

Our STN: BL 125694/0

**LATE-CYCLE
MEETING MEMORANDUM**

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 memorandum summarizing your March 28, 2019 Late-Cycle Meeting 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 in writing as soon as possible.

Please include a reference to the appropriate Submission Tracking Number (STN) in future submissions related to the subject product.

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

Sincerely,

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

Late-Cycle Meeting Summary

Meeting Date and Time: March 29, 2019 1:00-2:30 PM
Meeting Format: Teleconference

Application Number: BLA 125694/0
Product Name: onasemnogene abeparvovec-xioi
Proposed Indications: Treatment of infantile-onset spinal muscular atrophy (SMA) with confirmed biallelic mutations in the *survival of motor neuron 1 (SMN1)* gene

Applicant Name: AveXis, Inc

Meeting Chair: Andrew Byrnes, PhD
Meeting Recorder: Candace Jarvis

FDA ATTENDEES

Andrew Byrnes, PhD, CBER/OTAT/DCGT
Candace Jarvis, CBER/OTAT/DRPM
Lei Xu, MD, CBER/OTAT/DCEPT
Mike Singer, MD, CBER/OTAT/DCEPT
Angela Whatley, PhD, CBER/OTAT/DCGT
Hyesuk Kong, PhD, CBER/OCBQ/DBSQC
Feorillo Galivo, Ph D CBER/OTAT/DCEPT
Wei Wang, PhD, CBER/OCBQ/DMPQ
Deborah Thompson, MD, MSPH, FACPM, CBER/OBE
Erin McDowell, CBER/OCBQ/BiMO
Ramani Sista, PhD, CBER/OTAT/DRPM
Kimberly Benton, PhD, CBER/OTAT

Denise Gavin, PhD, CBER/OTAT/DCGT
Annie Lin, PhD, CBER/OBE/DE
Rachael Anatol, PhD, CBER/OTAT
Wei Liang, PhD, CBER/OTAT/DCEPT
Lori Peters, PhD, CBER/OCBQ/DMPQ
John Eltermann, CBER/OCBQ/DMPQ
Dennis Cato, CBER/OCBQ/BiMO

APPLICANT ATTENDEES

James L'Italien, PhD

BACKGROUND

BLA 125694/0 was submitted on October 1, 2018, for onasemnogene abeparvovec.

Proposed indication: Treatment of infantile-onset spinal muscular atrophy (SMA) with confirmed biallelic mutations in the *survival of motor neuron 1 (SMN1)* gene

PDUFA goal date: May 31, 2019

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on March 18, 2019.

DISCUSSION

1. Discussion of Substantive Review Issues **27 Minutes**

CMC

- a. Only a few months of stability information have been submitted for the DS and for the DP commercial presentation. We acknowledge your plans to submit additional stability data by March 31, 2019. We may decide to approve a shorter shelf life than the (b) (4) that you have requested. A PMC will be necessary to provide (b) (4) of stability data in order to support the requested (b) (4) shelf life for DS and DP. You will also need to provide evidence that DP is stable for (b) (4) following manufacture from DS that has been (b) (4).

Discussion: The applicant agreed to submit the additional stability data by March 31, 2019 and agreed that there will be a stability PMC if the BLA is approved. FDA will need to evaluate the stability report to determine if the (b) (4) shelf life is acceptable.** The applicant stated that the requested information is on track for the March 31st due date. FDA also requested RPT-1002 (freeze/thaw stability report). The applicant agreed to submit the RPT-1002 report by April 10th.

****Update:** FDA received the stability data on March 29, 2019. FDA has significant concerns that the stability data do not support the proposed shelf life for DS and DP.

- b. On February 14, 2019, FDA inspectors noted that primary reference standard RS-002 had not been extensively bridged to interim reference standard AAV9SMN0613, leading to uncertainty about the (b) (4) of RS-002 and AAV9SMN0613. For (b) (4), there is currently just one data point evaluating the (b) (4) of AAV9SMN0613 relative to RS-002. For (b) (4), there are only a few data points characterizing the (b) (4) of AAV9SMN0613 and RS-002, and some of the data may have been affected by (b) (4) of AAV9SMN0613 and RS-002. You agreed to perform additional assays comparing AAV9SMN0613 and RS-002 using (b) (4) of AAV9SMN0613. Please submit the resulting data to the BLA.

Discussion: The applicant stated they are on track to submit the supplemental information comparing AAV9SMN0613, the RS-002 reference standard and (b) (4) by early April.

- c. The acceptance criteria are not agreed for the following lot release assays:
 - i. (b) (4) You are currently revising the (b) (4) assay and will propose a new acceptance criterion, as described in submission number 43 (February 26, 2019). Please submit the revised SOP-263, the proposed acceptance criterion, and justification for the proposed acceptance criterion.

Discussion: The applicant stated that they will provide the revised SOP-263, the proposed acceptance criterion as well as the justification by the April 10th due date.

- ii. (b) (4): The (b) (4) assay is currently under investigation and is suspected of producing inaccurate results. Please provide the investigation report, CAPA, the proposed acceptance criterion, and justification for the proposed acceptance criterion.

Discussion: The applicant stated that they will provide the requested information by the April 10th due date.

- iii. Total protein: In IR #23 (January 7, 2019) and our mid-cycle communication, we listed multiple concerns with the DP total protein concentration that have not been resolved. You informed us in submission number 40 (February 25, 2019) that the total protein assay is currently under investigation. The investigation will determine whether the variability in total protein is due to variability in the assay or the product, and you may take other actions as a result of the investigation. Please provide the investigation report, the proposed acceptance criterion, and justification for the proposed acceptance criterion.

Discussion: The applicant notified FDA that they are working on providing the requested information, but they are relying on a third-party contractor and unfortunately may not meet the April 10th deadline. The applicant indicated that they believe the data are explained by poor assay precision. The original assay validation was not performed correctly, and they are revalidating the assay to determine the precision. FDA acknowledged their response. If it is not possible to submit the information by April 10th, FDA requested that the applicant provide an update on April 10th, including a summary of the status and the expected timeframe for submission.

- iv. (b) (4): We tentatively agree with your plan in submission number 43 (February 26, 2019) to set acceptance criteria for these three assays at (b) (4) in conjunction with an alert limit that will trigger a non-conformance and investigation if exceeded. Please submit clarification to the BLA that the alert limit for these assays will be (b) (4), and that any non-conformance investigations triggered by the alert limits will be resolved before release of lots.

Discussion: The applicant stated that they will provide the requested information by the April 10th due date.

- d. On February 8, 2019, you informed the FDA inspectors that, after the Sterile Filtration and (b) (4) step, you will no longer need to perform an optional (b) (4) and will modify the MBRs for DP manufacturing accordingly. You also stated that the (b) (4) is needed and has been performed to manufacture additional Drug Product lots due to deviations (e.g. (b) (4) outside of action limit). Please submit the updated MBRs and provide a summary report of (b) (4) validation data based on the data from the manufacturing of (b) (4) Drug Product lots to the BLA. Please submit a (b) (4) SOP to the BLA.

Discussion: FDA indicated that (b) (4) should be confined to instances of specific equipment or mechanical failures. FDA cannot prospectively approve (b) (4) in cases of human error, including cases where the vector concentration is outside of control limits. FDA directed the applicant to FDA's March 27, 2019 information request regarding the applicant's 483 responses. The applicant indicated that they will provide historical experience and data regarding (b) (4) of several lots, along with an SOP that contains detailed written procedures for (b) (4).

- e. The (b) (4) assay (SOP-137) has not been adequately validated for specificity. In discussion with FDA inspectors on February 7, 2019, you agreed to validate specificity by demonstrating a negative result when the (b) (4) in SOP-137. Please provide this additional validation report to the BLA.

Discussion: The applicant stated that they will try to provide the additional validation report by the April 10th due date, but there may be a delay. FDA acknowledged their response and asked that if the information was not submitted by April 10th that they provide us with a summary of the status and the expected timeframe for submission.

- f. The process for labeling of frozen DP vials has not been validated. Please validate the labeling process and submit the validation report to the BLA.

Discussion: FDA acknowledged receipt of this information, and there are no questions or concerns at this time.

- g. On February 6, 2019, you informed FDA inspectors that a single DP lot may be (b) (4) for different markets. FDA inspectors informed you that each lot (b) (4) of DP intended for the US market must be tested for identity after completion of labeling operations, to comply with 21 CFR 610.14. Please confirm that you will perform identity testing in this manner. Please submit to the BLA an updated labeling MBR.

Discussion: FDA noted that identity testing should be performed on all lots and (b) (4) after labeling. The applicant stated that they will provide the requested information.

- h. Based on discussion between FDA inspectors and the firm on February 7, 2019, our current understanding is that the secondary packaging will consist of a carton that can hold between 2 and 9 vials. Please submit shipping validation reports for this new configuration, updated variable labels for the kit, and an updated package insert.

Discussion: FDA acknowledged receipt of the shipping validation report; however, FDA had additional questions about how the shipment would be routed through a specialty pharmacy. The applicant stated that once the specialty pharmacy receives the shipment, they will open the shipper to verify the contents and the label in its frozen state, and then they will forward the shipment to the requesting physician. FDA asked the applicant to provide further description to the BLA, including whether the carton seal is broken and whether the same courier will be used to ship from the specialty pharmacy to the requesting physician. The applicant agreed to provide the requested information.

- i. Regarding control and qualification of reference materials used in assays, you agreed in submission number 38 (February 19, 2019) to implement an SOP by March 15, 2019 to control inventory and lot-to-lot variability of reference materials. Please submit this SOP to the BLA, and list which reference materials this SOP will apply to.

Discussion: FDA stated that SOP 488 need to be submitted to the BLA. The applicant stated that the SOP will be sent in shortly.

Clinical

- j. Please submit the final autopsy report and other relevant results of the subject who died in Study AVXS-101-CL-302 as soon as they become available.

Discussion: The applicant noted that the autopsy was performed in the UK, and they expect that the report will be completed by the end of April or early May. The timing of the autopsy report is controlled by the coroner. With regard to the biodistribution report, they have completed the DNA and protein studies and are now in the process of reviewing the data and preparing the reports. RNA studies were not performed due to the condition of the tissue samples. The applicant will provide a biodistribution report by the April 10th due date.

2. Discussion of Minor Review Issues 15 Minutes

CMC

- a. In information request number 38, sent on March 6, 2019, we asked you to provide data demonstrating the amount of time required to thaw the 9-vial kit. In submission number 43, received on March 11, 2019, you agreed to perform a study to determine the thaw time of the 9 × 8.3 mL vial kit at both room temperature and refrigerated temperature, and to update the thaw times in the package insert accordingly. Please submit the study report and the updated package insert to the BLA.

Discussion: The applicant states they plan to submit the requested information to the BLA by April 10th.

- b. The (b) (4) assay (SOP-137) lacks a positive control for (b) (4) activity. In submission number 36 (February 15, 2019), you provided a plan to develop an appropriate positive control method and to add this control method to SOP-137. Please provide the method development report and the updated SOP-137 to the BLA.

Discussion: The applicant states they plan to submit the requested information to the BLA by April 10th.

- c. The (b) (4) assay (SOP-328) does not include an assay validity criterion for each run to ensure that the (b) (4) of the reference standard falls within an appropriate range. In submission number 28 (January 25, 2019), you agreed to update SOP-328 to incorporate this assay validity criterion and to update the BLA. Please provide the updated SOP-328 to the BLA.

Discussion: The applicant states they will try to submit the requested information to the BLA by April 10th, but the assay is performed by a contractor and there is a risk for a late submission. FDA acknowledged their response and asked that if the information was not submitted by April 10th that they provide a summary of the status and the expected timeframe for submission.

- d. In information request number 21, sent on January 7, 2019, we asked you to provide data demonstrating the robustness of (b) (4) lot release assays. In submission number 38 (February 19, 2019), you replied that you will evaluate the robustness of the (b) (4) assay and that you will submit the additional validation data for this assay to the BLA. You also stated that it is not necessary to evaluate robustness of the (b) (4) assay or the (b) (4) assay. We disagree that it is not necessary to validate the robustness of the (b) (4) assay and (b) (4) assay. Please provide data demonstrating the robustness of the following assays:

- i. (b) (4)

Discussion: The applicant stated that robustness validation results are on target to be submitted by the April 10th due date for the (b) (4) assay and the (b) (4) assay. For the (b) (4) assay, the applicant states that the submission of this data may be delayed, and they will provide an update as soon as possible.

- e. We acknowledge the data in submission number 40 (February 25, 2019) that demonstrates (b) (4) and undetectable concentrations of (b) (4) in (b) (4). You agreed in submission number 40 to provide an additional process validation report to support that the manufacturing process has sufficient clearance capacity to remove (b) (4) to a safe level for humans. Please provide this additional validation report and more detailed information on the (b) (4) assay procedure and assay qualification.

Discussion: The applicant stated that the assay is proprietary to the contractor and developing a new assay could take months. FDA acknowledged the applicant's response and stated that FDA is not requiring a lot release assay for (b) (4) at the current time. The applicant should provide the requested information to the BLA.

- f. On February 14, 2019, FDA inspectors asked you to develop procedures to ensure that managed documents are promptly updated in regulatory submissions, when needed. You agreed to update your procedures and to submit the updated procedures to the BLA, along with any managed documents that need to be updated in the BLA. Please update the BLA accordingly.

Discussion: The applicant stated the information requested is on track for a submission date of April 10, 2019.

- g. On February 7, 2019, FDA inspectors noted that frozen materials are not physically separated in freezers. You agreed to separate frozen materials by adding (b) (4) on freezer shelves. You agreed to implement these (b) (4) by March 31, 2019 and to submit confirmation to the BLA. When this change has been implemented, please provide confirmation to the BLA that frozen materials are physically separated in freezers.

Discussion: The applicant stated the information requested is on track for a submission date of April 10, 2019.

- h. The acceptance criterion for (b) (4) testing of (b) (4) is "tested." In submission number 38 (February 19, 2019), you indicated that all parent lots of (b) (4) that have been used in manufacturing have tested negative for (b) (4) and that the parent lots must test negative before they are used in manufacturing. Please update the acceptance criteria for the (b) (4) test to "negative."

Discussion: The applicant noted that it would be difficult to update the specification to read negative. They stated they are currently working

through their options to manage this and will provide a response by April 10th. The applicant stated that the (b) (4) manufacturing process contains steps that are validated to inactivate viruses. FDA noted that this process validation information has not been submitted to the BLA. The applicant agreed to submit this information.

- i. We agree with the addition of (b) (4) supplier. However, we do not agree that PLAN-296 is sufficient, on its own, to qualify additional new (b) (4) suppliers. Please acknowledge that any future (b) (4) suppliers will be submitted as a PAS.

Discussion: The applicant stated they are reviewing additional suppliers and agree to submit as a PAS if they add additional suppliers in the future. The applicant stated the information requested is on track for a submission date of April 10th.

- j. In information request #29, sent on January 17, 2019, we asked you to qualify the mycoplasma (b) (4) method for the (b) (4). In submission number 26, received on January 23, 2019, you agreed to perform this qualification and to submit the qualification report by March 29, 2019. Please submit this qualification report to the BLA.

Discussion: The applicant stated that they will provide the response by April 10th.

****Update:** The mycoplasma assay validation report was received by FDA and is under review.

3. Inspections **1 Minute**

Inspections are complete. A Final recommendation is pending at this time.

Discussion: The sponsor stated that they are on track to complete all 36 CAPA reports and confirmed that they received the IR from CBER/DMPQ regarding incomplete 483 responses.

4. Additional Applicant Data **0 Minutes**

No discussion.

5. Information Requests **3 Minutes**

Outstanding IRs

Information Request # 39 due March 22, 2019

Information Request # 40 due March 18, 2019

Information Request # 42 due March 28, 2019

Information Request # 43 due March 21, 2019

Discussion: FDA acknowledged receipt of IR#'s 39, 42, 43 and 44. The applicant acknowledged receipt of IR 45 and will provide a response by the April 10th due date. The applicant also noted that a response to IR 40 will be submitted by April 1st.

6. Discussion of Upcoming Advisory Committee Meeting **1 Minute**

An Advisory Committee meeting is not planned

7. Risk Management Actions (e.g., REMS) **1 Minute**

We have not identified any issues related to risk management. We do not believe that a risk management action (e.g., REMS) is needed at this time.

8. Postmarketing Requirements/Postmarketing Commitments **2 Minutes**

As indicated in section 2 comment *a*, a PMC will be necessary to provide additional DS and DP stability data.

Based on currently-available information, we do not anticipate a need for a PMR.

Discussion: The applicant acknowledged that a PMC will be necessary. FDA raised the possibility of removing the (b) (4) assay from ongoing stability studies and adding the (b) (4) assay to ongoing stability studies, subject to further discussion.

9. Major Labeling Issues **15 Minutes**

- a. Dosage and Administration section: We do not agree with the proposed weight-limit on dosing. We strongly recommend that the dose should be 1.1×10^{14} vg/kg without weight restriction. However, we recommend including the following:
 - i. Administration of ZOLGENSMA to premature neonates before reaching full term may adversely affect neurological development, due to the concomitant treatment with corticosteroids. Therefore, delay administration of ZOLGENSMA until the corresponding full term age is reached.

Discussion: FDA recommended that the product should not be administered to premature neonates due to the risk of development issues from corticosteroids. With regard to the high weight range, the benefit/risk profile has not been established. The applicant agreed that there will not be “flat dosing” above 13.5 kg, but they still strongly prefer to have the weight range restricted to 2.6 kg to 13.5 kg. FDA did not agree to the weight restrictions. The applicant asked for clarification regarding the definition of “infantile-onset SMA,” and FDA indicated that this term was

intended to provide flexibility and was not intended to restrict the indication to only symptomatic patients.

FDA stated that FDA edits to the package insert will likely be completed soon and then sent to the applicant. FDA suggested that the weight range topic be revisited in a teleconference after the applicant receives the FDA revisions to the package insert.

- b. Following the Indication Statement: Limitation of Use: The benefit / risk profile of ZOLGENSMA in patients with advanced SMA (e.g., complete paralysis of limbs, permanently ventilator-dependent) is not established.

Discussion: The applicant agreed with this statement.

10. Review Plans **2 Minutes**

Review is ongoing based on information received. The final determination will be made after receipt of outstanding information. Responses to all review issues listed in this late cycle meeting agenda should be submitted to the BLA no later than **Wednesday April 10, 2019.**

11. Applicant Questions **0 Minutes**

12. Wrap-up and Action Items

- a. All outstanding requests will be responded to by April 10, 2019. However there are a few requests that will be delayed and the applicant stated they would provide an update on the status of the outstanding requests on April 10th.
- b. The applicant will follow up with DMPQ to discuss the suitability of their Container Closure Integrity Test method as outlined in information request 45.

This application has not yet been fully reviewed by the signatory authorities, Division Directors and Review Committee Chair and therefore, this meeting did not address the final regulatory decision for the application.