



Our STN: BL 125700/0

**LATE-CYCLE
MEETING MEMORANDUM**

March 19, 2020

FKD Therapies, Oy
Attention: Elizabeth Wishart, B.Sc., MBA
Mapi USA, Inc.
2343 Alexandria Drive, Suite 100
Lexington, KY 40504

Dear Ms.Wishart:

Attached is a copy of the memorandum summarizing your February 19, 2020, Late-Cycle Meeting with CBER. This memorandum constitutes the official record of the meeting. If your understanding of the meeting [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 Zakaria Ganiyu at (240) 402-8329.

Sincerely,

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

Late-Cycle Meeting Summary

Meeting Date and Time: February 19, 2020 at 11:30 AM, EST
Meeting Location: FDA WO Campus – Bldg 71/Rm 1206
Application Number: BL 125700/0
Product Name: nadofaragene firadenovec
Indication: For the treatment of High-grade, Bacillus Calmette-Guerin (BCG) unresponsive non-muscle invasive bladder cancer
Applicant Name: FKD Therapies Oy

Meeting Chair: Ramjay Vatsan, PhD
Meeting Recorder (RPM): Zakaria Ganiyu, MS, MBA

FDA ATTENDEES

Ohenewaa Ahima, MD, CBER/OBE
Marie Anderson, MS, PhD, CBER/OCBQ/DBSQC
Rajiv Agarwal, PhD, CDER/OPQ/ONDP
Robert Aksamit, PhD, CBER/OTAT/DCGT
Kimberly Benton, PhD, CBER/OTAT
Wilson Bryan, MD, CBER/OTAT
Laronna Colbert, MD, CBER/OTAT/DCEPT
Christine Drabick, OCBQ/BIMO
Bradley Dworak, CBER/OCBQ/DMPQ
John Eltermann, RPh, MS, CBER/OCBQ/DMPQ
Laura Fontan, CBER/OCBQ/DMPQ
Zakaria Ganiyu, MS, MBA, CBER/OTAT/DRPM
Jiang Hu, PhD, CBER/OBE
Yuxia Jia, MD, PhD, CBER/OTAT/DCEPT
Carolyn Laurencot PhD, CBER/OTAT/DCGT
Jun Lee, PharmD, PhD, OCBQ/APLB
Wei Liang, PhD, CBER/OTAT
Ke Liu, MD, PhD, CBER/OTAT/DCEPT
Yen Phan, PhD, CBER/OCBQ/DBSC
Carolyn Renshaw, CBER/OCBQ/DMPQ
Anurag Sharma, PhD, CBER/OTAT/DCGT
Ramani Sista, PhD, CBER/OTAT/DRPM
Edward Thompson, OTAT/DRPM/BII
Lori Tull, CBER/OTAT/DRPM
Ramjay Vatsan, PhD, CBER/OTAT/DCGT
Xiaofei Wang, PhD, CBER/OTAT/DCEPT
Zhenzhen Xu, PhD, CBER/OBE/DB
Zhili Xu, MD, CBER/OTAT/DCGT

APPLICANT ATTENDEES

(b) (4)

Minna Karhinen

Anna-Kaisa Lentivarra

(b) (4)

Outi Näränen

(b) (4)

Dr. David Sawutz

(b) (4)

Robert Shaw

(b) (4)

Elizabeth Wishart

Operations Director, FVT (dialed in)

Regulatory Affairs Manager, QP, FVT (dialed in)

Responsible Director, Quality Director, QP, FVT (dialed in)

Chief Operating Officer, FKT Therapies Oy (dialed in)

Director, FVT

Mapi, Inc. (US Agent to FKT Therapies Oy)

BACKGROUND

STN BL 125700/0 was submitted on February 26, 2019, for nadofaragene firadenovec (ADSTILADRIN).

Proposed Indication: For the treatment of High-grade, Bacillus Calmette-Guerin (BCG) unresponsive non-muscle invasive bladder cancer

PDUFA Goal Date: May 1, 2020

In preparation for this meeting, FDA issued the Late-Cycle Meeting Materials on February 10, 2020.

DISCUSSION

1. Substantive Review Issues to be discussed during the LCM

The following substantive review issues have been identified to date:

a. Division of Manufacturing and Product Quality (DMPQ)

1. We have significant concerns with Finn Vector Oy's ability to consistently manufacture a quality product that complies with current good manufacturing practices (CGMPs). This was illustrated by the 11 observations listed on the FDA Form 483 that was issued on January 28, 2020, at the conclusion of the pre-license inspection (PLI)
 - a. The following issues illustrate the overarching concerns observed:
 - i. The Quality Unit is not sufficiently responsible for oversight of manufacturing and release of the drug substance (DS) and the drug product (DP).

MEETING DISCUSSION:

FDA informed FKD that remediations should be implemented properly and take into account any changes needed to the overall quality systems, not just the specific SOPs that needed to be revised. FDA also advised the applicant that a reinspection may be necessary in order to evaluate the changes made to the quality systems.

FKD confirmed that, as the highest priority, it will implement a series of updates to the Quality Management System and reinforce the Quality Unit's responsibility for full oversight of the manufacturing and release of the drug substance and drug product. FKD also stated that they are open to reinspection.

- ii. Good manufacturing practices were not followed during the production of the DS and DP lots manufactured to date.

MEETING DISCUSSION:

FKD confirmed that Drug Product PPQ batches are not for commercial release.

Revisions to procedures will be made to ensure all future commercial batches will be fully GMP compliant.

A risk/impact assessment is being prepared for the Drug Substance batches manufactured in 2019. This will evaluate issues raised in Form 483 and determine the impact of any GMP deficiency for each

batch. This assessment will establish if the batch can be released for manufacture into drug product and potentially commercial supply.

The issues raised during the pre-approval inspection concerning the aseptic filling will be fully addressed and solutions implemented prior to commencing any commercial drug product filling. This includes:

(b) (4)



FDA accepted the applicant's proposed remediations.

- iii. We are not assured of the accuracy of test results because a maximum duration that QC samples may be stored prior to shipment has not been established, and shipping procedures are unclear.

MEETING DISCUSSION:

FKD's current Quality Control SOPs require testing to start within (b) (4) days of sampling. In order to support this, the shipping SOP will be harmonised with the QC SOPs by the end of February to clarify a maximum storage time of (b) (4) between all sampling and shipping.

This time limit is consistent with sample type, storage condition and supporting stability data. Once the SOP is updated, the handling of the historical samples will be verified against the mandated timelines in order to provide assurance of the test results.

FDA reminded FKD that all justifications should include supporting data and FKD agreed.

- iv. Sterility test samples were not shipped under conditions conducive to the detection of microbial contaminants.

MEETING DISCUSSION:

FKD confirmed that future sterility samples will be shipped at (b) (4) in accordance with the recently finalised FDA guidance.

FDA accepted the applicant's proposed planned response.

- v. (b) (4) used to manufacture DS and DP lots were not fully qualified.

MEETING DISCUSSION:

FKD confirmed that, historically, the (b) (4) step commenced (b) (4), in line with the continuous manufacturing of biologic products. In the future, before being used in the (b) (4) step, the (b) (4) will be released in accordance with the (b) (4) specification.

Stability data up to (b) (4) months are available to support the (b) (4) month expiry applied to the (b) (4). These data were provided on January 14, 2020 (Sequence 0026, response to Question # 5A).

As detailed in the Form 483 response, a rationale is being written to consolidate the information on the (b) (4) and to justify a defined limit of up to (b) (4) Drug Substance batches which can be manufactured from each (b) (4) lot.

FDA stated that the issue of (b) (4) used to manufacture multiple lots of DS and DP should be treated as (b) (4), and were not fully qualified for their intended use. Qualification strategy for the (b) (4) should be revised consistent with the release specifications for a (b) (4). FKD acknowledged this and agreed to implement it as a part of the qualification strategy for (b) (4).

- vi. Out of specifications (OOS) findings were not adequately assessed and corrective and preventive actions (CAPAs) were not fully implemented.

MEETING DISCUSSION:

FKD noted that improvements are being made to the systems and associated SOPs to ensure adequate, timely assessment and closure of Out of Specification findings and full implementation of CAPAs. These improvements will be implemented by end of April 2020.

- vii. Cleaning validation studies in the multiproduct manufacturing facility (b) (4) are incomplete.

MEETING DISCUSSION:

FKD notified FDA that it has taken the decision that no products other than ADSTILADRIN® will be manufactured in (b) (4) until cross contamination studies are complete.

Studies are ongoing to address the PAI observation on room cleaning and decontamination. These studies cover the use of the new cleaning agents and the spillage, cross contamination and decontamination procedures.

The updates to the spillage and decontamination procedure will be implemented by the end of February 2020. The studies planned to confirm the efficacy of the new cleaning agents will be completed by the end of June 2020.

The validation study to test (b) (4) is scheduled for completion and QA approval by the end of February 2020.

- viii. The process of shipping the DP is not acceptable and the validation of shipping must be repeated.

MEETING DISCUSSION:

FKD is investigating alternative shipping solutions that will allow ADSTILADRIN® to reach the U.S. without (b) (4). Once identified, validation studies will be completed on the new shipping system. These studies will include (b) (4), to mimic seasonal variation, and (b) (4) as well as mock shipments. It is proposed that these studies are completed as a post-approval commitment.

FDA informed the applicant that shipping validation and retesting of product must be performed.

- ix. The drug product container closure integrity test method is unacceptable and must be revalidated.

MEETING DISCUSSION:

FKD confirmed that the container closure integrity test method will be re-validated, to include (b) (4). This will be completed by April 2020.

- x. Critical facility GMP issues occurred with your Water for injection (WFI) system and HVAC system during production in (b) (4) however, manufacturing of lots continued prior to conducting impact assessments on the product.

MEETING DISCUSSION:

FDA noted that it would welcome information on what FKD plans to submit to the BLA and requested that the risk/impact assessments be

submitted as soon as possible. FKD offered to provide FDA with a monthly schedule of activities and would welcome regular teleconferences with FDA at which updates can be provided and discussed as needed. FDA agreed to these meetings and stated that FKD should propose dates for the meetings. FKD can also contact the RPM for the BLA to request *ad hoc* meetings if needed.

- xi. Employees are not adequately trained and/or qualified.

MEETING DISCUSSION:

FKD committed to improving the training, and monitoring of the training, for all employees. This activity will be overseen by QA and (b) (4) will deliver GMP training for all staff and management. A review of all training records and retraining as required will be performed across the company, and FKD will ensure that all staff are qualified with an up to date training record. An electronic training management system will be introduced by the end of 2020 to document and automate the monitoring of all training.

- xii. Visual inspection parameters to determine product quality are not fully defined.

MEETING DISCUSSION:

FKD confirmed that a criticality assessment has been completed which defines the three classifications of the visual inspection defects (critical, major and minor). The SOP will be updated, and retraining completed by the end of February 2020.

- b. To date, the responses to the PLI observations have not been received. Please note that all 483 observations must be addressed for your response to be considered complete.

MEETING DISCUSSION:

There was no discussion of this item during the meeting.

- c. The GMP concerns must be addressed in full prior to approval of this BLA. Please note that a re-inspection of Fin Vector Oy may be required prior to approval. We will make this determination upon review of your 483 responses.

MEETING DISCUSSION:

FKD confirmed that this issue was fully understood and FKD is committed to ensuring that the GMP concerns are addressed in full.

- 2. There are currently several outstanding information requests for CMC data that must be reviewed to approve the BLA.

- a. Updated stability data for the RTU formulation with information on the stability of Syn3 NODA functional excipient throughout the proposed storage period.

MEETING DISCUSSION:

FKD confirmed that receipt of the request for the SYN3NODA is to be analysed as part of the drug product stability testing, the assay was added to the protocol for the ongoing stability study with the RTU. The test was introduced for each batch at the next available timepoint. The updated stability data for the drug product was presented during the inspection and provided on February 12, 2020 (Sequence 0034), and this included data for the Syn3NODA.

FDA acknowledged receipt of the submission and stated to the applicant that the review of the submission still ongoing.

- b. Complete stability testing and data for the (b) (4)

MEETING DISCUSSION:

FDA stated that the information shared in Sequence 0026 was good, but the work performed was not typically what is done for a (b) (4). A comparability exercise is needed to show that changes made between the clinical and commercial material have no impact. A comprehensive risk evaluation should be provided to support the maximum number of lots proposed to be manufactured from one (b) (4) lot. FDA noted that there appeared to be a trend towards increased RCA level in commercial lots. FDA acknowledged that the sensitivity of the method has changed between (b) (4) and commercial testing; however, FDA asked FKD to perform an analysis of the data trends. FKD agree to provide this information.

- c. A complete description of the critical and key process parameters with an analysis of the data trends for the DS and DP manufactured to date.

MEETING DISCUSSION:

FDA noted that it would like to see trend data and an analysis of the trend. If a change in trend is seen, increases or decreases vs. the accepted range should be justified. FKD's response to Question 5b was considered by FDA to be acceptable but observed changes should be justified. FKD noted that this work was currently ongoing.

- d. Updated lot release acceptance criteria for DS and DP, including updated acceptance criteria for replication competent adenovirus.

MEETING DISCUSSION:

FDA acknowledged the updates made to the acceptance criteria but queried the endotoxins and RCA method updates discussed during the PAI. FKD confirmed the discussed changes have been implemented and were submitted to the BLA on February 12, 2020 (Sequence 0034). The impact on the RCA calculation was discussed and FKD confirmed the (b) (4) has been added as system suitability criteria to the method and therefore the current calculation is valid. Again, FDA recommended that FKD examines the trends for clinical vs. commercial material for the RCA assay and provides comment on whether trends are due to assay sensitivity or other reason. FKD confirmed that RCA results between (b) (4) were observed in both the (b) (4) and recently manufactured commercial lots. FDA also suggested that if (b) (4) are available, these could be re-tested using the same method. FKD agreed to clarify the validity of the RCA calculation as requested.

2. Discussion of Minor Review Issues:

FDA recommended that all responses to the FDA 483 be submitted comprehensively (instead of individual pieces).

3. Information Requests

Pending information request issues were discussed during the Late-Cycle Meeting, as elaborated in meeting summary to bullet 2.

4. Discussion of Upcoming Advisory Committee Meeting

No Advisory Committee Meeting issues were discussed during the Late-Cycle Meeting.

5. Risk Management Actions (e.g., REMS)

No Risk Management Actions issues were discussed during the Late-Cycle Meeting.

6. Postmarketing Requirements/Postmarketing Commitments

No Postmarketing Requirements/Postmarketing Commitments issues were discussed during the Late-Cycle Meeting.

7. Major Labeling Issues

No Labeling issues were discussed during the Late-Cycle Meeting.

8. Review Plans:

The review of the application is currently ongoing.

9. Applicant Questions:

N/A.

10. Wrap-up and Action Items

FKD concluded its discussion by summarising it has taken the FDA's Form 483 observations seriously and was working diligently to review and make changes in an appropriate timeframe. FDA acknowledged this approach and welcomed the positive steps being taken by FKD and looked forward to working with the site. FKD agreed to submit a summary of its current overall timeline for completion of the planned activities related to the Form 483 content. FDA noted that, with many activities due from FKD, FDA will have additional discussions upon a review of future submissions. FDA was unable to provide any comment on potential post-approval commitments.

FKD requested a routine (monthly) teleconference to update FDA about the progress of the GMP implementation at the manufacturing site; FDA agreed.