

T 910.16: FILING MEETING AGENDA/SUMMARY

Application number: 125694/0
Product name: onasemnogene abeparvovec
Proposed Indication: Treatment of Spinal Muscular Atrophy (Type I)
Applicant: AveXis, Inc.
Meeting date & time: November 15, 2018, 10:00 AM – 11:00 AM
Committee Chair: Andrew Byrnes, PhD
Meeting Recorder/RPM: Candace Jarvis

Link to submission:

(b) (4)

Link to sharepoint site: (b) (4)

Background: Spinal muscular atrophy (SMA) is a genetic disease caused by insufficient expression of SMN protein, which leads to death of motor neurons. Onasemnogene abeparvovec is a non-replicating gene therapy vector that encodes the DNA sequence of SMN protein. This product is intended for treatment of SMA type 1 and is administered as a single intravenous injection. The mechanism of action (based on preclinical studies) is that the vector causes expression of SMN protein inside cells, which greatly improves survival of motor neurons. This product is also currently under investigation via other routes of administration (b) (4), but these will not be considered in this license application.

Table 1: Review Committee and Discipline Filing Decision Summary

Discipline/Organization	Name [with credentials (not title)]	Attended meeting	Fileable	RTF	Deficiencies Identified
Regulatory Project Manager (RPM)	Candace Jarvis	X			
Chair/CMC Reviewer and Inspector	Andrew Byrnes, PhD	X	X		Yes
Division Director/Deputy	Raj K. Puri, MD, PhD/Steven Oh, PhD	X	X		
Office Director/Deputy	Wilson Bryan, MD/Rachel Anatol, PhD	X	X		
Clinical Reviewer	Mike Singer, MD	X	X		Yes
Toxicology Reviewer	Feorillo Galivo, MD, PhD	X	X		No

Discipline/Organization	Name [with credentials (not title)]	Attended meeting	Fileable	RTF	Deficiencies Identified
CMC Reviewer (OTAT/DCGT)	Angela Whatley, PhD	X	X		Yes
CMC Reviewer (OCBQ/DBSQC)	Hyesuk Kong, PhD	X	X		Yes
OCBQ/DMPQ RPM	Amanda Trayer				
OCBQ/DMPQ Reviewer, Lead Inspector	Wei Wang, PhD	X	X		Yes
OCBQ/DMPQ/PRB Reviewer	Cheryl Hulme				
OCBQ/APLB Reviewer	Sonny Saini, PharmD	X	X		No
OCBQ/BIMO Reviewer	Erin McDowell	X	x		
OCBQ/DBSQC /LIB Reviewer	Varsha Garnepudi, PhD	X	X		Yes
OCBQ/DMPQ/Inspector, Consult Reviewer, Team Lead	Deborah Trout, PhD	X			Yes
Statistical Reviewer of clinical data	Xue (Mary) Lin, PhD	X	X		No
Postmarketing Safety Epidemiological Reviewer	Deborah Thompson, MD, MSPH, FACPM	X	X		No
Labeling Reviewer	Oluchi Elekwachi,				
Consult Reviewer(s)	Rainer Paine, MD, CDER/OND/ODEI/DNP				
Other Attendee(s)					
OTAT/DRPM	Ramani Sista, PhD	X	X		
OTAT	Kimberly Benton, PhD	X	X		
OTAT/DRPM	Ebla Ali Ibrahim, MS	X	X		
OTAT/DCEPT	Lei Xu, MD	X	X		
OTAT/DCGT	Denise Gavin, PhD	X	X		
OTAT/DCEPT	Iwen Wu, PhD	X	X		
OCBQ/DMPQ	Jay Eltermann	X	X		
OTAT/DRPM	Leyish Minie	X	X		
OBE/DE	Manette Nin	X	X		
OTAT/DCEPT	Ilan Irony	X	X		

Discipline/Organization	Name [with credentials (not title)]	Attended meeting	Fileable	RTF	Deficiencies Identified
OTAT/DCEPT	Tejashri Purohit-Sheth	X	X		
OBE/DE	Deepa Arya	X	X		

REGULATORY CONCLUSIONS / DEFICIENCIES

1. Does the application, on its face, appear to be suitable for filing or is the application unsuitable for filing and will require a RTF letter?

All attendees indicated that the application is suitable for filing.

2. If fileable, list any substantive deficiencies or issues that have significant impact on the ability to complete the review or approve the application:

a. CMC- Andrew Byrnes, Angela Whatley: - Fileable

- The stability data for storage of drug product (DP) at $\leq -60^{\circ}\text{C}$ are inadequate. Only 3 months of stability data have been submitted for the commercial presentation. Please provide additional stability data.
- DP shipping validation studies have not been completed. Please complete these studies and submit the shipping validation report to the BLA. Please note that any changes to the secondary packaging configuration may necessitate additional shipping validation studies (operational qualification and performance qualification).
- 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.
- 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.
- 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.
- Plans for continued process verification (CPV) are inadequate. Please submit detailed CPV plans to the BLA.

7. 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)

In addition, (b) (4) device-related issues were discussed:

1. Genetic assays that are used to help diagnose SMA 1. The BLA contains no information on these assays, which are lab-developed tests being performed at CLIA-certified labs. The landscape is changing due to the gradual introduction of newborn screening for SMA. Nusinersen was recently approved for treatment of SMA without a companion diagnostic device. Committee members plan to discuss this issue in a separate meeting.
2. Anti-AAV9 antibody assays that are used to detect pre-existing antibodies against the vector that may inhibit vector activity. Subjects in all studies were screened with a lab-developed ELISA test and were only enrolled if the antibody titer was 1:50 or less. The BLA contains information on this assay, including a SOP and validation report, and the CMC team will review these. The draft PI has a statement that safety and efficacy has not been established in patients with antibody titers above 1:50, plus a statement that patients should be tested for the presence of antibodies prior to treatment. Additional information is being requested regarding plans for antibody testing after licensure.

b. DBSQC- Hyesuk Kong, Varsha Garnepudi - Fileable

1. A lot release protocol template has not been submitted, possibly because the Applicant does not understand our requirements. DBSQC will include this issue in the filing letter and will send an IR with more detailed instructions and an example template.

c. DMPQ- Wei Wang, Deborah Trout-Fileable

1. The submission does not contain certifications indicating that drug product release testing facilities are ready for inspection.

2. The submission does not describe (b) (4) (Drug Product (b) (4) steps in details and does not contain the (b) (4) validation study reports.
3. The submission does not contain shipping validation study reports.
4. In addition, the secondary packaging for the product was discussed. Based on the weight of each patient, AveXis will assemble a “kit” in a secondary carton that can hold up to (b) (4) of DP together with a single PI. Because each carton may contain multiple different DP batches, DMPQ is not certain whether this packaging configuration is compliant with cGMP regulations. Because of the potential for this issue to cause serious delay to the BLA, DMPQ will reach a final determination (which will include consultation with APLB) before the filing letter is sent out. If the secondary packaging is unacceptable, the Applicant will be notified in the filing letter that they must change the packaging.

d. Clinical- Mike Singer: -Fileable

1. The filing letter will include a request for certain missing information: Financial Disclosure forms, coding dictionary, case report forms. These items will also be requested in an IR.
2. Currently, the application does not contain much information on subjects in the phase 3 trial in subjects with SMA1 (AVXS-101-CL-303) due to a cutoff date of May 8, 2018. The clinical team will ask the Applicant (in the filing letter) to include as much updated data on efficacy and safety of the ongoing trial as possible about subjects in study AVXS-101-CL-303 in the 4 month safety/efficacy update. The cutoff should be as late as possible (e.g., early January, 2019).

e. Statistical- Xue (Mary) Lin: -Fileable

1. The review is ongoing; Two IRs have been sent to the sponsor; No pending IRs

a. Toxicology- Feorillo Galivo: -Fileable

1. Received IR responses from the sponsor, there is still one outstanding.

f. Epidemiology- Deborah Thompson: - Fileable

1. No deficiencies identified. One IR sent to sponsor, response is pending.

g. BiMO- Erin McDowell - Fileable

1. The AVXS-101-CL-101 study site (Nationwide Children’s Hospital) was already inspected, no concerns. EMA will inspect Nationwide in January. In order to determine whether more inspections will be needed, the Applicant needs to provide a more comprehensive listing of where subjects in the phase 3 studies

were treated. An IR was sent requesting this information, but the response is past due.

h. APLB- Sonny Saini: - Fileable

1. DMPQ will coordinate with APLB about issues with the secondary packaging.

3. If RTF, list any substantive deficiencies or issues that would make this application unsuitable for filing: [If none, indicate "NA"]

NA

FILING MEETING DISCUSSION, IF FILED:

4. Indicate any comments on the status of the proprietary name review (PNR).

The PNR review of ZOLGENSMA has been accepted and the PNR- Accepted letter was issued on 11/6/18.

5. Indicate whether the product sh/would be subject to lot release, surveillance, or exempt from lot release. Verify sample availability.

We will perform lot release protocol review only

6. Confirm review schedule of this application. [Standard Review, Priority Review, or Expedited Review]

The attendees confirmed that this submission will be conducted under Priority Review.

7. Indicate the decision regarding the need for an Advisory Committee.

This will be discussed at a later date, but before the filing deadline.

8. Indicate whether the submission triggers PREA; if yes, a PeRC meeting is needed.

This submission does not trigger PREA as they have Orphan Drug Designation

9. Is a comprehensive and readily located list of all clinical sites included or referenced in the application?

This will be followed up with an IR

10. Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?

Yes

11. Indicate any updates since the First Committee Meeting on pre-license inspection, pre-approval inspection, or BIMO sites requiring inspections (Is the establishment(s) ready for inspection?)

BIMO – Need more information on sites for the phase 3 studies

DMPQ – AveXis has one manufacturing facility in (b) (4). DMPQ will arrange dates for inspection. AveXis also operates a testing facility in (b) (4) that performs potency assays for release of drug product. This site has no previous inspection history, and DMPQ and DCGT will request the district office to arrange an inspection.

12. If the application is affected by the Application Integrity Policy (AIP), has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A

13. Is the product an Original Biological Product or a New Molecular Entity (NME) for an NDA?

Original Biological Product

FOR APPLICATIONS IN THE PDUFA PROGRAM (NME NDAs/Original BLAs), IF FILED

14. Confirm that any late submission components were submitted within 30 days. List any late submission components that arrived after 30 days.

N/A

15. Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?

Yes

ADMINISTRATIVE DETAILS, IF FILED:

16. Review the Milestone Schedule and indicate if there are any issues with the schedule. Note: This is a confirmation to capture any changes made since the First Committee Meeting.

Filing Meeting	November 15, 2018
Applicant Orientation Mtg	November 30, 2018
Filing Action	November 30, 2018
Team Meeting	December 19, 2018
Internal Mid-Cycle Mtg	January 11, 2019
Mid-Cycle Communication	by January 31, 2019
Late-Cycle Meeting Internal	TBD
Late-Cycle Communication	by March 17, 2019
PMC Study Target	April 18, 2019
Labeling Target	April 18, 2019
***First Action Due	May 17, 2019
Proprietary Name Review	December 30, 2018 (completed)

The internal target date for sending the filing letter will be November 27, 2018.
The Action Due date that will be communicated to the Applicant in the filing letter will be June 1, 2019.

The internal First Action Due date of May 17, 2019 will be subject to revision (either earlier or later) dependent on the state of the review, and will be discussed at the internal mid-cycle and internal late-cycle meetings.

17. eMRP 3.0- Has launched. Please ensure that there are no outstanding tasks pending.