



Our STN: BL 125694/0

**BLA FILING NOTIFICATION**

November 28, 2018

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

Dear Dr. L'Italien:

This letter is in regard to your Biologics License Application (BLA) received on October 1, 2018, under section 351(a) of the Public Health Service (PHS) Act for onasemnogene abeparvovec.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Under 21 CFR 601.2(a), we have filed your application today. The review classification for this application is **Priority**, the review action due date is May 31, 2019. This acknowledgment of filing does not mean that we have issued a license, nor does it represent any evaluation of the adequacy of the data submitted.

This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA). Refer to <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserfee/ucm446608.htm>.

We are reviewing your application according to the processes described in the guidance for review staff and industry: *Good Review Management Principles and Practices for PDUFA Products* at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079748>. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). We plan to hold our internal mid-cycle review meeting on January 11, 2019. Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by May 2, 2019.

We are not currently planning to hold an advisory committee meeting to discuss this application.

While conducting our filing review, we identified the following potential review issues:

Chemistry, Manufacturing, and Controls (CMC)

1. The stability data for the storage of your drug product (DP) at  $\leq -60^{\circ}\text{C}$  are inadequate. Only (b) (4) months of stability data have been submitted for the commercial presentation. Please provide additional stability data.
2. 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.
3. 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.
4. Please note that, per 21 CFR 610.14, identity testing is required after all labeling operations are completed. Please confirm that you are performing identity testing after labeling.
5. Plans for continued process verification (CPV) are inadequate. Please submit detailed CPV plans to the BLA.
6. Your BLA does not contain sufficient information about (b) (4) manufacturing at the (b) (4) manufacturing site. Please clarify how you ensure the purity of your (b) (4) manufactured at (b) (4) and assess (b) (4) for cross contamination from other (b) (4) manufactured at the same facility. This information should include evidence such as:
  - a. A description of the quality unit at (b) (4),
  - b. A list of all raw materials and manufacturing equipment used to make the (b) (4) and denote the materials and equipment that are (b) (4)
  - c. Cleaning validation studies for equipment or raw materials which are (b) (4).
7. The data that you have provided for method SOP-263 (analytical (b) (4)) are insufficient to demonstrate the accuracy of this method. We are unable to evaluate the accuracy of this method because the extinction coefficient for (b) (4) capsids may have been determined using a (b) (4) of (b) (4) capsids. In RPT-779, the (b) (4) capsid extinction coefficient was determined using only a (b) (4) capsid sample (PRO 417), and PRO 417 was found to have a substantially higher extinction coefficient at (b) (4) than the DP. This finding indicates either that PRO 417 contains (b) (4) substances that are absent from the DP, or that PRO 417 has much higher (b) (4) than the DP does. Please investigate and (if appropriate) take corrective action to ensure that SOP-263 produces accurate results. Please evaluate the possibility that PRO 417 might be

contaminated with a (b) (4). Refer to (b) (4) (2002), (b) (4) Journal 1(3):57-61 for an illustrative example.

#### Facility

8. The submission does not contain certifications that drug product release testing facilities are ready for inspection.
9. The submission does not describe reprocessing (Drug Product sterile (b) (4) to the filling) steps in detail and does not contain the reprocessing validation study reports.
10. The submission does not contain shipping validation study reports.

#### Clinical

11. Based on our discussion at the pre-BLA meeting in July 2018, you agreed to provide an updated efficacy dataset from the ongoing study, AVXS-101-CL-303, and safety and efficacy data from your Long-Term Follow-up Study of subjects treated in Study AVXS-101-CL-101, with the required 4-month safety update (due February 1, 2019) following the BLA submission. We would like review as much safety and efficacy data as possible from both studies. Therefore, a data cutoff date close to the 4-month BLA safety update, such as a cutoff date of early January, is strongly recommended.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application. Following a review of the application, we shall advise you in writing of any action we have taken and request additional information if needed.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the indication you are requesting has orphan drug designation PREA does not apply.

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

Sincerely,

Kimberly Benton, PhD  
Associate Director for Regulatory Management  
Office of Tissues and Advanced Therapies  
Center for Biologics Evaluation and Research