

RECORD OF TELEPHONE CONVERSATION

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OTAT

Product AVXS-101-onasemnogene abeparvovec;

Sponsor: AveXis, Inc.

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Purpose: Follow-up discussion to discuss the stability of the product and the impact of product stability on interpretation of study CL-101.

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Summary of Discussion:

The sponsor submitted pre-read materials to aid in discussion of the stability of the product and the impact of product stability on interpretation of study CL-101 (attached).

The applicant presented two potential models for the stability of vector genome concentration in DP at $\leq -60^{\circ}\text{C}$. Both models show a meaningful decline in concentration over time. Model A is equivalent to the FDA model from the April 9, 2019 teleconference (linear regression fit to \log_{10} data). Model B is the applicant's alternate model that is dependent on the (b) (4) of time. In

RECORD OF TELEPHONE CONVERSATION

model A, the concentration of DP decreases by a constant percentage per unit time. In model B, the rate of decrease is not constant (b) (4)

The applicant stated that AveXis lots at the (b) (4) different concentrations (b) (4) need to be analyzed separately because they appear to have different stability trends, especially at very early time points. The applicant stated that model A appeared to be an acceptable fit to the (b) (4) lots, but model B was a better fit to the (b) (4) lots. FDA disagreed and stated that the data from all (b) (4) lots were (b) (4) (slopes not significantly different, ANCOVA) and therefore the data from all lots should be analyzed together using a global fit where the slopes are the same and the intercepts are different. FDA noted that the (b) (4) values were not very different for the models A and B on slide 6. The applicant stated their opinion that model B was a better fit by eye.

FDA also noted a problem with the applicant's position that only the 2E13 vg/mL data are representative, and the (b) (4) data are not representative – if this is true, FDA asked why should we assume that it is appropriate to use the 2E13 data to predict the stability of lot (b) (4), which has a concentration of about (b) (4)

On slide 7, the applicant presented a newly-measured vector genome concentration point from lot (b) (4) at (b) (4) months of age (b) (4) in (b) (4). This (b) (4) month point has a concentration that is (b) (4) lower than the (b) (4) month point (b) (4) in (b) (4). In response to an FDA question, the applicant indicated that the (b) (4) month and (b) (4) month assays had been performed on (b) (4) while the (b) (4) month assays had been performed on (b) (4) vials. FDA noted that the (b) (4) month data confirm that the vector genome concentration of lot (b) (4) is currently still declining, even when samples are acquired from the (b) (4) (months (b) (4)). The applicant stated that fitting a local regression to all (b) (4) data points indicates a decline of (b) (4) between month (b) (4), which is a better fit to model B (predicted (b) (4) decline) than to model A (predicted (b) (4) decline).

On slide 9, the applicant provided new in vitro relative potency data with lot (b) (4) at (b) (4) months. The potency was measured relative to reference standard vector lot RS-002, which has an assigned potency of (b) (4). The potency of (b) (4) at (b) (4) months was (b) (4), which the applicant noted is close to (b) (4) (FDA agreed). The applicant confirmed that the potency measurement at (b) (4) months was based on the (b) (4) concentration of lot (b) (4) at (b) (4) months, and the potency measurement at (b) (4) months was based on the (b) (4) concentration at (b) (4) months. FDA stated that the data suggest that the ratio of potency to vector genomes remains constant over time. Another way of stating this is that the decline in potency is likely not any faster than the decline in vector genome concentration. FDA noted that this conclusion was

RECORD OF TELEPHONE CONVERSATION

tentative because the potency and the concentration of the reference material RS-002 were likely also declining with time. On slide 10, the applicant presented potency data from (b) (4) DP lots that were fit to an exponential decay model, and stated that the potency data support a DP shelf life of (b) (4) months, based on the intersection of the 95% CI with the lower acceptance criterion of (b) (4) potency.

FDA noted that the (b) (4) is also decreasing over time, but the rate is uncertain because of the low precision of the assay and the possibility that this assay might be (b) (4). FDA indicated that the vector genome concentration data are the best data for making decisions about stability and shelf life, because the (b) (4) assay is much more precise than either the potency or (b) (4) assay, and there is no concern about assay (b) (4) with the (b) (4).

On slide 12, the applicant presented DS vg concentration stability data. The applicant stated that the lower acceptance limit of (b) (4) for DS is based on a safety margin that allows AveXis to have a high enough concentration to prepare DP at 2.0×10^{13} vg/mL. The applicant's fit of some of the stability data to a simple (non-logarithmic) linear regression suggests that the DS will be not fall below the (b) (4) lower limit until (b) (4) months, although they noted that there was one OOS value at (b) (4) months. The applicant also stated that they had data from lots of DS that were kept at (b) (4) for up to (b) (4) before forward processing to DP, and these DS lots showed minimal loss of vg concentration. FDA asked the applicant to submit these data to the BLA.

The applicant revised their request for DS shelf life from (b) (4). FDA stated that they would consider this request for an (b) (4) DS shelf life after receiving the additional data mentioned by the applicant.

On slides 14-21, the applicant presented their analysis of the doses administered in studies CL-101 and CL-303. The applicant stated that model B was a better fit to the stability data. Applying model B to the doses administered in CL-101 cohort 2 suggests that subjects received doses that were very close to 1.1×10^{14} vg/kg.

FDA stated that sufficient stability data are only available for 1 year after manufacture – it is impossible to accurately extrapolate to (b) (4) based on the current data. Many different models (such as the applicant's model B) can be fit mathematically to the existing data, but that does not mean that the models are correct. Just as an example, there might be (b) (4) types of vector (b) (4). This model makes an excellent fit to the data, but there is no a priori mechanistic evidence for this mechanism of instability.

FDA stated that there are not enough data to discriminate among these models. The most standard method of analysis would be to assume that the rate of decline remains constant over time, and that is why FDA is using model A. FDA noted that even with this model, however, there is significant uncertainty about the rate over (b) (4), which makes it impossible to retrospectively determine the

RECORD OF TELEPHONE CONVERSATION

concentration of (b) (4) at the time of study CL-101. FDA stated that model B involves the (b) (4) – this is an extremely unusual stability model, and it is difficult to think of a biophysical explanation for why the rate of decline would vary with (b) (4) in the manner assumed in model B. If the applicant wishes to support model B in the future, they will need to provide additional data from very short time points (where the rate of decline is very fast in model B) as well as additional data from long time points (where the rate of decline is much slower).

There is unequivocal evidence that DP is unstable. FDA's position remains that the doses administered in CL-101 cannot be determined with certainty, but the doses were very likely higher than 1.1×10^{14} vg/kg.

Clinical:

The clinical team indicated that they could not determine which stability model to rely on. Therefore, it is most appropriate to rely on Study CL-303 to provide the primary evidence of effectiveness of the product, and the data from Study CL-101 are supportive but would not be sufficient.

FDA asked if the applicant could provide additional efficacy data for Study CL-303 with a later cutoff. The applicant stated that they would be able to provide additional data from study 303 with a March 8 cutoff by the end of April. The applicant also offered to provide additional data from studies 302 and 304, but FDA indicated that the update should be limited to Study CL-303 with focus on the 21 subjects with infantile-onset SMA (ITT population for efficacy analysis).

The applicant indicated that the subject in study CL-303 who was originally thought to be pre-symptomatic had been retrospectively reclassified as symptomatic by the investigator. FDA did not feel it is appropriate to change the ITT population in the middle of the trial.

FDA asked why the Agency continued receiving single patient expanded access INDs. The applicant replied that the treatment protocol is currently being reviewed by IRBs. The applicant is trying to move as expeditiously as possible.

CMC:

FDA stated that additional investigation needs to be done to determine the most appropriate stability model and whether the mechanism of instability is (b) (4), or some other mechanism. FDA noted that the applicant's data show better stability at 4C than at <-60C. It seems unlikely that the mechanism for instability at <-60C is (b) (4), because one would expect (b) (4) to be similar or worse at 4C.

There is insufficient time remaining in the BLA review period to investigate the mechanism, and FDA indicated that any such data would have to be submitted post-licensure. FDA also requested that the (b) (4) assay be added to the ongoing DP stability program.

RECORD OF TELEPHONE CONVERSATION

FDA briefly informed the applicant about the CBER lot release process: CBER will review the data from every lot, and CBER will need to approve each lot before it is released for commercial distribution. The CBER lot release process takes about one month, and additional information will be provided in the near future.