



Our STN: BL 125700/0

**MID-CYCLE COMMUNICATION  
SUMMARY**

January 15, 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 summary for your January 6, 2020 Mid-Cycle Communication 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 as soon as possible.

Please include a reference to BLA 125700/0 in your future submissions related to nadofaragene firadenovec.

If you have any questions, please contact Zakaria Ganiyu at (240) 402 – 8329.

Sincerely,

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

## Mid-Cycle Communication Teleconference Agenda

**Application type and number:** BLA 125700/0

**Product name:** nadofaragene firadenovec

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

**Applicant:** FKD Therapies Oy

**Meeting date & time:** January 6, 2019 at 12PM Eastern Time

**Committee Chair:** Ramjay Vatsan, PhD

**RPM:** Zakaria Ganiyu, MS, MBA

### FDA Attendees:

Rajiv Agarwal, PhD, CDER/OPQ/ONDP

Zakaria Ganiyu, MS, MBA, CBER/OTAT/DRPM

Denise Gavin, PhD, CBER/OTAT/DCGT

Candace Jarvis, CBER/OTAT/DRPM

Yuxia Jia, MD, PhD, CBER/OTAT/DCEPT

Leyish Minie, MSN, RN, CBER/OTAT/ DRPM

Raj Puri, MD, PhD, CBER/OTAT/DCGT

Anurag Sharma, PhD, CBER/OTAT/DCGT

Edward Thompson, CBER/OTAT/DRPM

Ramjay Vatsan, PhD, CBER/OTAT/DCGT

Xiaofei Wang, PhD, CBER/OTAT/DCEPT


Zhili Xu, MD, CBER/OTAT/DCGT

### Applicant Attendees:

David Sawutz, PhD (Chief Operating Officer, FKD Therapies Oy)

Robert Shaw (Director, FKD)

(b) (4)




Minna Hassinen (CMC Coordinator, FKD)

Outi Närvänen (Responsible Director, Quality Director, QP, Finvector)

Anna-Kaisa Lehtivarjo (Regulatory Affairs Manager, QP, Finvector)

Minna Karhinen, PhD (Operations Director, Finvector)

(b) (4)



Elizabeth Wishart (Mapi Inc., US Agent to FKD)

**Agenda:**

To discuss the progress of the review.

**Discussion Summary:**

1. Any significant issues/major deficiencies, categorized by discipline, identified by the Review Committee to date.

The review team has not identified any significant issues/major deficiencies at this time

2. Information regarding major safety concerns.

The review team has not identified any major safety concerns at this time.

3. Preliminary Review Committee thinking regarding risk management.

The review team has no comments regarding risk management at this time.

4. Any information requests sent, and responses not received.

- a. Leachables and Extractables: We note that you have conducted a leachable and extractable study for the final container, using the product (b) (4). However, your BLA does not contain any testing of potential leachables and extractables from materials used (b) (4) process (eg., Please provide the leachables and extractables information for all (b) (4) materials. Please note that this test should be done under your (b) (4) conditions using your product (b) (4) and may be different from the information submitted by the material manufacturer). If this information is included in the BLA, please provide a reference to the location in the BLA where this can be found.

**Meeting Discussion:** The applicant acknowledged the above information request and agreed to have the information/data available during the inspection. FDA also reminded the applicant that this information should also be submitted to the BLA. The applicant agreed to submit the requested information, by the February 7<sup>th</sup>, 2020.

- b. Manufacturing capacity: Please provide details of your DS and DP manufacturing capacity (how many consecutive lots of DS and DP do you plan to manufacture during a given month) along with a list of all the DP manufactured in 2019 (including those that are still pending lot release and a list of any lots that have failed lot release tests), and the projected DS and DP manufacturing plans for 2020.

**Meeting Discussion:** FDA agreed to the applicant's request to give time till January 14<sup>th</sup>, 2020, and stated that they can combine this information along with responses to other pending responses to FDA's CMC related information requests (IR) and submit as one submission.

- c. Please provide a list of all the commercial ready DP that is currently available for CBER lot release testing.

**Meeting Discussion:** The applicant asked if their November 20<sup>th</sup> response to FDA's previous IR about the completed lots was insufficient. FDA indicated that the applicant's November 20, 2019 response lacked information on the DPs manufactured in 2019 and they had a lot that was still under investigation pending lot release. FDA also explained that their reason for this request is to better understand the manufacturing status, and to know how many lots of the materials (DS and DP) are currently in stock, and the status of the DS and DP lots manufactured in 2019. The applicant agreed to provide additional information to the BLA.

- d. Please provide a list of all the products manufactured in 2019 in your multi-product (b) (4) facility.

**Meeting Discussion:** The applicant agreed to provide a list of all products other than nadofaragene firadenovec, that were manufactured in 2019 in the (b) (4) facility during FDA's upcoming facility inspection and also submit the data to the BLA for review.

- e. Provide details of the Adenovirus reference standards and reference standard qualification studies. The reference standards are used in the (b) (4) studies.

**Meeting Discussion:** The applicant acknowledged the receipt of the information request and agreed to have all requested information for review during the inspection and will also submit the information to the BLA.

- f. Syn3NODA: Please provide responses to the following questions:
  - i. Provide the (b) (4) of the syn3NODA.
  - ii. As per (b) (4), provide the Post approval stability protocol/commitment for the syn3NODA in Section 3.2.A.3.7.2.
  - iii. Update the application with any newly generated stability data on syn3NODA.

- iv. The Agency acknowledge your rationale but disagrees that the syn3NODA is just a common excipient. Syn3NODA is utilized to “enhance” the delivery of SCH 721015 substance and acts as a functional excipient that serves as a permeation/penetration enhancer or facilitator and its stability during storage should be evaluated as a part of stability testing in line with other permeation/penetration enhancer in the Agency. The Agency recommends that you evaluate the assay of Syn3 NODA functional excipient throughout the proposed storage period until sufficient experience is achieved.
- v. Amend the stability protocol for drug product in Section 3.2.P.8.2 to include assay testing of syn3NODA and provide the validated analytical method to review

**Meeting Discussion:** The applicant agreed to provide all the requested information for Syn3NODA by January 14, 2020 and also agreed to submit additional stability data by the end of February 2020.

- 5. The following information requests are to be sent separately no later than January 14, 2020:

- a. Stability information: You have provided a drug substance (DS) stability data for (b) (4) months when stored at (b) (4) (data from (b) (4) PPQ lots and (b) (4) (b) (4)). We also note that you have proposed to provide additional stability data from (b) (4) lots for a total of (b) (4) months storage at (b) (4). We acknowledge your proposal to submit the additional DS stability data by the end of February 2020 and will review it within the BLA review cycle when these data are submitted to the BLA.

We also acknowledge that you have proposed to provide additional drug product (DP) stability data from (b) (4) developmental lots and (b) (4) PPQ lots in support of your proposed DP shelf life of 12 months. While we agree to review the additional stability information if they are submitted by the end of February, please be aware that only the complete stability data that evaluates all the stability indicating parameters of the product and the novel excipient in the ready to use (RTU) formulation, stored in the commercial containers and quantities, will be able to support your stability claims.

- i. In-process stability: We note that you have proposed to store the (b) (4) (section 3.2.S.2.2) for a maximum period of (b) (4) months. Please provide supporting data for this in-process storage. Additionally, please provide stability test results for all storage periods starting from the (b) (4) stage to the final (b) (4) stage (including the time taken for labeling etc.).

- b. Critical/Key parameters: We note that you have marked in-process acceptance criteria based on NOR (Normal operating range) and have not distinguished between the critical parameters and Key parameters. Please describe what has been set as critical parameters. Please note that critical parameters should have rejection limits, and key parameters should have action limits. From the information included in the BLA, it is not clear if there are any rejection limits (Section 3.2.S.2.4 “failure of any of the parameters (key/critical) may not result in the failure of the batch”). You have also not defined a NOR for some parameters (eg., Under the (b) (4) process the NOR for (b) (4) are listed as “to be defined”; under (b) (4) processing” the NOR has not been defined for any of the parameters;). You have not specified PAR (Proven Acceptable Range) for many of the (b) (4) (b) (4) specifications (Table # 9) (b) (4) parameters (Section 3.2.S.2.4 Tables 2, 3, 4, 5, 6, 7, 8 and 10). Please explain. Please set critical and key parameter values for both (b) (4) process steps and describe your corrective and preventive actions to be taken in the event of manufacturing deviations.
- c. Process qualification: You have set process qualification parameters based on a Failure Mode and Effects Analysis (FEMA), and have a calculation of risk based on Severity x Occurrence x Detectability scores. Please provide examples of these calculations.
- d. Lot release criteria: Please make the following changes to the lot release criteria:
- Drug Substance Section 3.2.S.4.1 (Table 3): Please change the third column title from “specification” to “Acceptance criteria”. Please note that specifications are Acceptance criteria and assay methods, while acceptance criteria are numerical limits.
  - Drug Substance (b) (4) assay: You have proposed an acceptance criterion for (b) (4).  
(b) (4)  
(b) (4) You have also provided data from (b) (4) lots (Section 3.2.S.4.4) of the drug product manufactured using either process 2.2 (data from (b) (4) lots : (b) (4) or Process 2.3 (the current commercial process; data from total of (b) (4) lots: (b) (4).  
(b) (4) Based on the information provided in your batch records, the (b) (4) have ranged between (b) (4).  
(b) (4) Based on your manufacturing experience, the acceptance criteria for (b) (4) should be set to (b) (4) as proposed. Please note that setting tight acceptance criteria based on your manufacturing experience will ensure lot-to-lot

consistency of the product and we recommend that you revise your acceptance criteria for (b) (4) accordingly.

- iii. Drug substance (b) (4) assays: You have proposed to use (b) (4) different assays to confirm the (b) (4) (b) (4) ; Table 3: Drug Substance Specification). However, this method does not specify the (b) (4) (b) (4) to be used as a part of methods nor does it list the expected (b) (4) as a part of the acceptance criteria. Please include this information in the Drug Substance specifications table.
- iv. Drug Product Section 3.2.P.5.1: Please change the fourth column title from “specification” to “Acceptance criteria”. Please note that specifications are Acceptance criteria and assay methods, while acceptance criteria are numerical limits.
- v. Drug product identity: You have proposed to use a (b) (4) method to positively identify drug product. However, the acceptance criteria does not list any specific (b) (4) expected. Please revise this table to say the expected (b) (4) as a part of the acceptance criterion for this assay.
- vi. Drug product potency: You have proposed to use a commercial quantitative (b) (4) method to measure the rAD-IFN (b) (4) . However, the acceptance criterion for (b) (4) does not include a numerical value for the (b) (4) IFN. Please revise the acceptance criterion for IFN (b) (4) to include acceptable numerical limits.
- e. We note that you use a (b) (4) called (b) (4) as a component of (b) (4) . The (b) (4) contains (b) (4) . Please provide additional information on the (b) (4) including vendor information, certificates of analysis (CoAs), origin and source of the (b) (4) , and list any quality control tests done to ensure safety and reliability of the (b) (4) component.

**Meeting Discussion:** The applicant agreed to respond to all items under information request #5 by January 14, 2020, except 5(c) regarding process qualification, which the applicant will provide a response by end of January 2020. FDA agreed.

- 6. Proposed date for the Late-Cycle meeting (LCM).

- a. The LCM between you and the Review Committee is currently scheduled for February 19, 2020 at 11:30 AM and the LCM Materials will be sent on or before February 10, 2020.
- b. If these timelines change, we will communicate updates to you during the review.

7. Updates regarding plans for the Advisory Committee (AC) meeting:

There are no plans to present this to an AC meeting at this time.

8. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates:

Tentative Labeling Target Date: April 3, 2020

Tentative PMC Target Date: April 3, 2020

**Additional Meeting Discussion:**

**Chemistry, Manufacturing, and Controls (CMC)**

During the meeting, the applicant wanted to know what the next steps in the BLA review process are and when the review is projected to be completed. FDA replied that the review of application is still ongoing and the application is classified as Priority Review and therefore, CBER expects to complete the review by the PDUFA deadline of May 1, 2020. FDA also stated that if additional need for information arises, it will be communicated to the applicant in an expeditious manner. The applicant acknowledged.

**Clinical Pharmacology**

The clinical pharmacology reviewer responded to the applicant's proposed question in their December 23, 2019 information request response and that the Phase 1 study clinical SAS datasets can be submitted directly to FDA-CBER and to the BLA.

**END**