

## RECORD OF TELEPHONE CONVERSATION

**Submission ID:**

BLA 125694

**Office:**

OTAT

**Product** AVXS-101-onasemnogene abeparvovec;

**Sponsor:** AveXis, Inc.

---

**Telecon Date/Time:** 9- April-2019 12:00 PM **Initiated by FDA?:** Yes

**Telephone Number:** ( ) -

**Author:**

Candace Jarvis

**Purpose:** To discuss the stability of the product and the impact of product stability on interpretation of study CL-101.

**FDA Participants:**

Lei Xu

Andrew Byrnes

Mike Singer

Candace Jarvis

Ilan Irony

Tejashri Purohit-Sheth

Steven Oh

Raj Puri

Ramani Sista

**Sponsor Participants:**

James L'Italien, Ph.D., Chief Regulatory Officer, SVP, Regulatory Affairs;

Olga Santiago, MD, Chief Medical Officer, SVP

Doug Feltner, MD, VP, Head of Clinical Development

Nancy Bowman, MD, Senior Vice President, Global Regulatory Affairs

Hermine Mante, PharmD, Senior Vice President, Global Regulatory Affairs EMA

Frank Sasinowski, JD, Regulatory Consultant

**Summary of Discussion:**

FDA expressed concern with the proposed shelf life and the calculation of doses used in the CL-101 study. The stability data that were provided in BLA amendment 53 (March 29, 2019) indicate that the drug product (b) (4) are not stable at the long-term storage temperature of  $\leq -60^{\circ}\text{C}$ .

The sponsor acknowledged the pre-read documents that were sent to them explaining the FDA's analysis. The sponsor agreed that – based on the stability data that are available – there is a decay curve. The sponsor stated that the product is sufficiently stable over a 12 month window.

## RECORD OF TELEPHONE CONVERSATION

FDA stated that their major concern was the impact of instability on the NCH lot that was used in study CL-101. FDA stated that doses in the range used in the clinical studies are probably on the steep portion of the dose-response curve, and this is suggested by the animal studies in particular. If this is true, then small differences in dosage of product might lead to large differences in the benefit-risk ratio. The sponsor agreed. FDA's overall position is that if the NCH lot is unstable, then we cannot understand what dose was used in CL-101. The sponsor was unable to provide their position on this issue as they were unprepared to discuss the impact on CL-101 at this time, and requested another teleconference.

The sponsor noted FDA's analysis of the stability data and agreed with the downward trend for in vitro potency. They propose to adopt a 12 month drug product shelf life. Additionally, for future production they would propose to (b) (4) DP concentration (b) (4) current concentration of  $2.0 \times 10^{13}$  vg/mL (b) (4), while keeping the dosing volume at 5.5 mL/kg. FDA asked if the sponsor was proposing an (b) (4), and they confirmed yes. In addition, the sponsor has already manufactured (b) (4) lots of DP at the  $2.0 \times 10^{13}$  vg/mL concentration, and if these lots are less than 12 months old, they propose to sample and perform a (b) (4) of (b) (4) and in (b) (4) potency to determine whether the product has decayed. Moving forward, future lots would be manufactured at a concentration of (b) (4).

FDA acknowledged the sponsor's proposals and noted that FDA was not able to agree with them immediately, but would certainly consider the proposals. FDA asked that this information be sent in to the BLA within the next few days, along with list of the lots that have already been manufactured. The information should include the lots' manufacturing dates and stability data, and the acceptance criteria that the sponsor is proposing for (b) (4).

### Drug substance shelf life:

FDA stated that most of the sponsor's drug substance lots have been forward processed rather quickly to drug product: within (b) (4) after the drug substance was manufactured. The sponsor stated that they also have data on drug substance lots that were forward processed at up to (b) (4). The sponsor proposed a (b) (4) shelf life for drug substance, and the sponsor will include data in their response. They believe they are (b) (4) that are used for stability testing. (b) (4). FDA stated that we do not know mechanism for the instability. FDA asked if the sponsor was claiming that the stability data may not represent the true stability of product. The sponsor does not know and will provide information to support a hypothesis.

### Issues regarding potency:

Potency is calculated relative to a reference vector, and FDA expressed concern that any instability of the reference vector would affect the accuracy of the potency measurements. The sponsor has a protocol where they are generating comparability data, and they are in the process of preparing that report.

## RECORD OF TELEPHONE CONVERSATION

### Dosing in clinical trials:

The sponsor stated that they will prepare a response to FDA's concerns about the doses in studies CL-101 and CL-303, and they requested a second meeting next week.

FDA stated that the current dose of  $1.1 \times 10^{14}$  vg/kg was calculated based on the (b) (4) lot that had been frozen for (b) (4) before being measured using the (b) (4) assay. Because the stability data indicate a decline over time, FDA now thinks that the proposed commercial dose of  $1.1 \times 10^{14}$  vg/kg is lower than the dose that the subjects in the CL-101 study received. FDA asked the sponsor to provide justification for whether the CL-303 study would provide the primary evidence of effectiveness of the product. FDA also asked the sponsor what dose they would recommend on the PI. The sponsor stated that they will prepare this information for the next interaction.