

Our STN: BL125694/0 **MID-CYCLE COMMUNICATION**

SUMMARY
February 14, 2019

AveXis, Inc
Attention: James L'Italien, PhD
2275 Half Day Road, Suite 200
Bannockburn, IL 60015

Dear Dr. L'Italien:

Attached is a copy of the summary of your January 29, 2019 Mid-Cycle Communication Teleconference with CBER. This memorandum constitutes the official record of the Teleconference. If your understanding of the Teleconference outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER as soon as possible.

Please include a reference to BLA 125694/0 in your future submissions related to onasemnogene abeparvovec.

If you have any questions, please contact Candace Jarvis at (240) 402-8315.

Sincerely,

Raj Puri, PhD
Director
Division of Cellular and Gene Therapies
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research

Mid-Cycle Communication Teleconference Summary

Application type and number: BLA 125694/0
Product name: onasemnogene abeparvovec
Proposed Indication: Treatment of Spinal Muscular Atrophy (Type I)
Applicant: AveXis, Inc.
Meeting date & time: January 29, 2019, 1:00PM-2:00PM
Committee Chair: Andrew Byrnes, PhD
RPM: Candace Jarvis

FDA Attendees:

Andrew Byrnes, PhD, CBER/OTAT/DCGT
Angela Whatley, PhD, CBER/OTAT/DCGT
Denise Gavin, PhD, CBER/OTAT/DCGT
Mike Singer, MD, PhD, CBER/OTAT/DCEPT
Lei Xu, MD, PhD, CBER/OTAT/DCEPT
Wei Wang, PhD, CBER/OCBQ/DMPQ
Candace Jarvis, CBER/OTAT/DRPM
Min (Annie) Lin, PhD, CBER/OBE
Feorillo Galivo, MD, PhD, CBER/OTAT/DCEPT
Iwen Wu, PhD, CBER/OTAT/DCEPT
Deborah Trout, CBER/OCBQ/DMPQ
Caroline Renshaw, CBER/OCBQ/DMPQ
John Eltermann, RPh, MS, CBER/OCBQ/DMPQ
Deborah Thompson, MD, MSPH, FACPM
Sonni Saini, PhD, CBER/OCBQ/APLB
Steven Oh, PhD, CBER/OTAT/DCGT
Wilson Bryan, MD, CBER/OTAT
Kimberly Benton, PhD, CBER/OTAT
Raj Puri, MD, PhD, CBER/OTAT/DCGT
Wei Liang, PhD, CBER/OTAT/DCEPT

Sponsor Attendees:

James L'Italien, Ph.D., Chief Regulatory Officer, SVP, Regulatory Affairs;
Brian Kaspar, Ph.D., SVP, Chief Scientific Officer;
Nancy Boman, M.D., Ph.D., SVP, Regulatory Affairs;
Mark Roache, SVP, Quality Assurance;
Andrew Stober, SVP, Manufacturing and Supply Chain;
Robert Hodge, VP, Technical Services;
Eric Couture, Ph.D., Global Head of Regulatory Affairs, Novartis;
Doug Feltner, M.D., VP, Clinical Development;
Olga Santiago, M.D., SVP, Chief Medical Officer;
Robert Baker, Director, CMC Regulatory Affairs.

Agenda:

Discussion Summary:

1. Any significant issues/major deficiencies, categorized by discipline, identified by the Review Committee to date.

Chemistry, Manufacturing, and Controls

1. The removal of a process-related impurity – (b) (4) – has not been evaluated, and it is unknown whether (b) (4) is present in the drug product (DP). (b) (4) is known to be toxic by the i.v. route. We requested data on (b) (4) removal in IR #23 (sent 1/7/19, response due 2/15/19).

Meeting Discussion: The sponsor will provide their complete response by February 15, 2019. An assay was developed for (b) (4), and it will be used to measure process clearance and the (b) (4) levels in (b) (4) DP.

2. There are multiple concerns regarding the total protein concentration in DP. We requested responses to these issues in IR #23 (sent 1/7/19, response due 2/15/19):
 - a. The protein assay may not be completely specific for protein.
 - b. The variability in protein concentration among lots is unexpectedly high, suggesting the presence of uncharacterized impurities in some lots.
 - c. The proposed acceptance criterion for protein is too wide.
 - d. Some DP lots have such high protein concentration that it calls into question whether all of the AveXis lots are comparable to lot AAV9SMN0613.

Meeting Discussion: The sponsor will provide their complete response by February 15, 2019. They agree that the lots have high variation in protein concentration. They are evaluating validation of the protein assay and the variability in protein concentration.

3. The analytical (b) (4) assay has major flaws in design and validation. This is a critical assay to measure the quality of the product, because only (b) (4). The assay does not appear to be sufficiently accurate, precise or robust. It is not clear whether the lot release acceptance criteria are appropriate. Additional information was requested in IR #17 (sent 12/20/18, response requested by 1/22/19, response currently due 1/29/19).

Meeting Discussion: The sponsor requests an extension until February 15, 2019 for providing a complete response to this deficiency. Their team is looking at the design of the analytical (b) (4) assay and the accuracy of the data. FDA agreed to the extension of the deadline and stated that this issue can be further discussed during the inspection at (b) (4). FDA noted that information requests and discussions of this assay have focused mainly on concerns about assay accuracy. While accuracy remains a concern, FDA indicated that assay precision is even more important than accuracy.

4. Insufficient stability data have been submitted for the DS and for the DP commercial presentation. We may not agree to the requested (b) (4) shelf life for DS and DP. A PMC will be necessary to provide additional stability data. These additional data will need to be provided in a prior approval supplement in order to support a (b) (4) shelf life for DS and DP.

Meeting Discussion: The sponsor is evaluating the current data and intends to provide additional data points for stability, especially for the in vitro potency assay. The sponsor stated their intention to draw parallels to other data that supplement and support the current DS and DP data. They will also provide additional justification for the requested shelf life. Additional stability data will be provided to the BLA before the end of March.

5. The manufacturing process operating ranges are not adequately justified. The process performance qualification studies did not vary the process parameters sufficiently to justify the operating ranges. A teleconference was held on 1/24/19 to discuss this issue.

Meeting Discussion: The sponsor is updating the process validation sections of the BLA to provide additional support, data and explanation for the manufacturing process operating ranges, as was discussed at the January 24, 2019 teleconference with FDA. The sponsor will respond by February 15, 2019.

6. Information provided in the original BLA submission (STN 125694/0) regarding reprocessing at the AVXS-101 Drug Product manufacturing process steps was deficient. CBER/DMPQ requested additional information in IR #27 (sent 1/11/2019, response due 1/25/2019).

Meeting Discussion: The sponsor submitted a response to IR #27 on January 25, 2019. FDA reviewed the sponsor's response and considered that the data are inadequate to demonstrate the validation of (b) (4) procedures. The sponsor will revise their responses and make sure the requested information is covered. The sponsor will look at the status of the PPQ lots and will have this information available for discussion next

week (the week of February 4th, 2019). FDA agreed to discuss further during the upcoming pre-license inspection of the (b) (4) facility.

7. The (b) (4) assay (SOP-137) has not been adequately validated for specificity. Please validate that the assay does not detect an irrelevant AAV vector and provide the additional validation report to the BLA. This deficiency was communicated in the filing letter on 11/28/18. Your response in submission number 21 (received on 1/17/19) is not acceptable. The current assay validation does not rule out the possibility that the (b) (4) might react nonspecifically to process-related impurities that are present in AAV vectors, including (b) (4). Your demonstration that the assay does not detect a (b) (4) of irrelevant (b) (4) does not address this deficiency. Please demonstrate that the assay does not detect an *irrelevant AAV vector*.

Meeting Discussion: The sponsor will provide an action plan for validating the specificity of the (b) (4) assay by February 15, 2019. They will also provide supporting information regarding the uniqueness of the (b) (4). FDA reiterated that the primary goal should be to validate that the assay produces a negative result when the test article is an irrelevant AAV vector.

8. The (b) (4) assay protocol must add a positive control for (b) (4) activity. Absence of this control may permit falsely high (b) (4) results that would lead to under-dosing of patients. We requested this change in IR #19 (sent 12/21/18, response due 2/15/19).

Meeting Discussion: The sponsor will provide a modified SOP for the (b) (4) assay by February 15, 2019. A (b) (4) will be included in each assay run as a system suitability criterion to ensure (b) (4) activity.

2. Information regarding major safety concerns.

CMC

A toxic process-related impurity (b) (4) may be present in drug product. This is a major safety concern.

Meeting Discussion: In addition to implementing the new (b) (4) assay and providing clearance data, the sponsor will summarize available toxicology data and will demonstrate that the amounts of (b) (4) in the product are below toxic levels.

3. Preliminary Review Committee thinking regarding risk management.

Based on currently-available information, we do not anticipate a need for a Risk Evaluation Mitigation Strategy.

There was no discussion of this item.

4. Any information requests sent and responses not received.

Information Request #17 original due date 1/22 extended to 1/29
Information Request #18 due date 1/21
Information Request #19 due date 2/15
Information Request #20 original due date 1/11 extended to 1/25
Information Request #21 due date 1/31
Information Request #23 due date 2/15
Information Request #25 due date 1/23
Information Request #27 due date 1/25
Information Request #29 initial response 1/22, full response expected 3/29
Information Request #30 due date 1/28
Information Request #31 due date 1/24

****Update:** The sponsor has responded to IR# 20, 25, 27, 30 and 31. They plan to submit IR# 18 by February 5, 2019 and IR#17 and 21 by February 15, 2019.

5. Any new information requests to be communicated.

None at this time. If any additional information requests are identified, we will provide them by email.

Meeting Discussion: A new CMC information request will be communicated by February 1, 2019.

6. Proposed date(s) for the Late-Cycle meeting (LCM).

The LCM between you and the Review Committee is currently scheduled for March 15, 2019.

- i.** We intend to send the LCM meeting materials to you approximately 3 days in advance of the LCM
- ii.** If these timelines change, we will communicate updates to you during the course of the review.

7. Updates regarding plans for the AC meeting.

We do not plan to hold an AC meeting.

8. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates.

Our target for communication of proposed labeling and any PMR/PMC requests remains May 2, 2019. However, communication may occur earlier than this date, if circumstances allow.

Additional Discussion:

1. FDA has identified the date for pre-license inspection for (b) (4)
[REDACTED]
2. FDA requested that a Word version of the revised package insert be sent via email. FDA stated that additional justification will need to be provided to support the proposed changes to weight-based dosing.
3. FDA noted that many of the documents submitted to the BLA since December have been submitted in module 1.11 as long concatenated pdfs, instead of being placed in the correct eCTD folders. FDA asked that this be corrected. FDA noted that it is very helpful to submit redlined versions of updated eCTD documents to module 1.11, and FDA asked that this practice continue when feasible. However, FDA indicated that non-redlined versions of updated documents should also be placed in the correct eCTD folders. The sponsor took note and will follow up with their publisher and correct retrospectively as well as moving forward.
4. The sponsor proposes a (b) (4)
vials to accommodate the new proposed weight ranges for patients. The current six vial container will support weights up to 9 kg. Their plan is to have a shipping validation study for a new (b) (4) vial kit completed well in advance of the labeling discussion target of May 2, 2019. They will also provide a new PI that will incorporate information about the new kit and NDC codes. If shipping validation for the new kit is not completed in time, the sponsor intends to (b) (4)
[REDACTED]