (which predicts a milder phenotype). All patients had baseline anti-AAV9 antibody titers of $\leq 1:50$, measured by enzyme-linked immunosorbent assay (ELISA). In both trials, ZOLGENSMA was delivered as a single dose via intravenous infusion.

Patients treated in both trials received a course of oral corticosteroid to suppress potential immune reactions to ZOLGENSMA.

Efficacy Endpoints

The two primary efficacy endpoints in the ongoing Phase 3 trial were:

- i. The proportion of patients achieving the milestone of sitting without support for at least 30 seconds at 18 months of age.
- ii. Survival at 14 months of age.

Survival was defined by avoidance of the combined endpoint of either (a) death or (b) permanent ventilation, which was 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.

An additional efficacy endpoint was the proportion of patients who are independent of ventilatory support at 18 months of age.

Clinical Efficacy Findings

Phase 3 Clinical Trial (ongoing)

The ongoing trial enrolled 21 infants with SMA from 16 sites in the United States. Before treatment with ZOLGENSMA, none of the 21 patients required non-invasive ventilatory (NIV) support and all patients were able to exclusively feed orally (i.e., no need for non-oral nutrition). The mean age of patients at the time of treatment was 3.9 months (range 0.5 to 5.9 months).

As of the March 2019 data cutoff, 19 patients were alive without the need for permanent ventilation (i.e., event-free survival) and continued in the trial; one patient withdrew from the study at age 11.9 months; and one patient died at age 7.8 months due to disease progression. The 19 surviving patients who were continuing in the trial ranged in age from 9.4 to 18.5 months. These patients were 7.9 to 15.4 months post-ZOLGENSMA infusion. The results for survival and achievement of the milestone of sitting without support for ≥ 30 seconds are shown in Table 2. Comparison of the results of the ongoing clinical trial to available natural history data of infants with SMA provides primary evidence of the effectiveness of ZOLGENSMA. In addition, 16 of the 19 patients had not required daily NIV use.

Table 2. Survival and Motor Milestone Achievement in the Ongoing Phase 3 Trial

Endpoints	Phase 3 trial (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 patients had reached 14 months of age by the data cutoff.

Phase 1 Clinical Trial (complete)

The completed clinical trial enrolled 15 infants with SMA from one site in the United States. Before treatment with ZOLGENSMA, 10 of the 12 patients in the high-dose cohort were free of NIV at baseline, and seven of the 12 patients were able to exclusively feed orally. The mean age of patients at the time of treatment was 6.3 months (range 5.9 to 7.2 months) in the low-dose cohort and 3.4 months (range 0.9 to 7.9 months) in the high-dose cohort. The mean CHOP-INTEND score at baseline was 28.2 (range 12 to 50).

The results for survival and motor milestone achievements at 24 months following ZOLGENSMA infusion are shown in Table 3. Comparison of the results of the high-dose cohort to the results of the low-dose cohort supports the effectiveness of ZOLGENSMA. In addition, seven (of 10 at baseline) patients in the high-dose cohort remained free of NIV use.

Table 3. Survival and Motor Milestone Achievements in the Completed Phase 1 Trial

Endpoints	Low-dose Cohort (N=3) n (%)	High-dose Cohort (N=12) n (%)
Survival	2 (67%)	12 (100%)
Sitting without support for ≥ 30 seconds	0	9 (75%)
Standing	0	2 (16.7%)
Walking	0	2 (16.7%)

Efficacy Conclusion

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. This conclusion is based on improvement in survival and achievement of developmental motor milestones such as sitting without support for ≥30 seconds.

Bioresearch Monitoring

Bioresearch Monitoring (BIMO) inspections were conducted at four clinical investigator sites that participated in the conduct of Studies AVXS-101-CL-101, AVXS-101-CL-303, or AVXS-101-LT-001. The inspections did not reveal any issues that impact the integrity of the data submitted in the BLA.

b) Pediatrics

Pediatric Research Equity Act (PREA) is not applicable to ZOLGENSMA for the treatment of spinal muscular atrophy (SMA) because ZOLGENSMA was granted orphan drug designation for the indication.

All the patients enrolled in Phase 1 and Phase 3 studies were pediatric patients (age 2 weeks to 8 months).

c) Other Special Populations

None.

7. SAFETY

The safety population included a total of 44 patients with SMA who received intravenous infusion of ZOLGENSMA in four clinical trials conducted in the United States, including the completed Phase 1 trial, two ongoing trials, and an ongoing observational long-term follow-up study. Forty-one patients received ZOLGENSMA at or above the dose of 1.1×10^{14} vg/kg, and 3 patients received a lower dose. The patient population ranged in age from approximately 2 weeks to 8 months at the time of infusion.

There was one death in the US clinical studies. The cause of death was respiratory failure secondary to disease progression. In addition, one patient in an ongoing non-US clinical trial

initially presented with respiratory insufficiency 12 days after ZOLGENSMA infusion. The patient then had episodes of serious hypotension, followed by development of seizures and leukoencephalopathy (brain white matter defects) approximately 30 days after ZOLGENSMA infusion. The patient died after withdrawal of life support 52 days after ZOLGENSMA infusion. It is unknown whether the events of seizure, leukodystrophy and death are related to ZOLGENSMA.

There were three serious adverse reactions, including acute serious liver injury in one patient, and elevation of aminotransferases to up to approximately $40 \times$ ULN in two other patients who were otherwise asymptomatic.

The most frequent adverse reactions (incidence $\geq 5\%$) observed in the 4 studies included elevated aminotransferases and vomiting.

Transient decreases in platelet counts, some of which met the criteria for thrombocytopenia, were observed at different time points after ZOLGENSMA infusion. Transient increases in cardiac troponin-I levels were observed following ZOLGENSMA infusion in clinical trials. The clinical importance of these findings is not known as there were no clinical cardiac sequelae.

In the ZOLGENSMA clinical trials, patients were required to have baseline anti-AAV9 antibody titers of $\leq 1:50$, measured using an enzyme-linked immunosorbent assay (ELISA). Evidence of prior exposure to AAV9 was uncommon. The safety and efficacy of ZOLGENSMA in patients with anti-AAV9 antibody titers above 1:50 have not been evaluated. Following ZOLGENSMA infusion, increases from baseline in anti-AAV9 antibody titers occurred in all patients. 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 resulting from the initial ZOLGENSMA infusion are expected to preclude the possibility of re-administration of AAV9 vector-based gene therapy.

In summary, the major serious risks associated with ZOLGENSMA infusion include acute serious liver injury and substantial increases in aminotransferases. These risks can be mitigated by routine medical management, appropriate labeling of Prescribing Information (PI), and the postmarketing plan proposed by the applicant.

Postmarketing Pharmacovigilance

The applicant will conduct long-term follow-up studies to collect safety and efficacy information on patients who participated in Phase 1 or 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, multinational, 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 safety data do not indicate the need for a Risk Evaluation and Mitigation Strategy (REMS), a safety postmarketing requirement (PMR) study, or a safety postmarketing commitment (PMC) study.

8. ADVISORY COMMITTEE MEETING

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.

9. OTHER RELEVANT REGULATORY ISSUES

Not applicable

10. LABELING

The proposed proprietary name, ZOLGENSMA, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on October 22, 2018, and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on November 6, 2018.

The APLB found the prescribing information (PI) and carton/container labels to be acceptable from a promotional and comprehension perspective.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

Based on the treatment effect demonstrated in the ongoing Phase 3 trial and supported by the completed Phase 1 study, the review team recommends regular approval for ZOLGENSMA.

b) Risk/ Benefit Assessment

Efficacy of ZOLGENSMA is based on improvement in survival, and achievement of developmental motor milestone such as sitting without support for ≥ 30 seconds.

The major risks associated with intravenous infusion of ZOLGENSMA include acute serious liver injury and substantial increases in aminotransferases, which might have serious consequences, especially if untreated. However, these risks can be mitigated by management within routine medical practice, 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 two years of age with SMA with bi-allelic mutations in the *SMN1* gene. The review team recommends regular approval of ZOLGENSMA with a recommended single dose of 1.1×10^{14} vector genomes (vg)/kg of body weight for each patient, administered by intravenous infusion.

c) Recommendation for Postmarketing Activities

The review committee agrees with the pharmacovigilance activities in the applicant's proposed pharmacovigilance plan. The pharmacovigilance plan includes long-term follow-up studies of the clinical trial subjects, a voluntary patient registry, and routine pharmacovigilance for adverse event reporting.

The applicant agreed to the following Postmarketing Commitments (PMCs):

1. AveXis agrees to develop and qualify a suitable method for quantifying (b) (4) providing the method qualification report and providing an additional process validation report for (b) (4)

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2. AveXis agrees to validate the robustness of the (b) (4) assay per protocol REC-2566 and will provide the validation report.

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3. AveXis agrees to update the (b) (4) assay to include the assay validity criterion for the reference standard and provide the supplemental validation report for robustness.

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4. AveXis agrees to revise the Bioburden Determination operating procedure (SOP-085) to be compliant with (b) (4), including (b) (4) on (b) (4). AveXis agrees to implement the revised SOP-085 for all bioburden tests and to provide the revised SOP-085.

Final Report Submission: July 1, 2019