

**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Division of Epidemiology (DE)**

PHARMACOVIGILANCE PLAN REVIEW MEMORANDUM

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Subject: Review of Pharmacovigilance Plan

Sponsor: AveXis, Inc.

Product: ZOLGENSMA[®] (onasemnogene abeparvovec-xioi)

BLA Number: STN 125694/0

Proposed Indication: ZOLGENSMA (onasemnogene abeparvovec-xioi) is an adeno-associated virus 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.

Submission Date: October 1, 2018

Action Due Date: June 1, 2019

1 Objective and Scope

This memo reviews the adequacy of the pharmacovigilance plan (PVP) proposed by the sponsor for the postmarketing safety surveillance of Zolgensma® (onasemnogene abeparvovec-xioi). The scope is safety concerns related to intravenous (IV) administration of Zolgensma.

2 Product Information

2.1 Product Description

Throughout this memo, italicized text is quoted verbatim from the source document.

ZOLGENSMA (onasemnogene abeparvovec-xioi; also referred to as AVXS-101 during clinical development) is a solution of an adeno-associated viral vector-based gene replacement therapy for intravenous infusion. It is a recombinant self-complementary AAV9 containing the cDNA of the human survival motor neuron (SMN) gene and under the control of the cytomegalovirus enhancer/chicken- β -actin-hybrid promoter. ZOLGENSMA expresses the human SMN protein.*

The sponsor proposes to supply Zolgensma as a kit containing two to nine vials with a combination of two vial sizes (5.5 mL or 8.3 mL). *Each vial of ZOLGENSMA has a nominal concentration of 2.0×10^{13} vg/mL and 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) containing 0.005% poloxamer 188; sterile filtered prior to filling into vials. The product contains no preservative.*

*Note: Zolgensma is used interchangeably with AVXS-101 throughout this memorandum.

2.2 Proposed Product Indication and Dosing Regimen

Zolgensma (onasemnogene abeparvovec-xioi) is an adeno-associated virus 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. Zolgensma is administered as a single-dose IV infusion with a recommended dose of 1.1×10^{14} ($1.1E14$) vector genomes (vg) per kilogram (kg) of body weight.

2.3 Pertinent Regulatory History

Pertinent regulatory history is shown in Table 1.

Table 1: Pertinent Regulatory History for Zolgensma

Date	Regulatory action
August 6, 2013	Investigational New Drug (IND) submission with request to conduct Phase 1 study in subjects with SMA Type 1; IND allowed to proceed by FDA
September 27, 2013	Fast Track Status approved
September 30, 2014	Orphan Drug Designation approved
July 15, 2016	Breakthrough Therapy Designation approved
August 22, 2018	Rare Pediatric Disease Designation approved

3 Materials Reviewed

Materials reviewed in support of this assessment include:

- Benefit-Risk Summary Assessment (Section 1.11.3)
- Draft Labeling Text (Section 1.14)
- Draft Labeling Text (Section 1.14.1.3, Amendment 125694/0.30)
- Risk Management Plan (Section 1.16)
- Introduction (Section 2.2)
- Clinical Overview (Section 2.5)
- Summary of Clinical Safety (Section 2.7.4)
- Clinical Study Report AVXS-101-CL-101 (Section 5.3.5.1)
- Integrated Summary of Safety (Section 5.3.5.3)
- Response to Information Request received November 30, 2018 (Amendment 125694/0.15)
- Response to Information Request received December 19, 2018 (Amendment 125694/0.17)
- Response to Information Request received February 26, 2019 (Amendment 125694/0.39)
- Response to Information Request received February 26, 2019 (Amendment 125694/0.40)
- Response to Information Request received April 24, 2019 (Amendment 125694/0.68)
- Response to Information Request received May 8, 2019 (Amendment 125694/0.76)
- Investigational New Drug (IND 15699) Protocol AVXS-101-LT-001, Version 4.0, (Amendment 015699/0.108)
- Investigational New Drug (IND 15699) Protocol AVXS-101-LT-002, Version 1.0 (Amendment 015699/0.108)
- 120-Day Safety Update for Zolgensma (Amendment 125694/0.31)
- Individual Patient Expanded Access IND Safety Reports (IND 018725)
- AVXS-101-CL-303 Efficacy and Safety Update (March 8, 2019 data lockpoint) received April 30, 2019 (email communication)

4 Summary of Prior Marketed Experience

This product does not have a history of regulatory approval outside the US.

5 Summary of Safety Database

The clinical safety database for Zolgensma included data from a total of four open-label studies conducted in the United States, including one completed clinical trial, ongoing clinical trials:

- Completed phase 1 trial: AVXS-101-CL-101
- Ongoing trials: AVXS-101-CL-303, AVXS-101-CL-304, AVXS-101-CL-302

The sponsor's data lockpoint date for the integrated summary of safety (ISS) was September 27, 2018.

5.1 Summary of Completed Phase 1 Study AVXS-101-CL-101

AVXS-101-CL-101, a Phase 1 gene transfer clinical trial, is the first clinical gene therapy trial for subjects with SMA Type 1 and the only completed study at the time of the Biologics Licensing Application (BLA) submission. The primary objective of the study was safety and the secondary objectives were efficacy with the primary endpoints of respiratory assistance or death. Safety outcomes

included serious adverse events (SAEs), treatment emergent adverse events (TEAEs), and adverse events (AEs) of special interest (i.e., elevated liver enzymes). The study was conducted from May 13, 2014 to December 14, 2017.

Sixteen patients were screened for enrollment; one patient failed screening due to a baseline AAV9 antibody titer >1:50 (exclusion criterion). Fifteen subjects with symptomatic SMA Type 1 were enrolled and followed for two years after receiving a single IV dose of AVXS-101. Enrollees had bi-allelic SMN1 gene mutations, two copies of SMN2, and lack of c.859G>C modification in exon 7 (due to predicted mild phenotype). The study included two sequential dosing cohorts (low dose and high dose). Due to decreases in the concentration of AVXS-101 over time and a retrospective change in the method of measuring concentration, the precise dosages of AVXS-101 received by subjects in CL-101 were unclear. Subjects in the low-dose cohort received one-third the dosage of the high dose cohort; the retrospectively estimated dosage range for subjects in the high-dose cohort was approximately 1.1E14 to 1.4E14 vg/kg IV, with uncertainty. Three subjects were enrolled in the low dose cohort and 12 subjects were enrolled in the high dose cohort. No subjects had an interruption of the AVXS-101 infusion and there were no deaths or premature study discontinuations.

The median age of the subjects was 4.1 months (range=0.9-7.9 months), 60.0% were female, 93.3% were White, and 86.7% were non-Hispanic. Fifteen subjects (100%) experienced a total of 237 TEAEs. The most frequently reported TEAEs were upper respiratory tract infection (n=11, 73.3%), pyrexia (n=8, 53.3%), vomiting (n=8, 53.3%), constipation (n=7, 46.7%), pneumonia (n=7, 46.7%), gastroesophageal reflux disease (n=6, 40.0%), and nasal congestion (n=6, 40.0%). Thirteen subjects (86.7%) experienced a total of 55 TEAEs with a severity of grade 3 or higher (13 subjects had grade 3 [severe] TEAEs and two of these subjects also had grade 4 [life-threatening] TEAEs). Both subjects with grade 4 TEAEs had elevated liver transaminases (Table 2). The most frequently reported grade 3 or 4 TEAEs among subjects were pneumonia (n=7, 46.7%), atelectasis (n=3, 20.0%), parainfluenzae virus infection (n=3, 20.0%), pneumonia respiratory syncytial virus infection (n=3, 20.0%), and respiratory failure (n=3, 20.0%).

Four subjects (26.7%) had a total of five TEAEs considered definitely-related to AVXS-101, all were TEAEs of elevated liver transaminases (AEs of special interest), and all resolved (Table 2). The maximum aspartate aminotransferase (AST) values were 9 times (×) the upper limit of normal (ULN) (median; range=3-37× ULN) and the maximum alanine aminotransferase (ALT) values were 18× ULN (median; range=2-35× ULN). None met criteria for Hy's Law.ⁱ Three subjects ((b) (6)) were premedicated with prednisolone (per the study protocol) and developed elevated transaminases; two of these subjects ((b) (6)) had their prednisolone doses increased and then tapered as transaminase values decreased. Subject ((b) (6)) had mild to moderate increased transaminase values (ALT=2× ULN and AST=3× ULN) that resolved without an increase in prednisolone dosing. One subject ((b) (6)) was enrolled before the protocol stipulated prophylactic administration of prednisolone prior to AVXS-101 infusion; this subject received prednisolone for treatment of elevated transaminases with resolution on Day 90.

Table 2: Treatment Emergent Adverse Events (TEAE) Definitely-Related to AVXS-101*

Patient Number	Cohort	MedDRA Preferred Term	Serious (Yes/No)	AE Grade ^a	Onset/End (Study Day)
(b) (6)	Low dose	Transaminases increased	Yes	4	27/90
	High dose	Transaminases increased	No	2	27/127
	High dose	Aspartate aminotransferase increased	No	1	9/27

ⁱ Hy's Law identifies a drug likely to cause severe drug-induced hepatocellular injury per the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation*.

		Transaminases increased	No	2	64/279
(b) (6)	High dose	Transaminases increased	Yes	4	34/111

*Taken from AVXS-101-CL-101 Clinical Study Report Table 40.

^a Based on Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

^b Subject enrolled before the protocol amendment that stipulated prophylactic administration of prednisolone prior to gene therapy.

5.2 Integrated Summary of Safety (ISS)

The integrated summary of safety (ISS) includes information from a total of four clinical trials in which subjects received IV AVXS-101: AVXS-101-CL-101 [section 5.1], the completed clinical trial, and three ongoing clinical trials (AVXS-101-CL-303, AVXS-101-CL-304, and AVXS-101-CL-302). Forty-six subjects received the proposed therapeutic dose of 1.1E14 vg/kg IV or higher of AVXS-101. A description of these studies is listed below. The sponsor's data lockpoint date for the ISS was September 27, 2018.

AVXS-101-CL-303 is a Phase 3, open-label, single-arm, single IV dose gene therapy clinical trial for subjects with SMA Type 1 with one or two SMN2 copies in which subjects are administered AVXS-101 (1.1E14 vg/kg IV dose). All 22 subjects who received AVXS-101 were confirmed to have bi-allelic SMN1 deletions and only two copies of the SMN2 gene without c.859G>C modification in exon 7; all subjects were symptomatic for SMA. Subjects were followed for up to 10.9 months post-infusion with a mean (SD) follow-up of 5.4 (1.9) months.

AVXS-101-CL-304 is a Phase 3, open-label, single-arm, single IV dose clinical trial for subjects with pre-symptomatic SMA Types 1, 2, or 3 in which subjects are administered AVXS-101 (1.1E14 vg/kg IV dose). Study CL-304 was originally designed to include subjects with bi-allelic deletion of SMN1 and two, three, or four copies of SMN2 who were ≤6 weeks of age at the time of treatment, and subjects with SMN1 point mutations or SMN2 gene modifier mutation (C.859G>C). The protocol was modified in October 2018 after the results from a Good Laboratory Practice (GLP) compliant three-month mouse toxicology study became available showing cardiac toxicity (e.g., evidence of dose-related inflammation, edema, and fibrosis in the ventricles; inflammation and thrombosis in the atria) (Section 5.3). As a result of these findings, enrollment of pre-symptomatic subjects with four copies of SMN2 was suspended by the sponsor as these patients generally have milder disease and, therefore, a different benefit-risk profile than others in the trial (no subjects with four copies had been enrolled). Additionally, cardiac safety monitoring (electrocardiograms [EKGs] and echocardiograms at additional study visits, 24-hour Holter monitoring, and Troponin I measurement, instead of CK-MB) was enhanced in the study. A total of seven pre-symptomatic subjects received AVXS-101 and were followed for up to 5.6 months post-infusion with a mean (SD) follow-up of 1.7 (2.0) months.

AVXS-101-CL-302 is a global, Phase 3, open-label, single-arm, single IV dose clinical trial for subjects with SMA Type 1 with bi-allelic mutations of the SMN1 gene and one or two copies of SMN2. Five subjects were dosed with AVXS-101 (1.1E14 vg/kg IV dose) and subjects were followed for up to one-month post-infusion with a mean (SD) follow-up of 0.5 (0.4) months.

In summary, a total of 49 subjects received AVXS-101 intravenously in four clinical trials; 46 subjects received AVXS-101 at the proposed therapeutic dose of 1.1E14 vg/kg IV or higher, and 41 (83.7%) subjects received the entire dose without interruption. Data on dosing has not yet been reported for Study CL-304 (n=7), and this information is missing from one subject in Study CL-302. Among the 46 subjects who received the proposed therapeutic IV dose or higher of AVXS-101, 42 (91.3%) experienced TEAEs. The most frequently reported TEAEs were upper respiratory tract infection (n=19, 41.3%), pyrexia (n=18, 39.1%), vomiting (n=13, 28.3%), and gastroesophageal reflux (n=10, 21.7%). There was one grade 5

TEAE (death due to respiratory arrest 171 days post-treatment in Study CL-303, unrelated to AVXS-101), and 18 subjects (39.1%) experienced grade 3 or 4 TEAEs. The most frequently reported grade 3 or 4 TEAEs were pneumonia (n=7, 15.2%), atelectasis (n=3, 6.5%), respiratory failure (n=3, 6.5%), and transaminases increased (n=3, 6.5%). Twenty (43.5%) subjects experienced 61 TEAEs that were considered treatment-related (Appendix A). The most common treatment-related TEAEs were AST increased (n=8, 17.4%), transaminases increased (n=6, 13.0%), ALT increased (n=5, 10.9%), and vomiting (n=3, 6.5%). A total of 14 (30.4%) subjects experienced treatment-related TEAEs involving elevated liver transaminases; the maximum AST values were 4× ULN (median; range=1-38× ULN) and maximum ALT values were 4× ULN (median; range=1-55× ULN). None met criteria for Hy's Law.

Three (6.5%) subjects in Study CL-303 experienced TEAEs of thrombocytopenia and all of these events resolved without therapy. The median platelet count was 93E9/L (range=74-100E9/L), median time to event onset was 10 days (range=7-63 days), and median time to resolution was 19 days (range=19-104 days). Three additional subjects experienced decreased platelet counts that were not identified as TEAEs by study investigators (two subjects in CL-303 and one subject in CL-302); all decreased platelet counts resolved. These three subjects had a median platelet count of 77E9/L (range=67-77E9/L), the median onset was 8 days (range=6-9 days), and the median resolution time was 16 days (range=13-16 days).

SAE after the data lockpoint date:

One death occurred in Study CL-302 (foreign study). The subject was a five-month-old male with SMA Type 1 who experienced increased upper airway secretions (onset 12 days post-treatment), respiratory distress (Day 14), increased transaminases (ALT=2771 U/L [62× ULN] and AST=4875 U/L [81× ULN], Day 27), decreased platelets (110E9/L, Day 27), and leukoencephalopathy (Day 31). The subject was intubated and ventilated with BIPAP and CPAP; respiratory secretion specimens were positive for coronavirus, rhinovirus, *Haemophilus influenzae*, parainfluenza virus type 3, and respiratory syncytial virus. The subject's platelet count reached a nadir of 37E9/L at Day 32 at which time he received a platelet transfusion. The elevated transaminases responded to treatment with hydrocortisone; AST decreased to 313 U/L (5× ULN) by Day 30 and ALT decreased to 91 U/L (2× ULN) by Day 42. The subject's bilirubin remained <2× ULN and Hy's Law was not met; nor did he have clinical signs or symptoms of liver failure. Thirty days post-treatment the subject experienced seizures and leukoencephalopathy was diagnosed on Day 31. The subject died on Day 52 after withdrawal of care. A post-mortem brain tissue culture was positive for *Raoultella ornithinolytica*. The TEAE of increased transaminases was considered definitely-related, as per investigator assessment, to AVXS-101, leukoencephalopathy was considered possibly-related, and respiratory distress and increased upper airway secretions were considered unrelated. No assessment was provided for the relationship between the decreased platelet count and AVXS-101 treatment.

One SAE of hydrocephalus occurred in Study CL-303 four months after AVXS-101 IV-dosing. This event occurred in a six-month-old male subject with Type 1 SMA who required a ventriculo-peritoneal shunt placement; hydrocephalus resolved following shunt placement. The etiology of hydrocephalus was reported as unknown and possibly-related to AVXS-101.

AVXS-101 is also available through an individual patient expanded access program. A five-month-old male with Type 1 SMA received IV-dosed AVXS-101 through this program and experienced acute liver failure approximately two months later. The patient had also been treated with nusinersen (SMN2 antisense oligonucleotide therapy indicated for treatment of SMA in pediatric and adult patients) four times prior to AVXS-101 dosing and one-time following AVXS-101 dosing. The patient had baseline elevated liver transaminases (ALT and AST 4× ULN) and received prophylactic prednisolone for one-month post-AVXS-101 dosing with an additional 12-day steroid taper. Approximately one-week after steroids were discontinued, the patient presented with jaundice and elevated liver transaminases; the patient's maximum ALT value was 45× ULN and the maximum AST value was 74× ULN. Hy's Law was

not met. The patient responded to steroid boluses at which time his liver transaminases decreased. Liver biopsy results showed massive ballooning degeneration of hepatocytes in Zone 3, massive mixed inflammatory infiltrate in the periportal areas (primarily CD8-positive lymphocytes), moderate periportal fibrosis with marked fibrosis of the central veins, marked bile ductular reaction with associated neutrophilic periductular inflammation, and an increased Kupffer cell population within the sinusoids. The ballooning degeneration was noted to be extensive and appeared to be relatively acute and simultaneous, while the fibrosis was noted to be more chronic in nature. The patient is recovering and has been discharged home.

Withdrawal of consent after data lockpoint date:

One subject discontinued Study CL-303 prematurely due to withdrawal of consent seven months post-treatment. This female subject with Type 1 SMA was IV-dosed with AVXS-101 at five months of age. This subject experienced a treatment-related TEAE, thrombocytopenia (platelets decreased to 100E9/L at Day 10 and resolved without therapy by Day 17), and other clinical events (e.g., dysphagia, pneumonia, respiratory distress) unrelated to AVXS-101 treatment.

5.3 Brief Summary of Non-Clinical Studies (Animal Studies)

In the two pivotal Good Laboratory Practice (GLP) compliant three-month mouse toxicology studies (n=558), the main target organs of toxicity were the heart and liver. Heart ventricle changes included inflammation, edema, and fibrosis; findings were present at all doses studied, were dose-related in severity, and showed evolution from inflammation to fibrosis over the three-month study. Atrial changes included inflammation and thrombosis with associated mortality; findings were dose-related and present at doses $\geq 2.4 \times 10^{14}$ vg/kg, which is approximately 2.2-fold higher than the recommended clinical therapeutic dose. Liver findings in mice included dose-related hepatocellular hypertrophy, Kupffer cell activation, and scattered hepatocellular necrosis; these findings were minimal in severity and partially reversible over the three-month study. Translatability of the above observed findings in mice to humans is not known.

6 Pharmacovigilance Plan (PVP)

6.1 Summary of PVP

The sponsor submitted a Risk Management Plan (version 0.2) proposing routine pharmacovigilance (PV) activities, routine risk communication and minimization activities, and four long-term follow-up safety studies (AVXS-101-LT-001, AVXS-101-LT-002, AVXS-101-LT-003, and AVXS-101-RG-001) (Table 3). The sponsor's routine PV activities are summarized in Appendix B. The sponsor's assessment of the important identified risks, important potential risks and missing information and proposed actions are summarized in Table 3.

Table 3: Summary of Safety Concerns and Planned Pharmacovigilance Activities

Safety Concern	Pharmacovigilance (PV) and Risk Minimization Activities
Elevated transaminases (Important identified risk)	<ul style="list-style-type: none"> Boxed Warning in US prescribing information (USPI): Acute serious liver injury and elevated aminotransferases may occur with Zolgensma. Patients with pre-existing liver impairment may be at higher risk. Prior to infusion, assess liver function of all patients by clinical examination and laboratory testing (e.g.,

	<p>hepatic aminotransferases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], total bilirubin, and prothrombin time). Administer systemic corticosteroids to every patient before and after Zolgensma infusion. Continue to monitor liver function for at least three months after infusion.</p> <ul style="list-style-type: none"> • Routine PV activities and targeted follow-up questionnaire • Routine risk communication: discussed in USPI - Dosage and Administration, Warnings and Precautions, Adverse Reactions, Use in Specific Populations, Patient Counseling Information • Long-term follow-up safety studies: AVXS-101-LT-001, AVXS-101-LT-002, AVXS-101-LT-003, AVXS-101-RG-001
Transient thrombocytopenia (Important identified risk)	<ul style="list-style-type: none"> • Routine PV activities and targeted follow-up questionnaire • Routine risk communication: discussed in USPI - Dosage and Administration, Warnings and Precautions, Adverse Reactions, Patient Counseling Information • Routine risk minimization - recommend specific clinical measures <ul style="list-style-type: none"> ○ Monitor platelets before Zolgensma infusion and on a regular basis afterwards (weekly for the first month; every other week for the second- and third-months post-infusion until return to normal reference range) • Long-term follow-up safety studies: AVXS-101-LT-001, AVXS-101-LT-002, AVXS-101-LT-003, AVXS-101-RG-001
Cardiac adverse events (Important potential risk)	<ul style="list-style-type: none"> • Routine PV activities and targeted follow-up questionnaire • Routine risk communication: discussed in USPI - Warnings and Precautions, Adverse Reactions • Routine risk minimization - recommend specific clinical measures <ul style="list-style-type: none"> ○ Monitor Troponin I for first three-months post-infusion or until return to normal reference range • Long-term follow-up safety studies: AVXS-101-LT-001, AVXS-101-LT-002, AVXS-101-LT-003, AVXS-101-RG-001
Off-label use (Missing information)	<ul style="list-style-type: none"> • Routine PV activities • Routine risk communication: discussed in USPI - Indications and Usage • Long-term follow-up safety study: AVXS-101-RG-001
Long-term effect of Zolgensma therapy (Missing information)	<ul style="list-style-type: none"> • Routine PV activities • Long-term follow-up safety studies: AVXS-101-LT-001, AVXS-101-LT-002, AVXS-101-LT-003, AVXS-101-RG-001

6.2 Study AVXS-101-LT-001

The sponsor submitted a final protocol for study AVXS-101-LT-001 (IND 15699), an ongoing, non-interventional, observational study collecting long-term follow-up safety data on subjects with SMA Type 1 who were treated in the AVXS-101-CL-101 clinical trial. Safety monitoring will be conducted for up to 15 years with in-person annual visits for the first 5-years and then annual phone contact for 10 years. Safety-related data collection at the in-person annual study visits will include gene therapy-related delayed AEs, SAEs, AEs of special interest, clinical laboratory evaluations, echocardiograms, and EKGs and 24-hour Holter monitoring. Annual phone contacts will include capture of gene therapy-related delayed AEs, SAEs, and AEs of special interest.

AEs of special interest include:

- Gene-therapy related delayed AEs
- Liver function enzyme elevations
- New malignancies
- New incidence or exacerbation of a pre-existing neurologic disorder
- New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
- New incidence of a hematologic disorder

Thirteen (86.7%) of 15 eligible subjects have been enrolled in Study LT-101 as of September 27, 2018 (sponsor's data lockpoint date) and subjects have been followed for up to 53.3 months post-treatment with a mean (SD) of 41.7 (6.7) months. There have been no treatment-related SAEs or AEs of special interest. The study milestones include an estimated date for the last subject completed of Quarter 4 (Q4) 2033 and a study report by December 31, 2033.

6.3 Study AVXS-101-LT-002

The sponsor submitted a draft protocol for AVXS-101-LT-002 (IND 15699), a future observational follow-up study to assess long-term safety and efficacy in subjects with SMA Types 1, 2, or 3 treated with AVXS-101 in clinical trials. Subjects will roll-over from their respective parent study and be followed annually for up to 15 years from the date of AVXS-101 dosing with in-person annual visits for the first 5-years and then annual phone contact for 10 years. Safety-related data collection at the in-person annual study visits will include gene therapy-related delayed AEs, SAEs, AEs of special interest, clinical laboratory evaluations, echocardiograms, EKGs, and 24-hour Holter monitoring. Annual phone contacts will include capture of gene therapy-related delayed AEs, SAEs, and AEs of special interest. The sponsor proposes to enroll 85 subjects. Proposed study milestones include recruitment start in Q4 2018 and estimated last subject completed Q4 2032.

6.4 Study AVXS-101-LT-003

The sponsor submitted a draft protocol for AVXS-101-LT-003 (IND 15699), a future long-term follow-up study to assess long-term safety and efficacy in subjects with SMA with three or four copies of SMN2 treated with AVXS-101 in clinical trials. Subjects will roll-over from their respective parent study and be followed annually for up to 15 years from the date of AVXS-101 treatment. This study will capture gene therapy-related delayed AEs, SAEs, and other AEs of interest. The sponsor proposes to enroll 85 subjects. Proposed study milestones include recruitment start in Q2 2018 and estimated last subject completed in Q4 2032.

6.5 Study AVXS-101-RG-001

The sponsor submitted a final protocol for AVXS-101-RG-001, a future prospective, multicenter, multinational, non-interventional, observational long-term registry of patients with a diagnosis of SMA (all types). The proposed objectives of the registry are to assess effectiveness of treatments for SMA, the long-term safety of patients treated with Zolgensma, and the overall survival of patients with SMA. This study will capture SAEs, deaths, and AEs of special interest (i.e., elevated liver function tests) in patients treated with Zolgensma. The sponsor proposes to enroll at least 500 patients with a diagnosis of SMA and to follow patients for 15 years from enrollment or until death, whichever is sooner. Proposed registry milestones include recruitment start in June 2018, end of recruitment in June 2023, end of data collection in June 2038, and completion of a final study report in October 2038.

Reviewer comment: Note that the above described proposed long-term follow-up studies are voluntary studies and not postmarketing commitment (PMC) or postmarketing requirement (PMR) studies.

7 DE Assessment of Sponsor's Pharmacovigilance Plan

7.1 Important Identified Risk: Elevated Transaminases

Elevated liver transaminases were among the most common TEAEs related to AVXS-101 in the clinical trials. Among subjects who received the proposed therapeutic IV dose of AVXS-101 or higher and experienced treatment-related elevated transaminases, AST values were $4\times$ ULN (median; range=1-81 \times ULN) and ALT values were $4\times$ ULN (median; range=1-62 \times ULN). TEAEs involving elevated transaminases were clinically asymptomatic, managed by prednisolone/corticosteroid prophylaxis and/or treatment, and resolved without clinical sequelae, except for the one subject in Study CL-302 (foreign study) who experienced respiratory distress and leukoencephalopathy and died 52 days post-treatment after withdrawal of care. This subject had a maximum ALT and AST values on study Day 27 (62 \times ULN and 81 \times ULN), which decreased to $2\times$ ULN and $5\times$ ULN, respectively, by Day 30 after treatment with hydrocortisone. This subject did not have clinical signs or symptoms of liver failure and laboratory values did not meet the criteria for Hy's Law. The sponsor suggests that elevated liver transaminases may be related to a T-cell immune response to the AAV9 vector capsid.[1]

In addition, one patient who received AVXS-101 through the individual patient expanded access IND program experienced acute liver failure approximately two months later, after cessation of prophylactic steroid dosing. The patient's maximum ALT value was $45\times$ ULN, the maximum AST value was $74\times$ ULN, and Hy's Law was not met. The liver biopsy report showed extensive hepatocyte degeneration which appeared to be acute and simultaneous with the inflammatory infiltrate consisting primarily of CD8-positive lymphocytes. This patient had also received a total of five doses of nusinersen and had elevated transaminases ($4\times$ ULN) prior to treatment with AVXS-101. This patient responded to re-initiation of steroid therapy with decreasing liver transaminases.

Reviewer comments: The sponsor's proposed action to conduct routine pharmacovigilance is acceptable. This safety concern is labeled in the following sections of the USPI:

- Boxed warning for acute serious liver injury
- Section 2.3, Laboratory Testing and Monitoring to Assess Safety
- Section 5.1, Warnings and Precautions: Acute serious liver injury and elevated aminotransferases

7.2 Important Identified Risk: Transient Thrombocytopenia

In Study CL-101, there was a decrease in mean platelet counts from baseline in study participants, however, the decrease in platelet counts was transient and counts remained above the lower limit of normal, with nadirs typically occurring seven days post-treatment. None of these events were considered clinically relevant and none were considered TEAEs. In Study CL-303, similar patterns of decreased platelet counts were noted, however, three subjects experienced TEAEs of thrombocytopenia or decreased platelet counts which resolved without therapy. In Study CL-302 (foreign study), one subject experienced thrombocytopenia and required a platelet transfusion; this subject also experienced leukoencephalopathy and died (after withdrawal of care) prior to resolution of thrombocytopenia. The sponsor indicated that the etiology for the transient platelet decreases and thrombocytopenia was unclear, but that it may be complement-mediated.

Reviewer comments: The sponsor's proposed action to conduct routine pharmacovigilance is acceptable. This safety concern is labeled in the following sections of the USPI:

- Section 2.3, Laboratory Testing and Monitoring to Assess Safety
- Section 5.2, Warnings and Precautions: Thrombocytopenia

7.3 Important Potential Risk: Cardiac Adverse Events

Eight (53.3%) subjects in Study CL-101 experienced elevations in cardiac Troponin I that met the pre-specified potentially clinically significant (PCS) criterion, however, two (25%) of these subjects had elevated Troponin I values prior to AVXS-101 infusion. None of the Troponin I elevations were considered clinically significant, were not considered TEAEs, and all Troponin I values had either returned to normal range or no longer met the pre-defined PCS criterion by the end of the clinical trial. Troponin I was not measured in the three other AVXS-101 clinical trials (CL-303, CL-304, and CL-302). The sponsor noted that levels of cardiac Troponin I in healthy newborns have an upper reference limit that is higher than in adults.[2, 3]

CK and CK-MB levels were also measured in the studies. In Study CL-101, all 15 subjects had elevated CK-MB levels prior to AVXS-101 administration and during most assessment points in the study; none of the CK-MB elevations were considered clinically significant and all subjects were asymptomatic. In Study CL-303, 12 subjects had CK-MB values measured prior to AVXS-101 administration, 11 (91.7%) of whom had elevated CK-MB values. One subject (Subject 003-001) had an elevated CK-MB (5× ULN) that was considered a TEAE possibly-related to AVXS-101 (onset 183 days post-treatment; no therapy given; not resolved). In Study CL-304, CK-MB elevations were noted at screening in six (85.7%) of seven patients; the two subjects with 30-day laboratory data available both had persistent mild CK-MB elevations that were reported as likely due to the underlying illness. In Study CL-304, total CK levels were mildly elevated in three (42.9%) of the seven subjects prior to AVXS-101 administration. Two (28.6%) subjects had elevated total CK levels that persisted through study Day 30, one of whom (Subject (b) (6)) had a TEAE of elevated CK (2× ULN) considered possibly-related to AVXS-101 (onset 14 days post-treatment; no therapy given; resolved by Day 35).

Two subjects in CL-303 experienced diastolic hypertension based on criteria for potentially clinically significant vital sign values. Both subjects had an elevated diastolic blood pressure at baseline and sporadically throughout follow-up. Neither subject had associated signs or symptoms; no therapy was given; there were no clinically significant changes in EKG or echocardiogram findings.

Additional cardiac studies included EKGs and echocardiograms. As of the data lockpoint date, study participants did not have consistent changes from baseline in QTc intervals, or clinically significant EKG or echocardiogram findings.

Reviewer comments: The sponsor's proposed action to conduct routine pharmacovigilance is acceptable. This safety concern is labeled in the following sections of the USPI:

- Section 2.3, Laboratory Testing and Monitoring to Assess Safety
- Section 5.3, Warnings and Precautions: Elevated Troponin-I
- Section 13.2, Animal Toxicology and/or Pharmacology

7.4 Missing Information: Off-Label Use

Off-label use may result in lack of an expected therapeutic effect and/or unexpected AEs. The safety of AVXS-101 in individuals with anti-AAV9 antibody titers >1:50 has not been studied. Zolgensma will be administered by healthcare professionals with experience in the management of SMA.

7.5 Missing Information: Long-Term Effect of Zolgensma Therapy

The sponsor proposes four long-term follow-up safety studies to help address the long-term safety and efficacy of Zolgensma therapy. Section 6 (Pharmacovigilance Plan) provides an overview of these studies. The three non-registry long-term follow-up studies proposed by the sponsor (AVXS-101-LT-001, AVXS-101-LT-002, and AVXS-101-LT-003) include five years of annual examinations and laboratory testing followed by 10 years of annual queries of study subjects as recommended in *Guidance for Industry: Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events* (November 2006) (Section 6.2-6.4). The sponsor proposes to conduct follow-up in the one registry study for 15 years (Section 6.5). Draft *Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products* (July 2018) indicates that replication-negative adeno-associated virus vectors generally present a lower risk of delayed adverse events and that long-term follow-up observations should be product specific with a duration of two to five years.

Reviewer comments: Following Zolgensma, increases from baseline in anti-AAV9 antibody titers occurred in all patients; in some of these cases, anti-AAV9 antibody titers exceeded 1:819,200. Immunogenicity is labeled in section 6.2 Adverse Reactions. Re-administration of Zolgensma in the presence of a high anti-AAV9 antibody titer has not been evaluated. OBE and OTAT discussed immunogenicity issues during review team meetings. This observed immunogenicity may lead to a decline in long-term effectiveness and preclude patients with SMA from receiving a repeat administration of Zolgensma. The safety and effectiveness of repeat administration of Zolgensma have not been evaluated and is included as a limitation of use in the USPI. Currently, when the product is administered at the recommended dose, the impact of the immunogenicity on the product's long-term effectiveness remains unknown. The sponsor plans to continue to obtain data from the long-term follow-up studies.

8 DE Conclusions

Based on review of available data, the safety concerns from the Phase 1 and Phase 3 clinical trials can be monitored through routine PV activities (including use of targeted follow-up questionnaires), risk communication and risk minimization measures as recommended in the USPI, including a Boxed Warning for acute serious liver injury and elevated aminotransferases, and the voluntary postmarketing studies proposed by the sponsor. The reviewed safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS). The available data do not suggest a safety concern that needs to be further evaluated in a study in the CBER Sentinel Program, or a postmarketing requirement (PMR) safety study, or a postmarketing commitment (PMC) safety study.

9 DE Recommendations

Should the product be approved, the sponsor's pharmacovigilance plan (Risk Management Plan, version 0.2) to conduct routine pharmacovigilance and adverse event reporting in accordance with 21 CFR 600.80

is adequate for the postmarketing safety monitoring for Zolgensma. The sponsor also plans to conduct voluntary studies for long term follow-up of treated patients. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon language for the label.

10 References

1. Hinderer, C., et al., *Severe Toxicity in Nonhuman Primates and Piglets Following High-Dose Intravenous Administration of an Adeno-Associated Virus Vector Expressing Human SMN*. Human Gene Therapy, 2018. **29**(3): p. 285-298.
2. Baum, H., et al., *Reference Values for Cardiac Troponins T and I in Healthy Neonates*. Clin Biochem, 2004. **37**(12): p. 1079-1082.
3. El-Khuffash, A.F. and E.J. Molloy, *Serum Troponin in Neonatal Intensive Care*. Neonatology, 2008. **94**: p. 1-7.

Appendix A: Overview of Treatment Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term for AVXS-101-CL-101, AVXS-101-CL-303, AVXS-101-CL-304, and AVXS-101-CL-302*

	Study CL-101	Study CL-101	Study CL-101	Study CL-303	Study CL-304	Study CL-302	
System Organ Class Preferred Term	Low IV Dose (N=3) n (%)	High IV Dose (N=12) n (%)	All (N=15) n (%)	Proposed Therapeutic IV Dose (N=22) n (%)	Proposed Therapeutic IV Dose (N=7) n (%)	Proposed Therapeutic IV Dose (N=5) n (%)	Proposed Therapeutic IV Dose or Higher (N=46)^a n (%)
Patients With At Least One Related TEAE	1 (33.3)	3 (25.0)	4 (26.7)	12 (54.5)	5 (71.4)	3 (60.0)	20 (43.5)
Blood and lymphatic system disorders	0	0	0	2 (9.1)	0	0	2 (4.3)
Thrombocytopenia	0	0	0	2 (9.1)	0	0	2 (4.3)
White blood cell disorder	0	0	0	1 (4.5)	0		1 (2.2)
Endocrine disorders	0	0	0	1 (4.5)	0	0	1 (2.2)
Cushingoid	0	0	0	1 (4.5)	0	0	1 (2.2)
Eye disorders	0	0	0	0	1 (14.3)	0	1 (2.2)
Eye discharge	0	0	0	0	1 (14.3)	0	1 (2.2)
Gastrointestinal disorders	0	0	0	1 (4.5)	4 (57.1)	0	5 (10.9)
Diarrhoea	0	0	0	1 (4.5)	1 (14.3)	0	2 (4.3)
Dyspepsia	0	0	0	1 (4.5)	0	0	1 (2.2)
Gastrooesophageal reflux disease	0	0	0	0	1 (14.3)	0	1 (2.2)
Vomiting	0	0	0	1 (4.5)	2 (28.6)	0	3 (6.5)
General disorders and administration site conditions	0	0	0	0	1 (14.3)	0	1 (2.2)
Malaise	0	0	0	0	1 (14.3)	0	1 (2.2)
Hepatobiliary disorders	0	0	0	0	0	2 (40.0)	2 (4.3)
Hypertransaminasemia	0	0	0	0	0	2 (40.0)	2 (4.3)
Investigations	1 (33.3)	3 (25.0)	4 (26.7)	8 (36.4)	2 (28.6)	1 (20.0)	14 (30.4)
Alanine aminotransferase increased	0	0	0	5 (22.7)	0	0	5 (10.9)
Ammonia increased	0	0	0	1 (4.5)	0	0	1 (2.2)
Aspartate aminotransferase increased	0	1 (8.3)	1 (6.7)	6 (27.3)	0	1 (20.0)	8 (17.4)

Blood creatine phosphokinase MB increased	0	0	0	1 (4.5)	0	0	1 (2.2)
Blood creatine phosphokinase increased	0	0	0	0	1 (14.3)		1 (2.2)
Blood pressure diastolic decreased	0	0	0	1 (4.5)	0	0	1 (2.2)
Blood urine present	0	0	0	1 (4.5)	0	0	1 (2.2)
Gamma-glutamyltransferase increased	0	0	0	2 (9.1)	0	0	2 (4.3)
Lymphocyte count decreased	0	0	0	2 (9.1)	0	0	2 (4.3)
Platelet count decreased	0	0	0	1 (4.5)	0		1 (2.2)
Transaminases increased	1 (33.3)	3 (25.0)	4 (26.7)	2 (9.1)	1 (14.3)	0	6 (13.0)
Weight decreased	0	0	0	1 (4.5)	0	0	1 (2.2)
White blood cell count decreased	0	0	0	1 (4.5)	0	0	1 (2.2)
Metabolism and nutrition disorders	0	0	0	1 (4.5)			1 (2.2)
Feeding disorder	0	0	0	1 (4.5)	0	0	1 (2.2)
Musculoskeletal and connective tissue disorders	0	0	0	1 (4.5)	0	0	1 (2.2)
Joint contracture	0	0	0	1 (4.5)	0	0	1 (2.2)
Nervous system disorders	0	0	0	1 (4.5)	0	0	1 (2.2)
Hydrocephalus	0	0	0	1 (4.5)	0	0	1 (2.2)
Vascular disorders	0	0	0	2 (9.1)	0	0	2 (4.3)
Diastolic hypertension	0	0	0	2 (9.1)	0	0	2 (4.3)

*Adapted from 120 Day Safety Update (Table 26) (data lockpoint September 27, 2018) and the CL-303 Efficacy and Safety Update Report (data lockpoint March 8, 2019)

^aTotal N treated with the proposed therapeutic IV dose or estimated IV dose between 1.1E14 to 1.4E14 vg/kg

Appendix B: Sponsor's Routine Pharmacovigilance Surveillance Activities

Routine Pharmacovigilance Surveillance Activities	Details
Adverse events collection and single case processing	<ul style="list-style-type: none"> • Collect and process AE reports from multiple sources (spontaneous reporting from healthcare professionals and consumers, regulatory agencies, scientific literature, clinical trials, and post-marketing studies) • Store AE reports in centralized and validated company safety database • Perform medical reviews to identify cases for follow-up and conduct follow-up to obtain medical information • Prepare and submit reports to relevant health authorities within specified timeframes • Use targeted/guided follow-up questionnaires to collect data for specific safety concerns (i.e., elevated transaminases, transient thrombocytopenia, and cardiac adverse events)
Aggregate reports	<ul style="list-style-type: none"> • Prepare and submit aggregate reports including periodic safety update reports, periodic adverse event drug experience reports, annual safety reports, and ad hoc reports as requested
Surveillance and signal detection	<ul style="list-style-type: none"> • Evaluate any signals detected and take action as needed (e.g., further assess through clinical or epidemiological studies, product label revision)