



Our Reference: BLA 125700/0  
CRMTS #12766

**MEETING SUMMARY**  
September 30, 2020

Ferring Pharmaceuticals A/S  
Attention: Elizabeth Wishart, B.Sc., MBA  
ICON Clinical Research LLC  
79 T.W. Alexander Dr  
4401 Research Commons, Suite 300, PO Box 14353  
Durham, NC 27709

Dear Ms. Wishart:

Attached is a copy of the memorandum summarizing your September 2, 2020, BLA meeting teleconference with CBER. This memorandum constitutes the official record of the meeting teleconference. If your understanding of the meeting 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 and CRMTS #12766 in your future submissions related to the subject product.

If you have any questions, please contact Zakaria Ganiyu at 240-402-8329.

Sincerely,

Lori Tull  
Deputy Director  
Division of Regulatory Project Management  
Office of Tissues and Advanced Therapies  
Center for Biologics Evaluation and Research

**Meeting Summary**  
**(Includes Preliminary Meeting Responses)**

**Meeting ID #:** CRMTS #12766  
**Submission type & #:** BLA 125700  
**Product name:** nadofaragene firadenovec [ADSTILADRIN]  
**Indication:** High-grade, Bacillus Calmette-Guerin (BCG) unresponsive non-muscle invasive bladder cancer  
**Sponsor:** Ferring Pharmaceuticals A/S  
**Meeting type:** Type A  
**Meeting category:** BLA  
**Meeting date & time:** September 2, 2020, 11:00 – 12:00  
**Meeting format:** Teleconference  
**Meeting Recorder/RPM:** Zakaria Ganiyu, MS, MBA  
**Preliminary Meeting Responses:** August 31, 2020

**FDA Attendees:**

Marie Anderson, MS, PhD, CBER/OCBQ/DBSQC  
Mona Badawy, CBER/OTAT/DRPM  
Kimberly Benton, PhD, CBER/OTAT  
Wilson Bryan, MD, CBER/OTAT  
Colleen Caldwell, CBER/OTAT/DRPM  
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  
Zakaria Ganiyu, MS, MBA, CBER/OTAT/DRPM  
Denise Gavin, PhD, CBER/OTAT/DCGT  
Andrea Gray, PhD, CBER/OTAT/DCGT  
Jiang Hu, PhD, CBER/OBE  
Ying Huang, PhD, CBER/OTAT/DCEPT  
Adnan Jaigirdar, MD, FACS, CBER/OTAT/DCEPT  
Larissa Lapteva, MD, MHS, MBA, CBER/OTAT/DCEPT  
Carolyn Laurencot PhD, CBER/OTAT/DCGT  
Wei Liang, PhD, CBER/OTAT/DCEPT  
Jing Ling, PhD, CBER/OCBQ/DBSQC  
Ke Liu, MD, PhD, CBER/OTAT/DCEPT  
Anna Kwilas, PhD, CBER/OTAT/DCGT  
Lydia Martynec, MD, CBER/OTAT/DCPT  
Darya Melnyk, CBER/OCBQ/DBSQC  
Steven Oh, PhD, CBER/OTAT/DCGT  
Yen Phan, PhD, CBER/OCBQ/DBSQC  
Raj Puri, MD, PhD, CBER/OTAT/DCGT  
Carolyn Renshaw, CBER/OCBQ/DMPQ  
Anurag Sharma, PhD, CBER/OTAT/DCGT

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<b>Attendee</b>	<b>Affiliation</b>	<b>Title</b>
Jørn Skibsted Jakobsen, MD. PhD.	Ferring Pharmaceuticals A/S	Vice President Science and Medicine, Therapeutic Area Urology/Uro-Oncology
Camilla Borglin, M.Sc.	Ferring Pharmaceuticals A/S	Director, Product Development, Formulation and Drug Delivery, Global Pharmaceutical R&D
Marianne Kock, M.Sc., M.B.A.	Ferring Pharmaceuticals A/S	Senior Vice President, Global Regulatory Affairs
Jens Ekelund, M.Sc.	Ferring Pharmaceuticals A/S	Associate Vice President, Global Regulatory Affairs
(b) (4)	Ferring Pharmaceuticals A/S	(b) (4)
Stine Kihl-Plambek	Ferring Pharmaceuticals A/S	Senior Global Regulatory Affairs Manager
Elizabeth Wishart, B.Sc., M.B.A.	ICON Clinical Research LLC	Senior Director, U.S. Regulatory Affairs, U.S. Agent Representative

**Background and Objectives:**

Ferring Pharmaceuticals A/S submitted a meeting request on July 22, 2020, to discuss the applicant's response strategy and to obtain confirmation that this will support a successful resubmission of the BLA. The pre-meeting materials were submitted on July 22, 2020.

FDA provided its preliminary meeting responses to Ferring Pharmaceuticals A/S's questions on August 31, 2020. After reviewing the preliminary meeting responses, Ferring Pharmaceuticals A/S notified FDA on September 1, 2020, of its decision to limit the meeting to discuss only questions 1 and 2.

## Sponsor Questions

**Sponsor Question 1:** *The Company intends to establish a (b) (4) (b) (4) for the storage, handling, and control of (b) (4), which has historically been treated as an intermediate. In its resubmitted BLA, the Company will provide updated release testing requirements and related specifications that conform to the characterization of the (b) (4) as a (b) (4). Does the Agency agree with the proposed approach for establishing, qualifying, and utilizing a (b) (4) for (b) (4) ?*

### FDA Preliminary Meeting Response to Question 1:

- a. Your proposal to establish a (b) (4) (b) (4) appears to be acceptable. The proposed tests to qualify the (b) (4) also appear to be acceptable. However, the final determination of acceptability will be made after review of all tests and methods when submitted in the BLA. Please provide all tests, and test methods in the BLA. Please be aware that if test methods were not validated in the (b) (4), the assays may need to be re-validated or otherwise justified.
- b. Please set a limit for the number of drug substance (DS) lots that can be manufactured from one lot of (b) (4). This limit should be based on data from characterization and engineering studies of DS lots manufactured at or beyond the maximum number of permissible lots that can be manufactured from one lot of the (b) (4), and supported by comparability studies with clinical lots manufactured during the Phase 3 clinical studies.

### Meeting Discussion for Sponsor Question 1:

The applicant agreed to establish a (b) (4) and committed to validate the assays in the (b) (4). Based on the data from previously submitted comparability studies, the applicant will limit the number of drug substance lots manufactured from one lot of (b) (4). This number will be provided in the BLA resubmission and will be supported by additional retrospective data analysis using the data from these extensive comparability investigations.

As described in the Type A briefing package, the applicant will conduct a prospective comparability study and include the protocol in the resubmission. FDA stated that this plan seemed reasonable.

**Sponsor Question 2:** *Given the Drug Substance release testing demonstrating that the (b) (4) used in its production was of appropriate quality, and the Company's commitment to retrospectively test (b) (4) samples, does the Agency agree that the Company may continue to use the existing inventory of (b) (4) (b) (4) until the (b) (4) is established and so long as the Drug Product batches manufactured using the existing (b) (4) are not released until successful completion of the retrospective testing?*

**FDA Preliminary Meeting Response to Question 2:**

- a. It may be acceptable to requalify the (b) (4) that were manufactured under GMP manufacturing conditions for the manufacture of new DS and DP. However, any (b) (4) that were manufactured during phases when the facility was not under full GMP compliance should be excluded.
- b. Please be aware that in addition to the issues identified with reference to the (b) (4), there were GMP failures in the manufacturing facility at the time many of the DS lots listed in Table 2 of the Type A meeting package were manufactured. You should assess how the GMP failures may have impacted the previously manufactured DS and DP lots.
  - i. However, we would caution you on reviving the manufacturing process prior to rectifying all the GMP failures cited in the 483 letter issued to the manufacturing facility.
  - ii. It may also be possible to complete all the tests for the (b) (4) to qualify them as (b) (4) in the same time frame as that required to address the GMP failures.

**Meeting Discussion for Sponsor Question 2:**

A full retrospective review is being conducted of batches manufactured prior to the Complete Response Letter, including (b) (4), DS, and DP. An independent third-party consultant has been engaged to support the retrospective review. The review includes batch records, test results, out-of-specification results, deviations, CAPAs, change controls and other relevant data. The suitability of material for commercial use will be based on this assessment. The applicant understands that some batches will not be appropriate for commercial supply. Products impacted by significant GMP failures will not be released for commercial use. The applicant will provide appropriate justification for any alternative use of this material e.g., use for process qualification or stability studies.

The FDA stated that it was pleased with the applicant's proposed plans to remediate and looks forward to seeing the data in the upcoming resubmission.

**Sponsor Question 3:** *The Company will submit updated shelf life information, as well as the supporting stability data, in its BLA resubmission. Prior to the BLA resubmission, the Company intends to extend the shelf life of the existing (b) (4) and Drug Substance lots in order to use this (b) (4) to manufacture Drug Product so long as the stability data support it. Does the Agency agree with this approach?*

**FDA Preliminary Meeting Response to Question 3:**

You may be able to extend the shelf life of the DS and the DP based on accumulated stability information, if the data is supportive. However, you will need to provide sufficient justification for the use of stability data from product lots that were manufactured when the facility was not in full compliance with all the GMP requirements. Please address the following in your BLA:

- a. Please be aware that in addition to the issues identified with reference to the (b) (4), there were GMP failures in the manufacturing facility at the time many of the DS lots listed in Table 2 of the Type A meeting package were manufactured. You should assess how the GMP failures may have impacted the stability of the previously manufactured DS and DP lots.
- b. The stability evaluations should also fully address all the issues identified in the CR letter, including an assessment the stability of SYN3 component at the specified storage temperatures, using validated assay methods.
- c. You should also address the CR letter comments # 13(d) with reference to the container closure integrity evaluation, and #13(e) on E&L testing of the (b) (4) storage containers.

**Meeting Discussion for Sponsor Question 3:**

There was no discussion of this question during the meeting.

**Sponsor Question 4:** *The Company will supplement the existing compatibility study of delivery devices (catheters and syringes). Does the Agency agree with our proposed methods for additional studies of delivery devices and that these are adequate to represent the worst-case scenario for clinical dose preparation?*

**FDA Preliminary Meeting Response to Question 4:** Your proposal to conduct additional compatibility testing simulating worst-case clinical conditions appears generally reasonable. However, we have the following comments and recommendations:

- a. You state that you “plan to provide additional information regarding the regulatory status of the catheters used in the 2016 in-use stability and compatibility study in our response to the CRL.” In your response to CRL, please also provide the regulatory status in the United States of the devices (i.e. catheters, syringes, luer connector, etc.) used in your additional compatibility study.
- b. You propose to use syringes constructed from polypropylene, because “polypropylene is the most widely used syringe material.” You state the vented vial adaptor will be constructed from polycarbonate and the luer connector will be constructed from polypropylene. We acknowledge that you state the vial adaptor and luer connector have small contact area and that the possibility for DP/material interaction is low. The syringe, however, will have significant contact

with the DP. The corresponding USPI section of proposed labeling does not specify the compatible material(s) of construction for the syringe(s). As the syringe(s) is a significant component of the delivery system, please include a syringe material of construction specification in your labeling.

- c. The USPI section of the proposed labeling regarding withdrawal of the DP into syringes states “2 standard 50 or 60 mL Luer lock syringes or 1 Luer lock syringe equal to or greater than 75 mL” are required for this step. Although you indicate in the proposed additional compatibility testing that using the largest device surface area to volume ratio would simulate the worst-case clinical condition, you did not indicate what volume syringe would be used in the testing. Additionally, the specification for use of a single syringe only contains a lower bound (i.e. volume of at least 75 mL). Please clarify what volume of syringe will be used in the compatibility testing. Please also specify an upper limit for the syringe volume in the USPI or provide a justification for how the proposed compatibility study support the current syringe volume specification as currently stated.
- d. In the instillation section of the USPI proposed labeling, you state that “in-dwelling bladder catheters (b) (4) catheters) may be used” if inserted shortly before and removed following DP instillation. However, indwelling catheters are generally indicated for urine drainage, rather than instillation of a fluid. Use of indwelling catheters for instillation may represent a use outside of the cleared indications for use for such a catheter. We strongly recommend that you limit the catheter types in the labeling to those legally marketed (i.e. FDA-cleared or -approved) for passing of fluids to or from the urinary tract.
- e. The proposed test methods to evaluate any change in the physicochemical or biological properties of the drug product are acceptable. Please confirm that all the tests will be performed using fully validated test methods.

#### **Meeting Discussion for Sponsor Question 4:**

There was no discussion of this question during the meeting.

***Sponsor Question 5:*** A comprehensive summary of adverse events related to the catheterization procedure in patients was provided in the BLA, and the Company does not plan to submit additional, retrospective information regarding delivery-related adverse events broken down by catheter type, as the Phase III protocol did not require use of a specific kind of catheter or documentation regarding the catheter used. The Company will add the proposed critical device parameters of compatible catheters to the draft label (see above, Table 5, Background and Rationale for Question 4, for additional information). Does FDA agree with this approach?

**FDA Preliminary Meeting Response to Question 5:** Your rationale that catheter related adverse events would likely be captured within the analysis of adverse events related to the catheterization process appears reasonable. Please continue to refer to the responses to Question 4 above.



**Meeting Discussion for Sponsor Question 5:**

There was no discussion of this question during the meeting.

**Sponsor Question 6:** *In its CRL of April 24, 2020, FDA referenced the proposed acceptance criterion for the (b) (4) and requested that the Company revise it. The proposed acceptance criterion was revised from (b) (4) (Sequence 0026, 14 January 2020). In addition, the (b) (4) method was updated to add a system suitability criterion to ensure that at least (b) (4) (Sequence 0034, 12 February 2020). Given the revised proposed (b) (4) acceptance criterion and the updated system suitability criterion, does the Agency agree that the current (b) (4) acceptance criteria is acceptable?*

**FDA Preliminary Meeting Response to Question 6:**

Your modified specification of (b) (4) appears acceptable (b) (4) confidence), given the enhanced (b) (4) assay system suitability criterion that (b) (4). Please modify your (b) (4) assay SOP accordingly and submit re-validation data. In the BLA resubmission, please include statistical considerations and justifications as to why a (b) (4) for the (b) (4) is considered proof of positivity, to enable a complete review of the assay method.

**Meeting Discussion for Sponsor Question 6:**

There was no discussion of this question during the meeting.

**Sponsor Question 7:** *The Company will conduct a supplemental product-specific validation study to assess a lower quantitation limit of (b) (4) for the (b) (4) assay. If the (b) (4) quantitation limit is validated successfully, in connection with an assay containing a (b) (4), does the Agency agree that the Company can maintain the current acceptance criterion of (b) (4) in the Drug Substance?*

*If the supplemental product-specific validation is not successful in establishing the lower quantitation limit of (b) (4), the Company will revise the acceptance criterion based on the conclusion of the supplemental validation study and perform a risk assessment to justify the new acceptance criterion based on the updated quantitation limit of (b) (4).*

**FDA Preliminary Meeting Response to Question 7:**

Yes, if you re-validate the assay and confirm the assay sensitivity is (b) (4), you can maintain the current acceptance criterion of (b) (4) in the Drug Substance. Please submit your re-validation data in the BLA and provide a justification

for any revisions in the acceptance criterion for (b) (4) , should such a revision be necessary, based on your data.

**Meeting Discussion for Sponsor Question 7:**

There was no discussion of this question during the meeting.

**Sponsor Question 8:** *The Company received a letter (dated December 10, 2019) stating that CBER found its proprietary name request (PNR) for the name ADSTILADRIN® acceptable. The Company intends to use the name ADSTILADRIN® for the product upon approval of its BLA. Does the Agency agree that another PNR submission is not needed in the Company's resubmission of the BLA?*

**FDA Preliminary Meeting Response to Question 8:**

Yes, we agree that another PNR submission is not needed in the Company's resubmission of the BLA.

**Meeting Discussion for Sponsor Question 8:**

There was no discussion of this question during the meeting.

**Sponsor Question 9:** *The CRL dated April 24, 2020 did not outline any nonclinical or clinical deficiencies. Can the Agency confirm that, with respect to the nonclinical and clinical sections of BLA 125700, there are no concerns that would affect the approvability of the product?*

**FDA Preliminary Meeting Response to Question 9:**

Yes, we confirm that we have not identified any deficiencies in the nonclinical (pharmacology / toxicology) and clinical sections of the BLA.

**Meeting Discussion for Sponsor Question 9:**

There was no discussion of this question during the meeting.

**Additional FDA Comment(s)/Discussion:**

The applicant offered to submit its comprehensive QCIP to FDA in October 2020, followed by monthly compliance updates for FDA's feedback.

FDA acknowledged the request and the significant changes the applicant is making, but requested that the applicant submit a comprehensive response to the 483 observations and comments as highlighted in the Complete Response Letter when the applicant re-submits the BLA.

The applicant asked if it would be possible to interact with the Agency as the applicant moves forward. FDA stated it would be more meaningful to review the information holistically as one complete package given the inter-relationship between the parts. FDA stated there will be interaction with the applicant during the review of the resubmission of the BLA.

The applicant committed to responding to the Complete Response Letter with the BLA resubmission within one year. If possible, the applicant will resubmit sooner.

**END**