

RECORD OF TELEPHONE CONVERSATION

Submission ID: BLA 125694
Office: OTAT

Product AVXS-101-onasemnogene abeparvovec **Applicant:** AveXis, Inc.

Telecon Date/Time: 13- Mar-2019 1:30 PM **Initiated by FDA?:** Yes
Telephone Number: () -

Author: Candace Jarvis

Purpose: To discuss AveXis' concerns regarding patient weight and the appropriate corresponding dose of the intravenously-administered product

FDA Participants:

Candace Jarvis
Deborah Thompson, MD, MSPH
Lei Xu, MD, PhD
Andrew Byrnes, PhD
Mike Singer, MD, PhD

Applicant Participants:

James L'Italien, PhD, Chief Regulatory Officer, SVP, Regulatory Affairs;
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Background

FDA requested a teleconference to discuss issues related to the applicant's reply to Information Request #33, and the applicant's protocol for the Managed Access Program to permit multiple patients to receive the investigational product under an Expanded Access rubric.

FDA communicated the following message to the applicant via email:

We would like to have a brief teleconference, so that we can better understand your concerns regarding patient weight and the appropriate corresponding dose of your intravenously-administered product. (This issue relates to the product label, as discussed below, and also to the protocol for your Managed Access Program.)

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Unless safety findings indicate otherwise, we would prefer that the product label state a single weight-based dose for all patients (i.e., 1.1×10^{14} vg/kg), without specifying a lower or upper weight limit.

Since the AVXS-101-CL-101 trial demonstrated dose-dependent effects, we are concerned that using a fixed total dose for patients at or above a certain weight (e.g., 13.6 kg) may not represent a suitable balance of benefit and risk.

We are also not clear as to whether you feel the product label should state a minimum patient weight for treatment.

In your response to Information Request #33, you noted that "AveXis believes there should be a maximum number of vector genomes that can be administered at this time," due to uncertainty regarding adverse effects, including "a trend in quantity of vector genome administration and platelet decreases." Additional context would help us to understand the parameters you feel are important in determining intravenous dosing.

We recognize that results of your ongoing study AVXS-101-CL-102, investigating intrathecal delivery, may influence future decisions by clinicians regarding the preferred route of administration for a particular patient, and that the total amount of vector genomes to which the patient is exposed may be part of that consideration. However, we think that is more appropriate a topic for the future.

Summary of Discussion:

The following topics were discussed, based on the teleconference request above.

1. FDA asked that the applicant clarify the proposed lower weight limit of 2.6 kg for infants to receive the product. To provide greater latitude for clinicians to treat possible patients, FDA prefers that no weight limit be specified.

The applicant explained that eligibility criteria for the clinical trials specified that subjects be full-term, and that the lowest-weight subject was 2.6 kg. While in Japan babies at full term often weigh less than full-term babies in the US or Europe, for only a small percentage of live births are full-term babies below 2.6 kg.

Babies below 2.6 kg birth weight generally are premature, and still undergoing development of the brain, heart, and lungs. The consequences of exposure to the product in such circumstances are unclear. The applicant therefore feels that the lower weight limit of 2.6 kg is important to prevent such exposures. The lowest-content product package will contain a dose intended for a patient weighing at least 2.6 kg.

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FDA acknowledged the importance of these concerns, and stated that an FDA neonatologist noted that treatment of such premature infants with corticosteroids (as is necessary before and after receiving the product) could be detrimental to development. FDA suggested that instead of a weight limit, the product label specify that the product should only be administered to infants who are full-term or older. The applicant will consider that suggestion.

2. FDA expressed concern that using a fixed total dose (“flat dose”) for patients at or above a certain weight (e.g., greater than 13.5 kg, proposed by the applicant) may not represent a suitable balance of benefit and risk. Importantly, subjects in the AVXS-101-CL-101 trial demonstrated dose-dependent effects.

The applicant is not comfortable in dosing by weight for patients more than 13.5 kg. The applicant discussed several factors contributing to their proposed upper limit for dosing by weight:

- a. The applicant initially proposed an upper weight limit up to 8.4 kg for weight-based dosing, corresponding to the heaviest subject treated in clinical trials. The increased upper limit (13.5 kg) is in response to FDA feedback.
- b. Decreases in platelet levels have been observed in subjects receiving higher doses of product, in Study 101 and Study 303. When assessing total vector genomes given and the maximum decrease in platelets, a slight negative slope is apparent. The applicant will send FDA that data.
- c. Patients weighing more than 13.5 kg are likely to fall into two major groups: (1) those who have received prior treatment with nusinersen, and may have more remaining viable motor neurons than would be expected based on natural history at that age and weight; and (2) heavier patients who have not received nusinersen, and do not have much preservation of motor neurons.

The applicant states that it is being contacted by families of older patients; many families have expectation that the product can restore lost function. The applicant does not think that the product will be helpful to such patients; moreover, providing the product to such patients may result in a shortage of the product for younger patients, who could benefit from it. Dosing a patient weighing 13.5 kg is approximately equivalent to dosing 2-3 patients who are in the range where product has demonstrated the most benefit. The applicant is trying to supply (b) (4) patient doses in first year after product approval; that number is based on an average weight of 6.8 kg.

FDA responded that these concerns appear reasonable. FDA recommended that the label be worded to remove the upper weight limit so as to allow for flexibility by clinicians, but to address the issues raised by the applicant by excluding

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patients with advanced disease (such as patients with complete paralysis of all limbs, and patients who are ventilator-dependent), who are unlikely to benefit.

FDA emphasized, however, that we do not think that flat dosing for patients above 13.5 kg has a favorable benefit/risk profile, and should be removed from the product label.

FDA also requested that the applicant remove such flat dosing from the recently submitted treatment protocol. The protocol otherwise can proceed.

3. With regard to the indication for use on the label, FDA recommends changing the indication to “infantile onset” SMA, rather than specifying SMA type 1.

The applicant asked whether FDA intended “infantile onset” SMA to mean that a patient has already developed symptoms such as weakness or hypotonia.

FDA clarified that “infantile onset” SMA is not intended to refer specifically to symptoms, but rather to a general constellation of factors (including medical history, clinical examination, laboratory studies, genotype) that would lead a clinician to diagnose SMA in an infant. The intent is to increase flexibility for the clinician (e.g., to enable treatment in situations such as a patient whose genotype suggests that the patient will have milder disease, but whose physical examination indicates otherwise).

4. FDA asked when the applicant expects to have final autopsy results of the subject in the European trial who died after developing respiratory failure, seizures, and leukodystrophy.

The applicant believes that the final autopsy report will be complete at the end of April. Once received from the European examiner, the applicant will provide it to FDA as soon as possible. In addition, the applicant will provide the results of the AveXis analysis of the tissues from that subject.