

Mid-Cycle Meeting 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 11, 2019, 12:00PM-1:00PM
Committee Chair: Andrew Byrnes, PhD
RPM: Candace Jarvis

Link to submission:

(b) (4)

Link to sharepoint site: (b) (4)

Attendees:

Discipline	Name [with credentials (not title)]	Attended meeting?
Regulatory Project Manager (RPM)	Candace Jarvis	X
Chair/ CMC Inspector / CMC Reviewer	Andrew Byrnes, PhD	X
Clinical Reviewer	Mike Singer, MD	X
CMC Reviewers	Angela Whatley, PhD Hyesuk Kong, PhD	X X
Toxicology Reviewer	Feorillo Galivo, MD	X
OCBQ/DMPQ RPM	Amanda Trayer	X
OCBQ/DMPQ Reviewer /Lead Inspector	Wei Wang, PhD	X
OCBQ/DMPQ/Inspector/Consult Reviewer, Team Lead	Deborah Trout, PhD	
OCBQ/DMPQ/PRB Reviewer	Cheryl Hulme	
Statistical Reviewer of clinical data	Xue (Mary) Lin, PhD	X
Postmarketing Safety Epidemiological Reviewer	Deborah Thompson, MD, MSPH, FACPM	X
OCBQ/APLB Labeling Reviewer	Sonny Saini, PhD	X
OCBQ/BIMO Reviewer	Erin McDowell	X
OCBQ/DBSQ/LIB Reviewer	Varsha Garnepudi,	X
Consult Reviewer(s)	Rainer Paine, MD, CDER/OND/ODEI/DNP	
Other Attendee(s)		
OTAT/DCGT	Steven Oh, PhD	
OTAT/DRPM	Ramani Sista, PhD	X
OTAT	Kimberly Benton, PhD	X
OTAT	Wilson Bryan, MD	X
OTAT/DCGT	Raj Puri, PhD	X

Discipline	Name [with credentials (not title)]	Attended meeting?
OTAT/DCEPT	Lei Xu, MD	X
OTAT/DCGT	Denise Gavin, PhD	X
OTAT/DCEPT	Iwen Wu, PhD	X
OTAT/DCEPT	Ilan Irony, MD	X
OTAT/DCEPT	Tejashri Purohit-Sheth, MD	
OBE/DB	Shiowjen Lee, PhD	
OTAT	Rachael Anatol, PhD	X
OTAT/DRPM	Lori Tull	
OCBQ/DBSQC/QAB	Suzanne Carter	X
OGROP/ORA/OMPTO/OBPO/BPIS	Travis Chapman	X
OMPT/CBER/OBE	Manette Niu	X
OMPT/CBER/OBE/DE/PB	Wambui Chege	X
OCBQ/DMPQ	Laurie Norwood	X
OTAT	Ann Rowzee	X

Discussion Summary:

This is the Mid-cycle internal meeting to discuss the status of the review for this original BLA. We will discuss any outstanding review issues as well as determine the agenda for the Mid-Cycle Communication with the sponsor.

Report and Discuss:

1. Reviewer Reports.

DCGT

a. Andrew Byrnes, Angela Whatley

i. Substantive issues to report:

1. The removal of a process-related impurity – (b) (4) – has not been evaluated by the Applicant, and it is unknown whether or not (b) (4) is present in 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 (response due February 15).
2. Multiple problems with the total protein concentration in DP:
 - 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 acceptance criterion for protein is too wide. The Applicant was previously informed of this more than a year ago, under IND 15699.

- d. Information in the BLA shows that some lots have such high protein concentration (relative to the phase I lot from NCH) that it calls into question whether all of the AveXis lots are comparable to the NCH lot. This is new information that was not available at the time of the pre-BLA meeting, when we agreed that the AveXis and NCH lots were comparable. We requested responses to these issues in IR #23 (response due February 15).
3. The (b) (4) assay has major flaws in design and validation. This is a critically important assay to measure the quality of the product, because only (b) (4). Consult reviews for this assay were obtained from CDER/OBP in December, 2017 (under IND 15699) and again in December, 2018 (under the BLA). 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 from the Applicant in the filing letter and in IR #17 (response due January 22).
4. Only a few months of stability information have been submitted for the (b) (4) for the DP commercial presentation. Additional information will be submitted within the next 2 months, but this update will only include stability data through 9-12 months. We may decide to approve a shorter shelf life than the (b) (4) that the Applicant has requested. A PMC will be necessary for the Applicant to provide (b) (4) of stability data in order to support the requested (b) (4) shelf life for (b) (4) DP.
5. The manufacturing process parameter classification and operating ranges are not adequately justified, and the PPQ studies did not vary the process parameters sufficiently to justify the operating ranges. We requested additional information in IR #26 (response due January 15).
6. The applicant informed us in the initial BLA submission that shipping validation study reports would be submitted late. Although we had not agreed to late submission of this component, we decided to file the BLA. The lack of shipping validation was listed as a deficiency in the filing letter. The BLA states that shipping stability data will be ready for review by the time of the inspection.
7. 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 (response due February 15).

ii. Status of the review:

All assigned sections of the BLA have been reviewed. There are numerous unresolved CMC issues that are currently awaiting responses from the Applicant. Some of these unresolved issues are serious.

The pre-license facility inspections have not taken place.

- AveXis (b) (4) will be inspected (b) (4)
- The inspection of AveXis (b) (4) has not yet been scheduled but is anticipated to take place in (b) (4)

iii. Target date of review completion:

Primary discipline review will be ready for supervisor review by the internal late-cycle meeting (March 7), except for:

- Information requests that the applicant has not responded to or has not completely resolved.
- New matters that may arise during the AveXis (b) (4) and AveXis (b) (4) inspections, and cannot be immediately resolved.

DMPQ

a. Wei Wang

i. Substantive issues to report:

Information deficiency in Reprocessing at the AVXS-101 Drug Product manufacturing process was included in the filing letter. The sponsor's response is not received yet.

ii. Status of the review:

1. All assigned sections of the BLA have been reviewed, Review memo preparation is WIP. The Inspection Waiver Memo was uploaded to EDR for the AveXis DP release testing facilities (which have satisfactory GMP inspection outcomes from recent FDA Inspections). The Facility Table was sent to Jeffrey McGuire to enter the facility information into RMS-BLA.

The pre-license inspections of the AveXis (b) (4) facility (FEI: (b) (4)) will be performed during (b) (4)

2. Outstanding Information Request:

- a) Regarding the Patients' weight-dependent dosing: in STN 125694/0, the patients' weight range was stated as (b) (4) – 8.5

- kg in Section 2.2, or as 2.6 – 8.5 kg in Section 2.3, and in Slides (received 12/17/2018) as 2.6 – 8.5 or > 8.5 kg.
- b) Air Flow – In the Air Pressurization Plan (RG0.07A, Figure 6), Air Flow was illustrated from the Fill Suite (b) (4) out through (b) (4) and through (b) (4). However, the air pressures indicate that air flow direction is from (b) (4) into the Fill Suite. Air Flow from (b) (4) into the Fill Suite (b) (4) appears to be an issue. Please clarify this information discrepancy. Please clarify if doors of the (b) (4) may be open at a same time.
 - c) Please clarify if (b) (4) air (100% fresh air) is used. If not, please provide justifications.
 - d) Based on diagrams provided in Section 3.2.A.1. Facilities and Equipment – Diagrams of STN 125694/0, Cleanroom areas ((b) (4) served by (b) (4) seemed to be a standalone manufacturing unit with different controls of Personnel and Material Flows compared with flows in manufacturing cleanroom areas (such as (b) (4). Please clarify if cleanroom areas served by (b) (4) are used for AVXS-101 (b) (4) DP commercial manufacturing activities.
 - e) In Section 3.2.A.1. Facilities and Equipment – Diagrams of STN 125694/0, Bookmarks RG0.05, RG0.05A, RG0.05B, RG0.07 and RG0.07A did not match the actual Sheet Numbers of these diagrams. Product Flow information was incomplete. Please update the Section with correct and complete flow diagrams.
 - f) The (b) (4) serving the (b) (4) was not indicated in Table 4 “Cleanrooms, Environmental Classifications, and (b) (4)” of section 3.2.A.1 Facilities and Equipment of STN 125694/0.
 - g) Please indicate the air pressure for the room number (b) (4)

iii. Target date of review completion:

Primary discipline review will be ready for supervisor review by the internal late-cycle meeting (25Jan2019), except for information requests that the applicant has not responded to or has not completely resolved.

DBSQC

- a. Hyesuk Kong
 - i. Substantive issues to report:

1. No substantive issues at this time that would impact approval of this submission
 - ii. Status of the review:
 1. Review of primary material and information received from the first IR have been completed.
Drug Substance – (b) (4) Test Methods
Drug Product – Sterility and Bacterial Endotoxin Test Methods
 2. No outstanding IRs for this submission
 - iii. Target date of review completion
 1. Beginning of February, 2019
- b. Varsha Garnepudi
- i. Substantive issues to report:
 1. None at this time
 - ii. Status of the review:
 1. Review of these items are not complete to date:
 - a) *A lot release protocol template has been requested through an IR (1/4/2019).*
 - b) *The Laboratory Quality Product Testing Plan (TP) has been initiated.*
 2. IR for a revised lot release protocol template was sent on 1/4/19
 - iii. Target date of review completion
 1. January 25, 2019

Pharmacology/Toxicology

- a. Feorillo Galivo
 - i. Substantive issues to report:
 1. No substantive issues identified thus far
 - ii. Status of the review:
 1. *Review of nonclinical studies are ongoing*
 2. 2 outstanding IRs
 - a) 12/20/18 – Requested explanation for incongruent data from 2 mouse toxicology studies and biodistribution data for Subject (b) (6). Response from applicant is expected by 1/21/2019
 - b) 1/9/19 – Request for scientific justification for not conducting Developmental and Reproductive Toxicity (DART) testing
 - iii. Target date of review completion

1. Review memo will be completed and submitted to the Branch Chief by February 14, 2019 and submitted to the Division Director by March 14, 2019.

Clinical

a. Mike Singer

i. Substantive issues to report:

1. No major issues identified

2. Issues regarding indication

- a) The sponsor proposes the indication for the product as “treatment of pediatric patients with SMA (b) (4) [REDACTED] A problem with this proposed indication relates to how SMA (b) (4) would be defined. Initiating treatment as soon as possible is desirable to minimize loss of motor neurons. This issue could have a significant clinical impact, by denying or delaying treatment to patients in need.

Historically, SMA types have been defined by phenotype: Type 1 patients usually develop symptoms by age six months, are unable to sit independently; Type 2 patients show symptoms by 6-18 months, and are unable to stand; Type 3 patients generally manifest after age 18 months and can stand or walk, but often require assistance. Phenotype typically can be predicted by genetic testing to identify the number of copies of the *SMN2* gene: Type 1 patients generally have two copies, Type 2 patients three copies, and Type 3 patients three or four copies.

Correlation of phenotype and genotype, however, is not absolute: for example, three copies of *SMN2* have been detected in Type 1 patients, as well as in Type 3 patients.

Defining SMA Type 1 by phenotype could delay treatment, whereas basing the definition on genetic testing may cause treatment to be denied to patients who would benefit from it.

We therefore suggested to the sponsor the indication “for infantile-onset SMA,” to enable physicians to determine treatment based on a combination of examination findings, genetic testing, and clinical judgment.

3. Issues regarding weight limit

- a) The sponsor proposes both lower and upper limits on the weight of patients eligible for treatment based on their experience from the Phase 1 trial. Such a restriction would

exclude smaller or larger patients with infantile-onset SMA who otherwise would benefit from the product.

- ii. Status of the review:
 - 1. No outstanding IRs
 - 2. Review of financial disclosure information is not complete
 - 3. Will review the safety and efficacy update once submitted by the sponsor on February 1, 2019
- iii. Target date of review completion
 - 1. March 3, 2019

Statistics

- a. Xue (Mary) Lin
 - i. Substantive issues to report:
 - 1. No major deficiencies have been identified
 - ii. Status of the review:
 - 1. Safety data evaluation and part of efficacy evaluation review not complete
 - iii. Target date of review completion
 - 1. February 28, 2019

BiMO

- a. Erin McDowell
 - ii. Substantive issues to report:
 - 1. None to date
 - iii. Status of the review:
 - 1. No outstanding IRs
 - 2. BiMO inspections are pending
 - 3. Inspectional status and findings

Site	Study	#	Location	Inspection
001	AVXS-101-CL-101	15	Nationwide Children's Hospital	Pending
	AVXS-101-CL-303	3	Columbus, Ohio	
	AVXS-101-LT-001	11		
005	AVXS-101-CL-303	2	Boston Children's Hospital	Pending
			Boston, Massachusetts	
008	AVXS-101-CL-303	4	Stanford Neuroscience Health Center	Pending
			Palo Alto, California	
010	AVXS-101-CL-303	2	Nemours Hospital	Pending
			Orlando, Florida	

- iv. Target date of review completion
 - 1. Will be completed after all Establishment Inspection Reports (EIRs) are received and reviewed.

Epidemiology

a. Deborah Thompson

i. Substantive issues to report:

- 1. No major deficiencies have been identified.**
- 2. Current assessment of risk management issues:**

Assessment of Sponsor's Pharmacovigilance (PV) Plan

Important Identified Risk: Elevated Transaminases

Elevated liver transaminases were among the most common treatment emergent adverse events (TEAEs) related to AVXS-101 in clinical trials. Among subjects with elevated transaminases related to AVXS-101, aspartate aminotransferase (AST) values had a median of four times the upper limit of normal (ULN) (range two to 37 times ULN) and alanine aminotransferase (ALT) values had a median five times of ULN (range two to 35 times ULN). TEAEs involving elevated transaminases were managed by prednisolone prophylaxis and treatment (1-2 mg/kg/day with tapering doses) and resolved without clinical sequelae. None met criteria for Hy's Law. The sponsor indicates that elevated liver transaminases may be related to a T-cell immune response to the AAV9 vector.

Important Identified Risk: Transient Thrombocytopenia

In AVXS-101-CL-101, the sponsor reported that decreases from baseline in the mean platelet count were observed at multiple time points in subjects, but that decrease in platelet counts was mild ($>140 \times 10^9/L$ for all subjects at any visit) and not considered clinically significant. In AVXS-101-CL-303, one subject experienced a TEAE of thrombocytopenia related to AVXS-101, a grade 1 (mild) event (platelets decreased to $93 \times 10^9/L$ on study day seven; resolved on study day 19 without therapy). The sponsor indicates that the etiology for the transient thrombocytopenia is unclear, but it may be complement-mediated.

Important Potential Risk: Cardiac Adverse Events

Eight (53.3%) subjects in AVXS-101-CL-101 experienced elevations in cardiac Troponin I that met the pre-specified potentially clinically significant (PCS) criterion. Two (25%) of these eight subjects had elevated Troponin I prior to AVXS-101 infusion. The sponsor reported that none of the Troponin I elevations were considered clinically significant. All Troponin I values had either returned to normal range or no longer met the pre-defined PCS criterion by the end of the clinical trial. The sponsor notes that cardiac Troponin I levels in healthy newborns have an upper reference limit that is higher than in adults.

Additional cardiac study results reported for clinical trial AVXS-101-CL-101 included electrocardiograms (EKG) and echocardiograms. There were no consistent changes in QTc intervals and no persistent clinically significant EKG or echocardiogram findings.

Reviewer comment: The sponsor's proposed routine PV activities (including use of targeted follow-up questionnaires), routine risk communication, and routine risk minimization measures are adequate and appropriate based on the available safety data.

Missing Information: Off-Label Use

Off-label use may result in lack of an expected therapeutic effect. Zolgensma will be administered by healthcare professionals with experience in the management of SMA.

Missing Information: Long-Term Effect of Zolgensma Therapy

The sponsor proposes four long-term follow-up safety studies to help address the long-term safety and efficacy of Zolgensma therapy.

Reviewer comment: The three non-registry long-term follow-up studies proposed by the sponsor (AVXS-101-LT-001, AVXS-101-LT-002, AVXS-LT-003) all include five years of annual examination followed by ten years of annual queries of study subjects as recommended in *Guidance for Industry: Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events* (November 2006). The sponsor proposes to conduct follow-up in the one registry study for 15 years. Draft *Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products* (July 2018) indicates that replication-negative adeno-associated virus vectors generally present a lower risk of delayed adverse events and that long-term follow-up observations should be product specific with a duration of two to five years. The sponsor's proposal to address missing safety and efficacy information with routine PV and risk minimization activities and the proposed long-term studies is adequate.

3. There are no substantive issues to date from the epidemiology perspective that could prevent approval or impact the review timeline.

- ii. Status of the review:
 - 1. The review of the information received to date is complete
 - 2. The sponsor will be submitting a four-month safety data update by February 1, 2019.
 - 3. No outstanding IRs
- iii. Target date of review completion
 - 1. March 3, 2019

- 2. If the application will be discussed at an Advisory Committee (AC), review potential issues for presentation.

It has been determined that this file will not be discussed at an AC meeting.

- 3. Determine whether Postmarketing Requirements (PMRs), Postmarketing Commitments (PMCs), or a Risk Evaluation Mitigation Strategy (REMS) are needed.

At the current time, we do not anticipate any clinical PMR, clinical PMC or REMS.

As noted above, there will be at least one PMC for product stability data.

- 4. National Drug Code (NDC) assignments to product/packaging (excludes devices).

The NDCs will be reviewed and verified by DRPM

- 5. Proper naming convention.

The proper name for this product is onasemnogene abeparvovec. The suffix for the proper name is currently under review by APLB.

The proprietary name is ZOLGENSMA.

- 6. Status of inspections (GMP, BiMo, GLP) including issues identified that could prevent approval and the establishment inspection report (EIR).

Facility and site inspections are pending. See updates above from DCGT, DMPQ and BiMO.

Review

- 7. Major target and milestone dates from RMS/BLA. Discuss pending dates of targets and milestones (e.g. Late-Cycle meeting, Advisory Committee, labeling discussion).

Internal Mid-Cycle Meeting	11-Jan-2019
Mid-Cycle Communication with Sponsor	29-Jan-2019
Late-Cycle Meeting Internal	07-Mar-2019
Late-Cycle Meeting with Sponsor	15-Mar-2019
PMC Study Target	18-Apr-2019
Labeling Target	18-Apr-2019
Action Due Date	17-May-2019

8. Establish a labeling review plan and agree on future labeling meeting activities.

Labeling Discussion Meeting 22-Jan-2019

Proposed pairings and timeframes of meetings:

- a) Clinical, Epidemiology, Statistics, BIMO
 - a. The week of January 28th and February 4th
- b) CMC, DBSQC, DMPQ
 - a. The week of February 11th and 18th
- c) Pharm/Tox
 - a. The week of February 25th and March 4th
- d) Final Group Meeting
 - a. The week of March 4th

Confirm, as applicable

9. Components Information Table was obtained and notification was sent to the Data Abstraction Team (DAT) if discrepancies were found per *SOPP 8401.5: Processing Animal, Biological, Chemical Component Information Submitted in Marketing Applications and Supplements*. If not complete, indicate date it will be completed.

Dr. Ferro Bizec was assigned as a DAT reviewer on December 18.

10. New facility information is included in the application, requiring implementation of regulatory job aid (b) (4) [REDACTED]. If not complete, indicate date it will be completed.

This item has been completed.

11. Status of decisions regarding lot release requirements, such as submitting samples and test protocols and the lot release testing plan.

Currently under review, refer to update from Dr. Garnepudi above.

12. Unique ingredient identifier (UNII) code process has been initiated. See regulatory job aid (b) (4) for additional information.

The UNII code process was initiated on 12/18/19. Completion of this task is expected within 4 to 6 weeks.

13. PeRC presentation date is set, and the clinical reviewer has addressed waiver/deferral/assessment of the PREA decision.

Note: Remind the Review Committee that PeRC forms need to be submitted two weeks in advance of scheduled PeRC meeting.

Not Applicable

14.Action Items:

15. For applications subject to the PDUFA/BsUFA Programs:

- a. Reach agreement on information to be included in the Mid-Cycle Communication telecon with the Applicant (see section below).
- b. Reach agreement on dates for upcoming meetings such as the AC or Late - Cycle Meeting. **Note:** the RPM may choose to pre-populate these dates prior to the meeting.

Late-Cycle Meeting with Sponsor	15-Mar-2019
PMC Study Target	18-Apr-2019
Labeling Target	18-Apr-2019
*Labeling Meetings begin	22-Jan-2019

Mid-Cycle Communication Agenda/Summary

- *This section is intended to be CBER's internal agreement of what will be discussed in the Mid-Cycle Communication (MCC) Telecon with the Applicant. The Review Committee should come to agreement on the following items.*
- *The information should be completed in such a manner that it will serve as the basis of the Mid-Cycle Communication telecon agenda. Refer to (b) (4) [REDACTED] for additional information.*
- *During the MCC, the Review Committee may engage in detailed discussions on substantive review issues with the Applicant, as time permits, if the discussion could help facilitate the remainder of the review. CBER staff necessary for the appropriate dialogue should participate in the telecon and are expected to present their information during the telecon.*

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) [REDACTED] – has not been evaluated, and it is unknown whether (b) (4) [REDACTED] is present in the drug product (DP). (b) (4) [REDACTED] is known to be toxic by the i.v. route. We requested data on (b) (4) [REDACTED] removal in IR #23 (sent 1/7/19, response due 2/15/19).
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.
3. The analytical (b) (4) [REDACTED] assay has major flaws in design and validation. This is a critical assay to measure the quality of the product, because only (b) (4) [REDACTED]. 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).

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.
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.
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).
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*.
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).

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.

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.

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

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.

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.