

Addendum to the Statistical Review Memo

Application Type	Original BLA
STN	125694
CBER Received Date	October 9th, 2018
PDUFA Goal Date	June 1 st , 2019
Division / Office	DCGT/OTAT
Committee Chair	Andrew Byrnes
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Priority Review	Yes
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Review Completion Date / Stamped Date	
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Applicant	AveXis, Inc.
Established Name	AVXS-101
(Proposed) Trade Name	ZOLGENSMA
Pharmacologic Class	adeno-associated virus serotype 9 expressing the human Survival Motor Neuron gene
Dosage Form(s) and Route(s) of Administration	Single intravenous infusion
Dosing Regimen	1.1E14 vector genomes (vg)/kg
Indication(s) and Intended Population(s)	adeno associated virus (AAV) vector-based gene therapy indicated for the treatment of pediatric patients with infantile-onset spinal muscular atrophy (SMA) with confirmed biallelic mutations in the <i>SMN1</i> gene

Background

This is an addendum to the statistical review memo of the original biologics licensure application BLA 125694. After the statistical review memo was concurred on April 2, 2019, there was a new development. It turned out there was considerable uncertainty when converting the dose in Study AVXS-101-CL-101 using the new (b) (4) assay, due to uncertainty in the vector stability. The adjusted dose of the target therapeutic-dose in Study AVXS-101-CL-101 could be potentially higher than the proposed dose.

As a result, AVXS-101-CL-303 becomes the main source of evidence to support the efficacy and safety of the proposed dose. At the time of the original BLA submission, AVXS-101-CL-303 study had a data cutoff date of Dec 31, 2018. FDA made a request on April 16, 2019, asking the sponsor to provide an efficacy and safety update for study AVXS-101-CL-303 with a new cutoff date of March 8, 2019. On May 1, 2019 the sponsor submitted the efficacy and safety update. This addendum summarizes the key findings of the update.

Statistical evidence

Study AVXS-101-CL-303 is still on-going. In this update, the sponsor reported the key efficacy and safety results with additional two months of follow-up from the original submission.

21 subjects that were assessed as clinically symptomatic for SMA Type 1 at the time of enrolment in Study AVXS-101-CL-303 were included in this efficacy update. By the data cutoff date of March 8, 2019, one patient withdrew from the study while alive at age 11.9 months, one patient died at age 7.8 months due to disease progression and the remaining 19 subjects (90.4%) were known to have all survived without permanent ventilation and continued in the study, among them thirteen (13) reached 14 months of age by the data cutoff date. The 19 subjects ranged in age from 9.4 to 18.5 months. These patients were 7.9 to 15.4 months post-ZOLGENSMA infusion. The sponsor reported that 10 subjects (47.6%) were able to sit without support for at least 30 seconds.

Based on the natural history of the disease, patients who met the study entry criteria would not be expected to attain the ability to sit without support, and only approximately 25% of these patients would be expected to survive (i.e., being alive without permanent ventilation) beyond 14 months of age. Comparison of the results of the ongoing clinical trial to available natural history data of patients with infantile-onset SMA provides primary evidence of the effectiveness of ZOLGENSMA.

The sponsor reported the following non-fatal serious treatment emergent adverse events (TEAE). Ten (45.5%) subjects had at least one serious TEAE. The most common serious TEAE was infections and infestations (Table 1).

Table 1. Serious TEAE for subject in study AVXS-101-CL-303

Serious Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)		1.1E14 vg/kg (N = 22)
System Organ Class Preferred Term[1]		
Patients With At Least One TEAE		10 (45.5)
Cardiac disorders		1 (4.5)
Cyanosis		1 (4.5)
Gastrointestinal disorders		1 (4.5)
Dysphagia		1 (4.5)
Infections and infestations		6 (27.3)
Bronchiolitis		2 (9.1)
Device related infection		1 (4.5)
Pneumonia		2 (9.1)
Pneumonia bacterial		1 (4.5)
Respiratory syncytial virus bronchiolitis		2 (9.1)
Rhinovirus infection		1 (4.5)
Upper respiratory tract infection		1 (4.5)
Investigations		2 (9.1)
Alanine aminotransferase increased		1 (4.5)
Aspartate aminotransferase increased		1 (4.5)
Transaminases increased		1 (4.5)
Metabolism and nutrition disorders		2 (9.1)
Abnormal weight gain		1 (4.5)
Failure to thrive		1 (4.5)
Feeding disorder		1 (4.5)
Nervous system disorders		1 (4.5)
Hydrocephalus		1 (4.5)
Product issues		1 (4.5)
Device malfunction		1 (4.5)
Respiratory, thoracic and mediastinal disorders		3 (13.6)
Acute respiratory failure		1 (4.5)
Atelectasis		1 (4.5)
Respiratory arrest		1 (4.5)
Respiratory distress		2 (9.1)
Respiratory failure		1 (4.5)

Conclusion

The statistical analysis results provide evidence to support the applicant's proposed indication for ZOLGENSMA at the specific proposed dose in this BLA, and complement the evidence of efficacy at uncertain dosage from study AVXS-101-CL-101.