

## Consultative Review

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**Subject:** Consultative Review of BLA 125694

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**To:** Candace N. Jarvis Sr.  
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**Material Reviewed:** BLA submission and other reference documents.

**Date Received:** October 23, 2018

**Date Reviewed:** January 31, 2019

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### **EXECUTIVE SUMMARY**

#### **Background**

This is a consultative review of BLA 125694. The sponsor, AveXis, Inc., is proposing to use AVXS-101 onasemnogene abeparvovec, a vector-based gene replacement therapy, for the treatment of spinal muscular atrophy (SMA) Type 1. AVXS-101 replaces the mutated survival motor neuron 1 (SMN1) gene that causes SMA with a functional gene that encodes for the human survival motor neuron (SMN) protein, whose deficiency is the cause of SMA.

Spinal muscular atrophy (SMA) is an autosomal recessive disease with SMN protein deficiency that causes motor neuron loss in the brainstem and spinal cord, leading to weakness and muscle atrophy. Type 1 (infantile-onset) SMA is fatal, usually by 2 years of age, due to respiratory failure and infection. It is the most common genetic cause of infant mortality, with a global incidence of 8.5 to 10.3 per 100,000 live births.

There are multiple types of SMA (0-4), as shown in the following table. Classification into SMA types has historically been based on the age of symptom onset and the maximal achieved motor abilities. The survival motor neuron 2 gene (SMN2) produces a small amount of functional SMN protein, which partially compensates for a defective SMN1 gene. In general,

the severity of symptoms decreases and the age of onset is delayed with increasing SMN2 copy number and correspondingly increasing amounts of SMN protein, although different patients with the same SMN2 copy number can have different clinical phenotypes.

### **Classification of Spinal Muscular Atrophy. Source: Mercuri et al., 2012**

	Age of onset	Maximum function achieved	Prognosis	Proposed subclassification	SMN copy number
Type 0 (very severe)	Neonatal with prenatal signs	Never sits	If untreated, no survival beyond the first months after birth	..	..
Type 1 (severe)	0-6 months	Never sits	If untreated, life expectancy <2 years	1A, head control never achieved, signs in the neonatal period; 1B, head control never achieved, onset after neonatal period; 1C, head control achieved, onset after neonatal period	One or two copies of SMN2 in 80% of patients
Type 2 (intermediate)	7-18 months	Sits but never stands	Survival into adulthood	Decimal classification according to functional level, from 2.1 to 2.9	Three copies of SMN2 in >80% of patients
Type 3 (mild)	>18 months	Stands and walks	Survival into adulthood	3A, onset of weakness before 3 years; 3B, onset of weakness after 3 years	Three or four copies of SMN2 in 96% of patients
Type 4 (adult)	10-30 years	Stands and walks	Survival into adulthood	..	Four or more copies of SMN2

The consult request asks the following questions:

1. What should be the more appropriate indication: SMA1 vs infantile-onset SMA? The latter seems to us may also include SMA2 who have onset between 6-12 months
2. The applicant puts a weight range limiting for who can be treated, which we do not like. However, the kids who are older and with advanced SMA1 with quadriplegia and complete vent-dependence are unlikely to have sufficient motor neurons to benefit. Shall we consider putting some language like “ patients with SMA1/infantile-onset SMA who have sufficient lower motor neurons as determined by the treating physicians”?

### **Conclusions and Recommendations:**

1. We recommend that the indication be for infantile-onset SMA as opposed to a specific SMA type. Different patients with the same SMN2 copy number can have different clinical phenotypes and be classified into different traditional SMA types. For example, some patients with three copies of SMN2, usually associated with Type 2 SMA, could have more severe symptoms with an infantile onset. Because early treatment before irreversible motor neuron loss is critical to a positive outcome, patients with infantile onset of symptoms should not be excluded from treatment based on SMN2 copy number or traditional SMA type. A specific description of the population that was enrolled in the clinical trial could be included in Section 14 of the label.

2. It is not possible to generalize or precisely predict the degree of benefit that would be expected by SMN1 gene replacement in older patients who have already lost variable numbers of motor neurons. The decision to provide gene therapy to such older patients should be left to the clinical judgment of the treating physician in consultation with the patient and does not need to be specified in labeling.

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