

CBER CMC BLA Review Memorandum

BLA STN 125700

**Nadofaragene firadenovec-vncg
ADSTILADRIN**

Reviewers

**Zhili Xu, PhD, OTAT/DCGT/GTIB
Anurag Sharma, PhD, OTAT/DCGT/GTB1**

1. BLA#: STN 125700

2. APPLICANT NAME AND LICENSE NUMBER

Ferring Pharmaceuticals A/S
U.S. License # 2222

3. PRODUCT NAME/PRODUCT TYPE

Non-Proprietary/Proper/USAN: nadofaragene firadenovec-vncg
Proprietary Name: ADSTILADRIN
Company codename: rAd-IFN, rAd-IFN α 2b, SCH 721015
UNII Code: 0OOS0901FH
NDC Codes: 55566-100-00 (Vial); 55566-100-01 (Carton of 4 vials)

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

Pharmacological category: Adenoviral vector-based gene therapy
Dosage form: Suspension for instillation
Strength/Potency: 3 x 10¹¹ viral particles (vp)/mL
Route of administration: Intravesical instillation
Indication: For the treatment of adult patients with high-risk Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors.

5. MAJOR MILESTONES

Original BLA submission: September 3, 2019
Complete Response Letter: April 24, 2020
Type A meeting: September 2, 2022
Complete resubmission: June 30, 2022
Classification letter sent: July 14, 2022
Mid-cycle meeting: September 29, 2022
PDUFA action due date: December 30, 2022

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Anurag Sharma, PhD, OTAT/DCGT/GTB1	CR item # 1b, 1c, 1d, 13a-e, labeling
Zhili Xu, PhD, OTAT/DCGT/GTIB	CR item # 14a-c, 15a-c, 16a-b, stability, device compatibility, analytical assays

7. INTER-CENTER CONSULTS REQUESTED:

Rajiv Agarwal CDER/OPQ/ONDP/DNDPI/NDPB1	Review of CMC information of novel excipient – Syn3NODA
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8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
06/30/2022	125700/54	BLA resubmission
3/31/2020	125700/42	Responses to LCM 2/10/2020

4/15/2020	125700/43	Response to FDA 483 (PLI-Jan 2020)
11/2/2022	125700/75	Response to CMC IR dated 10/25/2022
12/2/2022	125700/89	Updated labels and PI
12/2/2022	125700/90	LRP template
12/2/2022	125700/91	Response to CMC IR dated 12/1/2022
12/5/2022	125700/93	Response to CMC IR dated 12/2/2022
12/9/2022	125700/94	Response to CMC IR dated 12/12/2022
12/13/2022	125700/97	Updated PI
12/13/2022	125700/98	Updated labels
12/14/2022	125700/99	Response to CMC IR dated 12/12/2022
12/14/2022	125700/100	Final PI and labels

9. Referenced REGULATORY SUBMISSIONS (e.g., IND BLA, 510K, Master File, etc.)

Submission type & #	Referenced Item	Holder	Letter of Cross-Reference	Comments/Status
IND 12547	Entire IND	Ferring Pharmaceuticals A/S	No; not required as the applicant is the holder of the IND	No outstanding issues

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

(Overall BLA)

Product description

ADSTILADRIN (nadofaragene firadenovec-vncg) is a suspension of adenoviral-vector based gene therapy for intravesical instillation. The active ingredient is recombinant, non-replicating adenovirus serotype 5 (Ad5) vector containing a transgene encoding the human interferon alfa-2b (IFN α 2b). The transgene (b) (4)

. The ADSTILADRIN (b) (4)
ADSTILADRIN is indicated for the treatment of patients with high-risk Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors. Intravesical instillation of ADSTILADRIN results in cell transduction and local expression of the IFN α 2b protein that is anticipated to have anti-tumor effects.

Manufacturing summary

The drug substance (DS) is manufactured by (b) (4)

(b) (4)

ADSTILADRIN is a suspension for intravesical instillation, supplied as single-use vials, packaged in a carton containing four (4) vials. Each vial of ADSTILADRIN has a nominal concentration of 3×10^{11} viral particles (vp)/mL and contains an extractable volume of 20 mL. The patients will receive 75 mL of ADSTILADRIN (i.e., total dose of 2.25×10^{13} viral particles), instilled once every three (3) months into the bladder via a urinary catheter.

The (b) (4) DP are manufactured by a contract research organization (CRO) FinVector Oy (Kuopio, Finland). Most of the (b) (4) DP lot release tests are done in-house by FinVector Oy.

Manufacturing Control strategy

Manufacturing process consistency is controlled by (1) raw material and reagent qualification programs, (2) in-process monitoring and in-process control testing, (3) validation of the manufacturing process, and (4) lot release tests. The manufacturer accepts raw materials based on specified quality attributes, including identity, concentration, and purity. Raw materials derived from biological sources are appropriately controlled to ensure the absence of microbial contaminants and Transmissible Spongiform Encephalopathies (TSEs) agents. The control strategy includes testing of the (b) (4), DP, and in-process materials for microbial contaminants, identity, purity, strength, and potency. (b) (4) DP quality are controlled and characterized by several release tests. These tests include a quantitative assay that measures the concentration of viral particles, an assay to measure (b) (4), an assay to quantitatively measure (b) (4), and a potency assay that measures the (b) (4)

Process Validation

The validation of the manufacturing process for the DS was performed by (b) (4)

Subsequently, with additional gain in process knowledge, the process control strategy was improved and an (b) (4) were manufactured. All the PPQ batches met the pre-defined PPQ acceptance criteria. The DS manufacturing process has been validated (b) (4) and has been shown to be reproducible and acceptable for commercial manufacturing.

The validation for the DP manufacturing process was conducted by manufacturing (b) (4) PPQ DP lots at FinVector Oy. Subsequently, with additional gain in process knowledge, the process control strategy was further improved and an (b) (4) PPQ batches were manufactured. The data demonstrate that the formulation, sterile filtration, filling, and labeling steps of the manufacturing process are effectively controlled to produce DP that consistently meets the established product quality acceptance criteria. Additional validation studies, including aseptic process simulation and shipping validation studies, were also performed.

Impurity profile

Impurities can be classified into product-related and process-related impurities. Product-related impurities include (b) (4)

Process-related impurities may include (b) (4)

Most process-related impurities are removed by the (b) (4) steps. The residual levels of impurities are further controlled by lot release specifications.

Manufacturing Risks

The risk of product contamination with other adventitious agents is minimized by ensuring adequate control of raw materials, especially those of biological origin that are used in the (b) (4), product manufacturing, and through testing of the (b) (4)

Stability

(b) (4)

The DP is stored and shipped frozen below -60°C. The Applicant proposed a shelf life of (b) (4) months for the DP, and the BLA contains data for storage up to (b) (4) months based on (b) (4) commercial lots. However, in the BLA resubmission, the Applicant modified the intended commercial DP manufacturing process that introduces a (b) (4) step for DP vials prior to labeling, which was not present in the original submission. The batches that are used to support long-term stability of the DP did not undergo this (b) (4) step and therefore, do not represent the intended commercial DP manufacturing process. Based on the data from (b) (4) DP batch that had undergone (b) (4) and was then followed under long-term stability, the shelf-life of the DP is assigned to be 18 months when stored below -60°C.

The available stability data also supports DP storage at the clinical site below -20°C for up to 3 months, and for up to 24 hours at room temperature (20°C to 25°C) or refrigerated at 2°C to 8°C after thawing prior to instillation.

ADSTILADRIN is compatible with the syringe and catheter materials recommended in the US prescribing information.

Comparability

Throughout clinical trials the manufacturing process was optimized and scaled up. For the phase 1/2 and phase 3 clinical trials, the vector suspension was supplied as a concentrate,

which was combined with a diluent and mixed with Syn3NODA at the hospital pharmacy to form an (b) (4) for instillation to the patient. For commercial supply, a ready-to-use (RTU) presentation (ADSTILADRIN), where the components of the (b) (4) are already mixed in the correct concentrations, was developed to provide a more convenient formulation. The comparability studies have demonstrated that the current manufacturing process produces the ADSTILADRIN DP with critical quality attributes that are comparable to those of the clinical (b) (4) used in phase 3 studies.

B. RECOMMENDATION

I. APPROVAL

This biological license application (BLA) provides an adequate description of the manufacturing process and characterization of the new drug product nadofaragene firadenovec-vncg. Based on the information submitted in the initial submission, the current resubmission, and applicant's response to complete response items, the CMC review team has concluded that the manufacturing process, along with associated test methods and control measures, can yield a product with consistent quality characteristics. This satisfies the CMC requirements for biological product licensure per the provisions of section 351(a) of the Public Health Service (PHS) Act controlling the manufacture and sale of biological products.

II. COMPLETE RESPONSE (CR)

None

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Zhili Xu, Ph.D. Biologist DCGT/OTAT	Concur	
Anurag Sharma, Ph.D. Acting Lead Biologist DCGT/OTAT	Concur	
Denise Gavin, Ph.D. Chief, Gene Therapy Branch 1 DCGT/OTAT	Concur	
Steven Oh, Ph.D. Deputy Director DCGT/OTAT	Concur	
Heather Lombardi, Ph.D. Director DCGT/OTAT	Concur	

Review of CTD

Table of Contents

EXECUTIVE SUMMARY (Complete resubmission)	3
Applicant's Response to Item 1.b (Lot-to-Lot Reproducibility):	4
Applicant's Response to Item 1.c (Cleaning and Disinfection):	9
Applicant's Response to Item 1.d (Accuracy of sterility test results):	9
Applicant's Response to Item 13.a (Qualification of (b) (4))	11
Applicant's Response to item 13.b (Evaluation of (b) (4))	13
Applicant's Response to Item 13.c (Comparability study with (b) (4))	13
Applicant's Response to Item 13.d (Stability of (b) (4))	14
Applicant's Response to Item 13.e (Leachable and extractables (L&E) testing for the (b) (4))	15
Applicant's Response to Item 14.a (b) (4) assay:	17
Applicant's Response to Item 14.b (b) (4) assay:	18
Applicant's Response to Item 14.c (Robustness of the (b) (4) assay):	19
Applicant's Response to Item 15.a (Drug product stability):	20
Applicant's Response to Item 15.b (Syn3NODA stability):	25
Applicant's Response to Item 15.c (Validation of analytical method for Syn3NODA):	25
Applicant's Response to Item 16.a (Regulatory status of catheters for administration):	25
Applicant's Response to Item 16.b (Device compatibility)	26
Additional changes or updates to the BLA since the original submission (non-CRL items):	30
DP stability stored at clinical site at -20 ± 5°C:	30
DS stability	32
(b) (4) effect on DP	35
Shelf life of rAd-IFN (b) (4) and RTU DP (ADSTILADRIN)	39
Post-approval commitment for collection of <i>stability data</i>	40
Potency assay (PLI re-inspection feedback):	41
(b) (4)	41
(b) (4)	44
(b) (4)	46
Addition of a new testing site: (b) (4)	48
Label Review	48
Full Prescribing <i>Information (PI)</i> :	48
Carton and Vial Label:	48

List of Tables:

Table 1: PCE definitions in the improved PCS	4
Table 2: Types of PCE limits and control during batch manufacturing	6
Table 3: Release specification for (b) (4)	11
Table 4: Real-time stability study results for rAd-IFN (b) (4)	14
Table 5: Extractable study design	16
Table 6: (b) (4)	18
Table 7: Parameter changes in the robustness study	19
Table 8: Effect of changed method parameters on viral particle concentration	20
Table 9: Stability results for batch (b) (4)	21

Table 10: Stability results for batch (b) (4)	23
Table 11: Regulatory status of catheters tested in study CM-FKD003-SUM-15-035	26
Table 12: Details of delivery devices used in study Q-Report-17329	27
Table 13: Overview of compatibility results, (b) (4) tests per administration device combination	28
Table 14: Stability results for batch (b) (4)	31
Table 15: Real-time stability results for confirmatory (b) (4) Batch (b) (4)	33
Table 16: Effect of (b) (4)	36
Table 17: Stability data of batch (b) (4)	38
Table 18: Updated stability data for (b) (4) DP with no cumulative factors considered	39
Table 19: Updated stability data for DP with cumulative factors considered	39
Table 20: Validation summary of (b) (4)	42
Table 21: (b) (4)	44
Table 22: Overview of (b) (4)	44
Table 23: (b) (4)	45
Table 24: Overview of (b) (4)	46
Table 25: (b) (4)	46
Table 26: (b) (4)	47
Table 27: (b) (4)	47

List of Figures:

Figure 1: Vial label	49
Figure 2: Carton label	49

EXECUTIVE SUMMARY

(BLA resubmission)

The BLA 125700 (ADSTILADRIN; nadofaragene firadenovec-vncg) was originally submitted on September 3, 2019 and a Complete Response Letter (CRL) was issued on April 24, 2020. The primary reason for the Complete Response (CR) was the GMP-related deficiencies that were observed during the pre-license inspection (PLI) of the product manufacturing facility (FinVector Oy) at Kuopio, Finland. The Chemistry, Manufacturing, and Controls (CMC) concerns included the qualification of (b) (4), deficient analytical assays for release testing, product stability, and compatibility with the administration device. After the CRL letter was issued, the BLA was subsequently transferred from the owner of the original submission (FKD Therapies Oy) to a new owner Ferring Pharmaceuticals A/S (Amd #44, dated July 16, 2020). A Type A meeting was held on September 2, 2020 with Ferring Pharmaceuticals A/S to discuss approach to resolving the CRL deficiencies.

The BLA was then resubmitted on April 11, 2022. However, the submission was not complete, and an incomplete response letter was issued on May 10, 2022. In the April 11, 2022, submission, the files were not uploaded properly and eCTD format was not followed. Many of the relevant, originally submitted files were deleted or replaced with the newer versions that were incomplete or revised to contain substantially less information than the previous versions. The applicant was asked to update the BLA modules to ensure a complete submission. The technical information submitted and the applicant's response to the CR was not reviewed.

The BLA was resubmitted again on June 30, 2022, and the submission was designated complete. In this resubmission, the applicant has adequately addressed all the CMC CR items. The product manufacturing facility (FinVector Oy, Kuopio, Finland) was reinspected by the DMPQ inspection team. Six 483 observations were made that were satisfactorily resolved.

Since the original submission, the applicant improved the process control strategy (PCS) to have better control over the manufacturing process and to ensure better lot-to-lot consistency. The (b) (4) manufacturing process itself has not been changed; only minor adjustments to the process parameters were made based on the gain in process knowledge and understanding since the original submission. Similarly, improved process control was implemented to the drug product (DP) manufacturing process. An (b) (4) was introduced to the DP manufacturing, which was not present in the initial submission. Adequate stability and labeling validation data are provided to support this change. Following the changes, additional PPQ lots were manufactured to verify that ADSTILADRIN manufacturing processes consistently result in the product meeting the quality requirements for batch release.

In addition, the (b) (4) has been qualified as (b) (4) (b) (4) and issues with some of the analytical assays identified in the CRL have been adequately addressed. The applicant has provided the updated long-term (b) (4) DP stability data. However, the requested shelf-life does not consider the worst-case scenario of cumulative stability of the DP derived from the (b) (4) (b) (4) batches (i.e., (b) (4) (b) (4) shelf-life prior to DP formulation, followed by maximum claimed duration of storage of the DP at intended storage conditions). In addition, the claimed shelf-life did not consider the newly introduced (b) (4). Therefore, we do not agree to the applicant's requested shelf-life for the (b) (4) (b) (4) (b) (4) and DP (b) (4) months below -60°C). Based on the data available, (b) (4) shelf-life of (b) (4) months (when stored below (b) (4) and DP shelf-life of 18 months (when stored below -60°C) will be assigned.

Recommendation: All the CRL issues have been satisfactorily addressed. The CMC team recommends approval.

This memo reviews the Applicant's response to the CMC complete response letter (CRL) items. Please refer to the DMPQ and DBSQC memos regarding response to additional CRL items.

CRL Item 1.b: Your manufacturing procedures are not sufficiently detailed to provide consistent lot-to-lot reproducibility of your finished product.

Applicant's Response to Item 1.b (Lot-to-Lot Reproducibility):
(reviewed by AS)

During the interval between the original filing and the resubmission of June 30, 2022, product development activities with ADSTILADRIN continued, leading to improved DS process understanding. To provide improved DS process control and lot-to-lot reproducibility for future manufacturing, the Applicant has capitalized on this enhanced process knowledge. Accordingly, the initial DS process control strategy (PCS) was refined and improved.

To achieve consistent lot-to-lot reproducibility, the Applicant improved on four major areas:

- implementing an enhanced process control strategy with specified performance limits,
- implementing additional qualification studies to improve the overall qualification program,
- implementing improved Batch Manufacturing Records (BMRs) and SOPs with detailed instructions to ensure the defined process is consistently executed and
- completing confirmatory runs and validation studies to ensure lot-to-lot reproducibility of the manufacturing process at commercial scale.

In the initial PCS, the process parameters had been classified in three categories based on criticality - critical process parameter, key process parameter and general process parameter. FinVector used the terms NOR (Normal Operating Range) and PAR (Proven Acceptable Range) in place of critical and Key attributes. This categorization of the process control elements (PCEs) was modified under the new PCS. The improved PCS was established with the compilation of a full list of PCEs containing both process inputs and outputs. According to the revised categorization, the classification of each PCE is determined by evaluating its impact on the step. The definition of each PCE is described in **Table 1**. The types of limits/ranges applied to the process parameters and attributes as well as their control during batch manufacturing and the impact of a failure for batch release are summarized in **Table 2**.

Table 1: PCE definitions in the improved PCS

Process parameter type	Description
Critical Process Parameter (CPP)	A process parameter whose variability has an impact on a Critical Quality Attribute and therefore should be monitored or controlled to ensure the process produces the desired Quality. A CPP should be operated within a Proven Acceptable Range (PAR).

Well controlled CPP (wc-CPP)	A Critical Process Parameter whose variability is easily controlled such that it is unlikely to result in a Critical Quality Attribute that is outside of the attribute's acceptable range. Parameters are mostly computer (automation) -controlled. A wc-CPP should be operated within a Proven Acceptable Range (PAR).
Key Process Parameter (kPP)	A key process parameter is a non-critical parameter of the manufacturing process that may not be directly linked to critical quality attributes but has an impact on process attributes and needs to be controlled to assure process consistency.
Non-key Process Parameter (nkPP)	A non-critical parameter that is neither critical nor key and that requires data to be collected (to gain process knowledge) and operated within acceptable ranges. nkPPs are parameters that are instructing operator in which range process is operated. An nkPP does not impact robustness, reproducibility of the process, or CQAs.
In-Process Control (IPC)	<p>Check performed during production to monitor and, if appropriate, to adjust the process and/or to ensure that the product conforms to its specifications.</p> <p>An IPC typically checks attributes of intermediates that are important to ensure that a product meets the final specifications and CQAs. For an IPC, failure to meet the AC triggers an out-of-trend (OOT) investigation. Confirmed OOT leads to Non-conformance investigation (NCO). Scientific rationale may provide justification for forward processing of the material, if result of an IPC is outside AC.</p> <p>In addition, results for certain IPCs are available only after processing is completed. These IPCs are not used for adjustment of the process and therefore forward processing is acceptable before the IPC result is available.</p> <p>An IPC is required to have specified Acceptance Criteria (AC), and when applicable, can additionally have a NOR that is contained within the AC.</p>
Specification (SPEC)	<p>A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance, drug product or materials at other stages of its manufacture should conform to be considered acceptable for its intended use.</p> <p>The Drug Substance specification includes the release testing performed on (b) (4) , as well as the final Drug Substance itself.</p>
Consistency Indicator (CI)	A subset of non-critical process control elements that are measurements or observations that are indicative of how the process has performed. CIs are not directly 'adjustable'; by definition, by the time a CI is measured no action can be taken that will impact the CI. They are differentiated from process indicators (PIs) because they are measured or observed when it is not possible to adjust them.
Process Indicator (PI)	A subset of non-critical process control elements that are outputs, measurements, or observations that are indicative of how the process is running, in real time. PIs are not directly 'adjustable.' Other PCEs must be adjusted to impact or change the PI. They are differentiated from Consistency Indicators (CIs) because they are measured or observed when the opportunity to make adjustments is still present.

Table 2: Types of PCE limits and control during batch manufacturing

	Parameter / attribute	Type of limit applied	Control during batch manufacturing and impact of a failure for batch release
Process parameters	CPP wc- CPP	<p>NOR: Normal Operating Range used for processing to ensure optimal process performance, contained within the PAR. NOR is shown in BMR and SOP.</p> <p>PAR: Proven Acceptable Range for the parameter, may extend outside NOR. PAR is shown in the BMR and SOP.</p>	A CPP has a PAR and NOR. In certain cases, NOR is the same as PAR. Excursion from a NOR for CPP will trigger a minor deviation, while excursion from a PAR will trigger a major deviation. In case of failure to meet the PAR, the batch disposition needs to be considered.
	kPP nkPP	<p>NOR: used for processing to ensure optimal process performance, contained within the AR. NOR is shown in BMR and the product manufacturing SOP.</p> <p>AR (optional): Acceptable Range that extends outside NOR. AR is shown in the product manufacturing SOP.</p>	<p>A kPP has a NOR and can additionally have a wider AR, where appropriate. Excursion from an AR for a kPP (or NOR, if no separate AR has been defined) triggers a minor deviation.</p> <p>A nkPP has a NOR and can additionally have a wider AR, where appropriate. Excursion from an AR for a nkPP (or NOR, if no separate AR has been defined) will lead to a technical investigation. The purpose of the technical investigation is to facilitate process knowledge acquisition. Based on the result of the technical investigation, a minor deviation may be raised</p>
Attributes	SPEC	<p>AC: Acceptance limits for determining acceptance/rejection of the product.</p> <p>NOR (optional): NOR in this case represents the normal output from process, which is contained within AC.</p>	<p>SPEC have Acceptance Criterion (AC), which determines if the product is approved or rejected. Non-compliance with AC triggers an OOS investigation. Confirmed OOS will lead to non-conformance and rejection of product.</p> <p>SPEC may have an additional NOR that is contained within the AC. Non-compliance with NOR will trigger OOT investigation. Confirmed OOT will lead to NCO. Confirmed OOT will not cause product/intermediate rejection. However, excursion from NOR indicates a potential issue in the processing of the batch and therefore, additional testing might be needed to support the evaluation of the impact on product quality.</p>

	IPC	<p>AC: Acceptance limits. Rationale for forward processing is required when AC is exceeded.</p> <p>NOR (optional): ideal range of process performance, contained within AC.</p>	<p>IPCs have a specified AC, and they can additionally have a NOR that is contained within the AC. Non-compliance with AC triggers an OOT investigation. Confirmed OOT will lead to NCO. In case of an IPC failure, scientific rationale is required to justify forward processing of the material and needs to be included in the OOT/NCO investigation.</p>
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The revised PCS includes revised PARs, in-process acceptance criteria (AC), acceptable ranges (AR), and NORs as applicable for process parameters and attributes. The side-by-side comparisons of the process control elements included in the initial BLA and improved PCS are provided in section 3.2.S.2.4 (Tables 5-11) of the BLA (not reproduced in this memo).

Reviewer's comment: The updates to the process control elements were reviewed and found acceptable.

To ensure the initial process validation performed in the (b) (4) manufacturing suite is still applicable under the improved PCS, the original PPQ was assessed relative to the improved PCS. For this the results (process control elements values) obtained from the initial PPQ runs were compared side-by-side between the original and improved PCS (provided in Tables 1-9 in section 3.2.S.2.5 in the BLA). The comparison shows that the initial PPQ batches met the acceptance criteria for CPP and IPC from both the original and the improved PCS, demonstrating that the initial PPQ complies to both PCS.

Following the implementation of the improved PCS, to verify the consistent performance of the process in the (b) (4) manufacturing suite, (b) (4) confirmatory PPQ DS batches (b) (4)) were manufactured. The results are provided in section 3.2.S.2.4 (Tables 12 and 13; not reproduced in this memo) and are available in the (b) (4) Confirmatory batches report (CM-FKD007-SUM-20-008).

Reviewer's comment: The summary of the confirmatory PPQ runs in the (b) (4) manufacturing suite, CPP, IPC, and DS release results were reviewed, and found acceptable.

Overall, sufficient details of the improved PCS are provided in the BLA.

The improved PCS was implemented with the aim to reduce variability and improve process consistency. These updates have no impact on the manufacturing process itself, and hence do not affect the quality attributes of the DS. The original PPQ performed in (b) (4) is therefore still applicable and valid. The original comparability package "Analytical comparability of rAd-IFN virus vector Drug Product between clinical Phase III batches and batches manufactured by commercial process" is also still valid. No additional comparability study is necessary to support the upgraded PCS.

(b) (4) **manufacturing suite:** There are (b) (4) manufacturing suites - (b) (4).

Initial submission: (b) (4) were included in the original submission as well. There were some differences in the (b) (4) in terms of manufacturing equipment used. In particular, the (b) (4)

(b) (4). The manufacturing process in (b) (4) manufacturing suites was demonstrated to be comparable.

Current resubmission - To further improve lot-to-lot reproducibility the (b) (4) system installed in the (b) (4) manufacturing suite has now been changed to be identical as the (b) (4) system in the (b) (4) manufacturing suite. *Now, the equipment in (b) (4) manufacturing lines are identical.*

Reviewer's comment: This update (identical manufacturing equipment in both manufacturing suites) is a significant improvement to ensure lot-to-lot reproducibility. Equipment validation was reviewed by DMPQ and found acceptable.

Following the equipment change, the manufacturing process was transferred from the (b) (4) facility to the (b) (4) facility and performed according to the improved PCS. The (b) (4) DS process was then verified by manufacturing (b) (4) PPQ batches (b) (4) in the (b) (4) facility. It was confirmed that the manufacturing process can produce a product that consistently meets pre-determined product quality attributes.

Reviewer's comment: The summary of the confirmatory PPQ in (b) (4) is provided (PPQ report CM-FKD007-SUM-20-009). The report was reviewed and was found acceptable. The CPP and IPC are within the specified limits and the DS meets the release specifications confirming that the update had no impact to the manufacturing process and to the product quality. The data is not reproduced as it complies with the prespecified limits of the PCE/PPQ runs previously reviewed in the OS BLA.

Drug product (DP): No specific CR item was identified regarding the DP manufacturing, however based on the overall CRL issues, the Applicant performed an additional process risk assessment to enhance process control and improve lot-to-lot reproducibility. This included a (b) (4)

Based on the risk assessment and the DP Quality Target Product Profile (QTPP), CQAs were identified to consider both severity of effect and quality consistency. As a result, CQAs include both (1) quality attributes with a high-severity-scoring impact on either patient safety or product efficacy, and (2) quality attributes important to batch-to-batch consistency of the manufacturing process.

Reviewer's comment: The QTPP and CQAs are outlined in the BLA, were reviewed, and found acceptable.

The Applicant identified and defined the CPPs, critical material attributes (CMAs), and in-process controls (IPCs) to ensure the product meets the release specifications and CQAs. The updated control strategy for the DP manufacturing process defines CMAs, IPCs and CPPs and their ranges.

Based on the updated PCS, (b) (4) DP PPQ batches were manufactured. Based on the executed PPQ it is concluded that the CMAs, CPPs and IPCs as defined in the manufacturing control strategy are adequate to ensure that the ADSTILADRIN manufacturing processes consistently result in product meeting the quality requirements for batch release and stability.

Reviewer's comment: In the revised DP manufacturing process, (b) (4), the DP (b) (4). This was considered a significant change

from the initial manufacturing process where the DP (b) (4). The changed manufacturing process introduces (b) (4) (b) (4) can potentially impact the product quality, including short and long-term stability for the DP. The Applicant was asked (IR dated December 1, 2022) to submit validation data for the (b) (4) (b) (4) as part of commercial manufacturing process. The Applicant submitted adequate data (response dated December 2, 2022; Amd #91) demonstrating that there is no impact of the (b) (4) on the product quality, including short and long-term stability (please refer to the [stability/shelf-life section below](#)). The Applicant also confirmed that the identity test is performed on the final labeled product according to 21 CFR 610.14. The update to the DP PCS is acceptable.

CRL Item 1.c: The cleaning and disinfection are not fully validated to demonstrate that the cleaning agents are effective, and that (b) (4) decontamination is effective for viral inactivation.

Applicant's Response to Item 1.c (Cleaning and Disinfection):
(reviewed by AS)

The (b) (4) facility is now fully *dedicated* to ADSTILADRIN manufacturing, and the manufacturer (FinVector Oy) has suspended the use of (b) (4) as multi-product facility. As a result, (b) (4) decontamination for viral inactivation is no longer necessary. As (b) (4) is also fully dedicated to ADSTILADRIN, this minimizes risk related to cross-contamination.

Reviewer's comment: The initial CR item was because of a deficient (b) (4) efficacy study to (b) (4) products that were also manufactured in the same facility. As a result of incomplete (b) (4) following (b) (4), there was a concern of cross-contamination of ADSTILADRIN with other (b) (4) products. Now that (b) (4) the manufacturing suites (b) (4) are completely dedicated to the manufacture of ADSTILADRIN, the risk of cross-contamination is not there. This is acceptable.

Other issues regarding introduction of new disinfection agents and validation of cleaning processes were reviewed by DMPQ and found acceptable. Please refer to the DMPQ memo.

CRL Item 1.d: There is lack of assurance of the accuracy of certain test results, including sterility. Your storage and shipping conditions of the sterility samples are not controlled or validated to sufficiently demonstrate that the sample has not been altered prior to testing.

Applicant's Response to Item 1.d (Accuracy of sterility test results):
(reviewed by AS)

Background: In the initial submission, the Applicant had been shipping the DP at -60°C to the testing facility for all tests including sterility tests. We recommended the DP to be shipped at (b) (4) to enable the detection of any microbial contaminants, as freezing the sample can potentially reduce the assay sensitivity. During the initial pre-license inspection of the manufacturing facility, it was also noticed that the test samples were also stored at -60°C for an unspecified period of time prior to shipment. These observations had resulted in 483 citations and were also CR items.

Accuracy of sterility sample test results

To assure the accuracy of sterility sample test results, the Applicant has conducted a suitability study, to evaluate sample storage and shipping conditions with respect to microbial recovery

rate. The study report titled "Microbial recovery study of ADSTILADRIN® Drug Product sterility test samples stored (b) (4) and below (b) (4) (CM-FKD003-SUM-20-006)" is provided and was reviewed. The test samples were (b) (4)

The study demonstrates that the samples stored below (b) (4) provide significantly better microbial recovery rate than samples stored at (b) (4). Consequently, the Applicant revised the procedures to require storage and shipping of sterility samples at temperature below -60°C. Based on the results of this study, ADSTILADRIN® DP sterility test vials can be stored for up to 3 months at storage temperature of below -60°C.

Reviewer's comment: The report CM-FKD003-SUM-20-006 was reviewed and the Applicant's conclusion was found to be acceptable.

In addition, a holistic review of samples stability and storage conditions was completed for all samples used for in-process control and release testing of ADSTILADRIN DS and DP. Results of the review are reported in "Rationale for storage before shipping (QC-RAT-20-01 v03)".

Reviewer's comment: The report was reviewed. The rationale for the duration and storage conditions are based on the actual validation results or scientific justification. The provided data and rationale were found to be acceptable.

The Applicant has updated the SOP-QC-003 to clarify the shipping temperatures and storage times before sample shipping according to this rationale. Shipping temperature of each sample type is reflecting the storing temperature.

The Applicant also stated that up to this date the testing has been done within the timelines described in the rationale. Therefore, it can be concluded that the testing of the samples has been acceptable and in-line with the current timelines of testing.

Overall, the Applicant has satisfactorily addressed the CRL item 1.d.

CRL Item 13: You proposed to store the (b) (4) for up to (b) (4) months and use the (b) (4) to initiate up to (b) (4) commercial lots. Use of a (b) (4) to manufacture commercial drug product lots makes this a (b) (4). However, the supporting data on the quality and stability for the (b) (4) is incomplete. Please provide data to show that:

(b) (4)

(b) (4)

Applicant's Response to Item 13.a (Qualification of (b) (4))
(reviewed by AS)

Background: The manufacturing process has (b) (4)

In the original submission, the Applicant had treated the (b) (4) in the manufacturing process of ADSTILADRIN DS. Based on the complete response (CR) letter, and discussion over the subsequent Type A meeting (dated September 2, 2020), the Applicant acknowledged the FDA concerns and agreed to manage the (b) (4) used for the manufacturing of ADSTILADRIN DS as a (b) (4) going forward. Accordingly, the Applicant has now established a (b) (4) for storage, handling, and control of (b) (4). To qualify this (b) (4)

(b) (4) lots have been tested according to release specification agreed upon with the FDA at the Type A meeting (**Table 3**). Multiple historical (b) (4) lots were also tested to confirm their compliance with the specifications set for the (b) (4), and the retrospective test results are submitted in the BLA. All lots comply with the AC as listed in the proposed (b) (4) release specification described in **Table 3**. The retrospective testing of (b) (4)

confirms that these lots are appropriately characterized as (b) (4) and supports their use for routine DS manufacturing.

The (b) (4) lots have undergone testing in a manner which is similar to that performed for the (b) (4)

According to the FDA's feedback, the number of DS batches manufactured from a (b) (4) has been set to a maximum of (b) (4) (b) (4) batches. The limit is set based on batch data of (b) (4) batches manufactured from a (b) (4) batch and is supported by previously submitted comparability studies.

Table 3: Release specification for (b) (4)

(b) (4)

1 page has been determined to be not releasable: (b)(4)

Reviewer's comment: The testing and overall qualification of the (b) (4) as a (b) (4) is acceptable.

Applicant's Response to item 13.b (Evaluation of (b) (4)

(reviewed by AS)

(b) (4)

Reviewer's comment: The Applicant has adequately evaluated the (b) (4) and has set acceptable AC based on the data generated.

Applicant's Response to Item 13.c (Comparability study with (b) (4)

(reviewed by AS)

Comparability study to show that the DP manufactured (b) (4) is comparable to the DP used in the confirmatory clinical trials:

The Applicant had agreed at the Type A meeting (September 2, 2022) to conduct a prospective study to confirm comparability between commercial DP that will be made from (b) (4) and the previously manufactured clinical DP (manufactured with (b) (4)). It was agreed that the Applicant will submit a comparability protocol in the BLA for review by the FDA and the results from the comparability study could be submitted post-approval. Accordingly, the comparability protocol "Assessment of comparability for ADSTILADRIN clinical Phase 3 batches and batches manufactured by (b) (4)" provided in Section 3.2.R Comparability protocols-18512.

Here is the summary of the comparability protocol:

- Risk assessment: The qualification of the (b) (4) and does not relate to a

manufacturing process change. Therefore, no potential impact on quality of ADSTILADRIN is expected.

Reviewer's note: This is accurate and any risk to the quality of ADSILADRIN is expected to be minimal.

- Number of lots to be used in comparability study:
 - (b) (4) batches produced from (b) (4)
 - (b) (4) batches produced according to the phase 3 manufacturing process

Only historical data from the phase 3 manufacturing process (manufactured during 2015-2017) will be compared to data from ADSTILADRIN. This is because the aged material could influence the comparability results.
- The comparability assessment is performed using quality attributes tested for release as well as additional characterization assays. The selected assays address the product quality biological activity, specific identity, and purity.

Reviewer's note: The list of attributes and assays are described and are acceptable. All methods used to support the comparability exercise are fit for purpose.
- Equivalence between batches manufactured during phase 3 and the ADSTILADRIN batches will be analyzed by statistical methods for equivalence. Results that are qualitative by nature will not be compared by statistical equivalence testing but must comply with the acceptance criteria. For quantitative quality attributes a statistical equivalence by TOST will be performed.
- The results of this comparability study will be provided as part of the annual report.

Reviewer's note: Considering the minimal risk to product quality, this is acceptable.

Reviewer's comment: The comparability protocol was reviewed and was found acceptable. Essentially, there is no difference in the (b) (4). The only difference is in the revised terminology and that the (b) (4) are now tested/qualified more comprehensively compared to (b) (4) (b) (4) that was previously referred to as (b) (4). Therefore, the implementation of (b) (4) does not relate to a process change and rather it provides additional control to the process.

Applicant's Response to Item 13.d (Stability of (b) (4))
(reviewed by AS)

A new stability program has been initiated for the (b) (4), which includes (b) (4). An overview of the long-term stability scheme going forward is described in the BLA. To date, stability data are available for up to (b) (4) months for (b) (4); supporting a shelf-life of (b) (4) months for the (b) (4). (b) (4) has been placed on stability and the stability study is ongoing.

Table 4: Real-time stability study results for (b) (4) (stored below (b) (4))

(b) (4)

(b) (4)

Reviewer's comment: The plan to monitor stability of the (b) (4) is acceptable. Results from the stability study conducted with (b) (4) are submitted in the BLA and data are acceptable.

Applicant's Response to Item 13.e (Leachable and extractables (L&E) testing for the (b) (4) storage):
(reviewed by AS)

(b) (4)

Table 5: Extractable study design

(b) (4)

(b) (4)

(b) (4)

Reviewer's comment: The testing for L&E in the (b) (4) is acceptable. The Applicant's assessment that L&E from (b) (4) pose minimal risk to the patients is reasonable and adequately supported by the data and risk assessment.

CRL Item 14: The following lot release tests used to assess the quality of the DP are incomplete or require recalculations:

(b) (4)

(b) (4)

3 pages have been determined to be not releasable: (b)(4)

(b) (4)

Reviewer's comment: (b) (4)

The CRL item 14c has been satisfactorily addressed.

CRL item 15: The stability information for the DP is incomplete. You proposed a shelf life of 12 months for the DP; however, the stability data included in the BLA for the proposed commercial product (RTU formulation) is only for 9 months. Please provide updated stability information. Please note that the stability information should also include stability data to address the following outstanding issues:

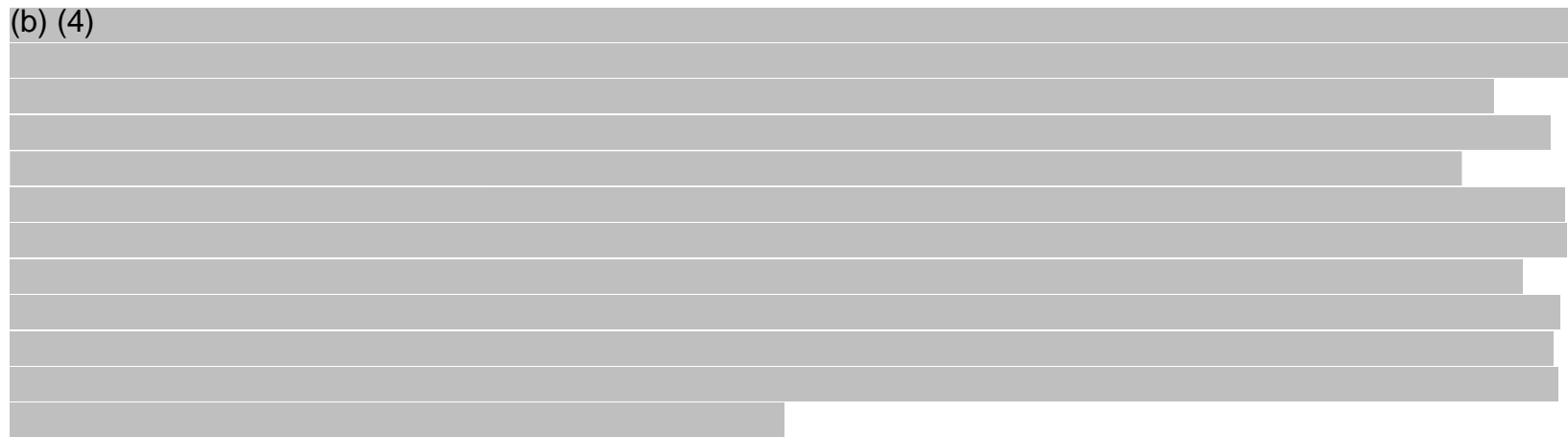
CRL item 15.a: Supporting data to show that the DP is stable when stored for 12 months. Please note that the stability evaluation should take into consideration the storage period for the (b) (4) to show that quality attributes of the DP are not compromised when the (b) (4) is stored initially for the proposed period of (b) (4) month prior to being formulated into the DP and stored for an additional 12 months.

Applicant's Response to Item 15.a (Drug product stability):
(reviewed by ZX)

The Applicant updated the stability data. The following are the data for a typical DP batch
(**Table 9**)

1 page has been determined to be not releasable: (b)(4)

(b) (4)



Reviewer's comment: Of note, for the (b) (4) of excipient Syn3, the assay was not validated for the early time points. This was not determined to be a big concern because Syn3 is a polymer that should be stable at (b) (4). This assay has now been validated ([see response to CRL item 15.c](#)). The data show that all the quality attributes for the typical batch of RTU formulation is stable at -60°C for up to (b) (4) months. It is acceptable to set the RTU DP shelf life at 12 months below -60°C.

DP batch (b) (4) was manufactured using a (b) (4) DS batch stored at temperatures below (b) (4). The stability data are listed as following (**Table 10**).

1 page has been determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

Reviewer's comment: The data show that all the quality attributes for the DP batch manufactured using a (b) (4) DS batch are stable at both (b) (4) for up to (b) (4) months. The CRL item 15.a has been satisfactorily addressed.

Please also refer to the section on Shelf life of rAd-IFN DS and RTU DP (ADSTILADRIN).

CRL item 15.b: You provided updated stability information to show that the novel excipient Syn3NODA is stable in the final formulation for a period of 12 months when stored at -60°C. However, you have not provided data to show that the Syn3NODA is also stable when the drug product is stored at (b) (4), the proposed storage temperature at the clinical site.

Applicant's Response to Item 15.b (Syn3NODA stability):
(reviewed by CDER consult RA)

Reviewer's comment: Assay of Syn3NODA in drug product remains within the proposed acceptance (b) (4) criterion at all timepoints analyzed when the drug product is stored at (b) (4), the proposed storage temperature at the clinical site. This is adequate. Please see the CDER review memo for additional details.

CRL item 15.c. You have not yet validated the analytical method used to detect the presence of the functional excipient, Syn3NODA, in the DP. Analytical method validation is required to support the stability of Syn3NODA in the DP. Please provide the assay validation for the detection of the functional excipient, Syn3NODA, in the formulated DP.

Applicant's Response to Item 15.c (Validation of analytical method for Syn3NODA):
(reviewed by CDER consult RA)

Reviewer's comment: The (b) (4) method has been validated to assay the functional excipient, Syn3NODA, in the drug product and is considered suitable for its intended use. This is adequate. Please see the CDER review memo for additional details.

CRL item 16: In Module 3.2.P.2 you provided Summary Report CM-FKD003-SUM-15-035 entitled "In-use stability and compatibility study for rAd-IFN in (b) (4)

. Please address the following:

CRL item 16a. In Section 5.1.2 of the summary report, you describe the (b) (4) catheters that were used for this testing (i.e., (b) (4)

. However, you did not provide information on the U.S. regulatory status of these catheters. Please provide information on the U.S. regulatory status of each of the (b) (4) catheters used in the compatibility study, including but not limited to whether the devices are U.S. FDA-cleared or -approved, the corresponding regulatory submission (e.g. 510(k) or PMA) numbers, and the cleared or approved indications for use.

Applicant's Response to Item 16.a (Regulatory status of catheters for administration):
(reviewed by ZX)

The Applicant provided the regulatory status information of the catheters (**Table 11**).

(b) (4)

Reviewer's comment: The 510(k) or pre-amendment status of the (b) (4) catheters are confirmed. The CRL item 16a has been satisfactorily addressed.

CRL item 16.b: In your draft labeling in Module 1.14.1.3, submitted in Amendment 25 dated January 10, 2020, you state in Sections 2.2 Preparation and Handling and 2.3 Administration, that the drug product should be withdrawn from (b) (4) vials into a syringe(s) and instilled into the bladder using a urinary catheter. However, you did not include critical parameters for these delivery devices. Please propose critical device parameters (e.g., volume, material(s) of construction, French gauge, length, coatings, colorants, connector style, tip style, etc.) to include in the labeling in order to guide the clinician in selecting a syringe and urinary catheter that are compatible with your DP. While it is possible these parameters may include a range of selections/values (e.g., different materials of construction, different lengths, etc.), all proposed parameters and selections/values should be supported by compatibility testing and suitable for clinical delivery of the product. If there are any catheter types that should not be used with your product (e.g., in-dwelling catheters, catheters with antimicrobial coatings, etc.), please also include this information in the labeling. To support your proposed parameters and selections/values, please provide:

- i. a discussion of how each proposed parameter and selection/value is supported by your compatibility data.*

Applicant's Response to Item 16.b (Device compatibility)
(reviewed by ZX)

Response to 16.b.i

To address this issue, the Applicant did a new compatibility study (Q-Report-17329) between ADSTILADRIN and syringe and catheters used in dose preparation and instillation by using

worst-case device parameters, worst-case drug preparation and mock instillation based on the proposed commercial labeling.

The ADSTILADRIN batch (b) (4) (manufacturing dated (b) (4) - RTU) was used in the compatibility study. This is the same batch used in the stability study of above 15a comment. The device components details are listed as the following (**Table 12**). Their regulatory status is clear: 510(k), Pre-amendment or Exempt.

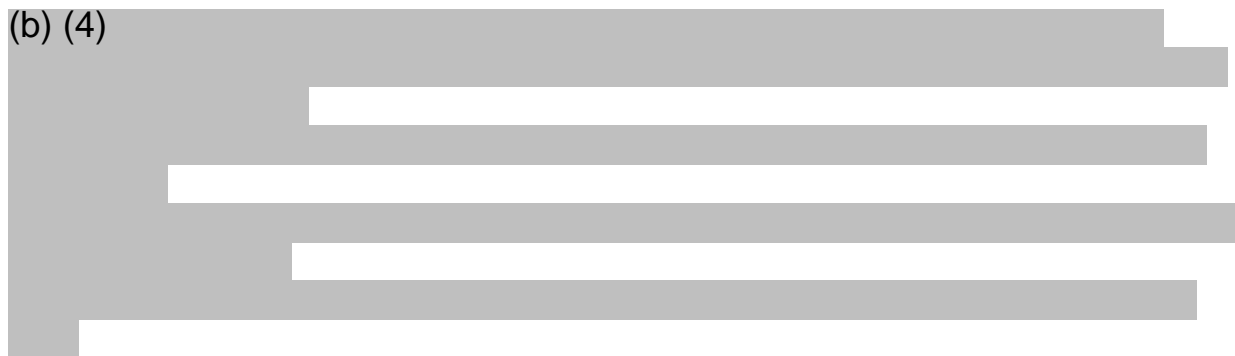
Table 12: Details of delivery devices used in study Q-Report-17329

(b) (4)

The comparison of critical device parameters in the compatibility study vs in the proposed labelling:

(b) (4)

(b) (4)

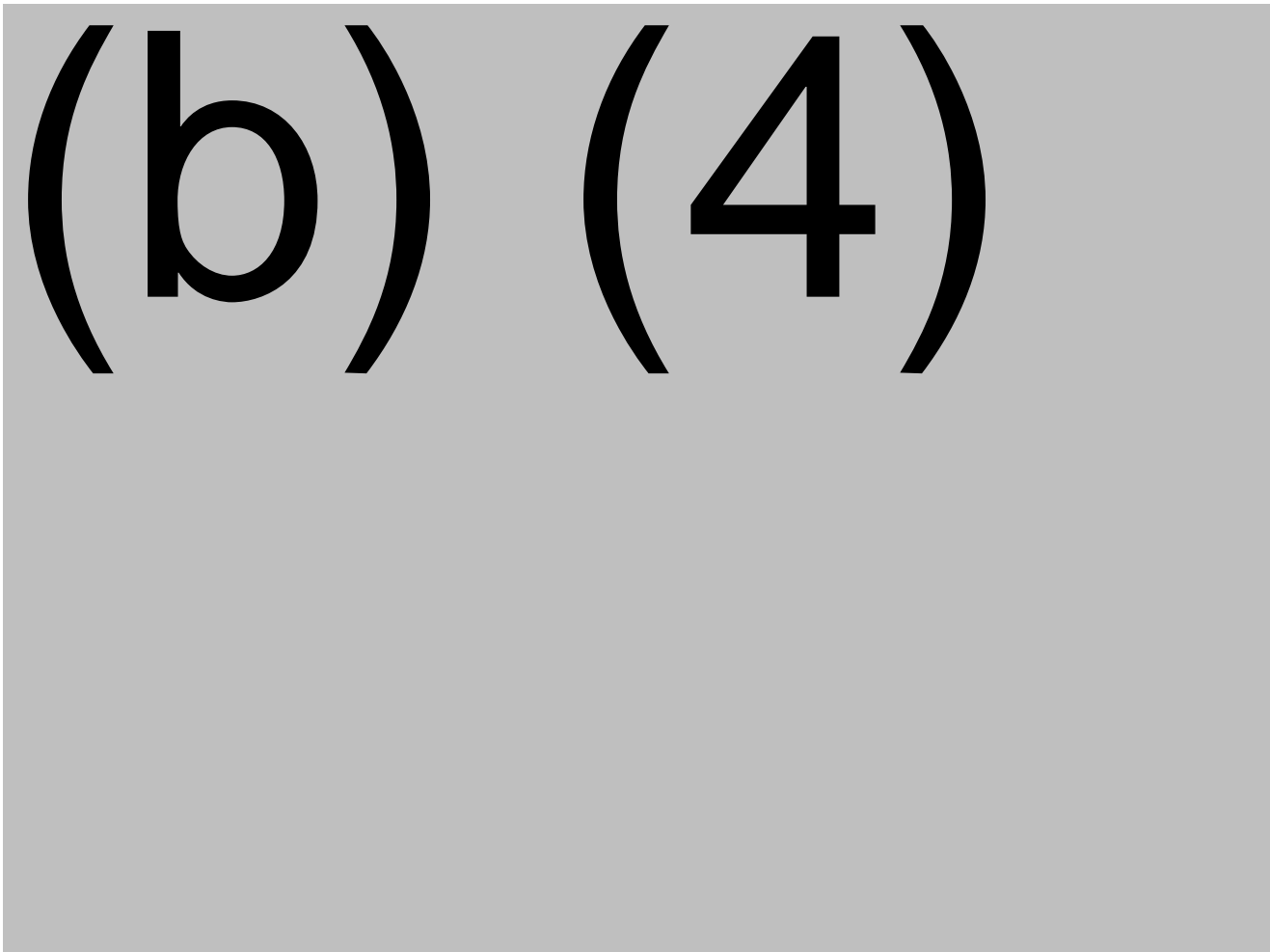
A large rectangular area of the document is redacted with a solid grey fill. Within this redacted area, there are several horizontal white bars of varying lengths, suggesting the presence of text that has been obscured.

Reviewer's comment: The critical parameters in the new compatibility study cover the potential worst case at the clinical site (conditions in the DP label).

Of note, the labeling has been revised to only use polypropylene syringes as in this compatibility study. The catheter materials in the labeling are the same as in the compatibility study: Red Rubber/Latex, PVC and silicone. The compatibility study data are summarized as the following (**Table 13**)

Table 13: Overview of compatibility results, (b) (4) tests per administration device combination

(b) (4)

A large rectangular area of the document is redacted with a solid grey fill. The text "(b) (4)" is printed in large, bold, black font across the top portion of this redacted area. The rest of the area is empty grey space.

(b) (4)

Reviewer's comment: All results comply with the acceptance criteria after worst-case clinical drug preparation and mock instillation as recommended in the label.

The CRL item 16b.i has been satisfactorily addressed.

- ii. *information regarding the catheters that were selected for use during your clinical studies, along with a summary of your clinical experience using these urethral catheters to deliver the DP (including any delivery-related adverse events) and how the catheters used in the clinical study compare to the catheters used in the compatibility testing and the proposed critical device parameters.*

Applicant's Response to Item 16b.ii:

(reviewed by ZX)

Reviewer's comment: The detailed information of the catheters used in the new compatibility study is included in the above 16b.i review. The conditions in the compatibility study cover the potential worst case in the clinical study. The CRL item 16b.ii has been satisfactorily addressed.

CRL item 16.b.ii. (cont.): According to Section 2.2 Preparation and Handling of the draft label provided in Module 1.14.1.3, submitted in Amendment 25 dated January 10, 2020, the DP is transferred from the container closure into a syringe using a vented vial adapter. However, according to Section 3 Introduction of Summary Report CM-FKD003-SUM-15-035, the DP in the compatibility testing was first (b) (4) prior to withdrawal into syringes, (b) (4) and administration via catheter. It is not clear how the dose preparation steps described in the testing summary report represent the actual dose preparation instructions in the draft labeling or worst-case clinical dose preparation scenario. Please provide a comparison between the dose preparation steps used in the compatibility study and the proposed labeling and provide a rationale for why the compatibility test methods are adequately representative of the worst-case scenario for clinical dose preparation.

Reviewer's comment: In the new compatibility study, no (b) (4) was used to (b) (4) DP prior to withdrawal into syringe. The DP was directly withdrawn into syringe, the same way as in the label. In summary, the Applicant did a new compatibility study to mimic the worst case at clinical site. The data show the DP is stable under the dosing conditions on the label. The CRL item 16 has been satisfactorily addressed.

Additional changes or updates to the BLA since the original submission (non-CRL items)
(reviewed by ZX)

DP stability stored at clinical site at $-20 \pm 5^{\circ}\text{C}$

(b) (4) batches of DP (Batch (b) (4) [REDACTED]) were stored at -60°C and then transferred to -20°C for (b) (4) months. The data of one batch are listed below
(Table 14)

Table 14: Stability results for batch (b) (4) , transferred to -20°C after (b) (4) months storage at below -60°C.

(b) (4)

Reviewer's comment: These data support that the DP shipped at <-60°C can be stored at the clinical site at -20 ± 5°C for up to (b) (4) months after (b) (4)-month storage at <-60°C.

DS stability

The Applicant updated the DS stability data (b) (4) up to (b) (4) months.

The following data table is just (b) (4) typical batch (batch (b) (4)) (Table 15).

2 pages have been determined to be not releasable: (b)(4)

Reviewer's comment: The data show the DS is stable at (b) (4) up to (b) (4) months.

However, the Applicant proposed to extend the shelf life of DS from (b) (4) months to (b) (4) months for (b) (4). The Supporting data provided are based on the stability data for the DP for phase 3 or earlier clinical studies. Those DP formulations were the same as the DS manufactured according to Process 2.0. (b) (4) batches of rAd-IFN (Batches (b) (4) are available for (b) (4) when stored below (b) (4) of these batches (Batch (b) (4)) was also monitored when stored at (b) (4) for (b) (4) years.

The stability data are submitted and reviewed.

Reviewer's comment: The stability data for early batches of DP with the same formulation as the DS manufactured according to Process 2.0 may support that the DS are stable for up to (b) (4) months at (b) (4). However, shelf-life determination of the DS should be based on stability of the DS made with the commercial process, and DP cumulative stability (DS used to make DP). It is not acceptable to extend the commercial DS shelf life to (b) (4) months at (b) (4) because lots stored this long were not used to make DP. The DP stability should be established based on the commercial formulation and storage temperature. The stability data so far only support a shelf life of (b) (4) months for the DS. See review at the section of **Shelf life of DS and RTU DP.**

(b) (4) effect on DP
(b) (4)

to demonstrate no adverse effect on DP stability (**Table 16**).

3 pages have been determined to be not releasable: (b)(4)

After (b) (4) of (b) (4), the DP is stable for up to 18 months at <-60°C. The study is scheduled to (b) (4) months long.

Reviewer's comment: During the (b) (4), the samples were (b) (4). This may simulate the worst-case scenario for the labelling and packaging step. This data also supports the introduction of the change to the manufacturing process to (b) (4).

Shelf life of rAd-IFN (b) (4) RTU DP (ADSTILADRIN)

The shelf life of (b) (4) DP should be determined based on the real-time stability data achieved up to the review period. However, the cumulative factors should also be taken into consideration when determining shelf life of the (b) (4) to support DP manufacturing, and the DP after (b) (4) storage. The following **Table 18** summarizes the longest stability data up to the review period for (b) (4) DP (b) (4).

Table 18: Updated stability data for (b) (4) DP with no cumulative factors considered

Condition	(b) (4)	RTU DP (ADSTILADRIN)
-60°C	(b) (4)	(b) (4) months (b) (4) batches, (b) (4)
-20°C	(b) (4)	(b) (4) months (b) (4)

The following Table 20 summarizes the longest stability data up to the review period for only (b) (4) batch of DP with (b) (4).

Table 19: Updated stability data for DP with cumulative factors considered

(b) (4)

Reviewer's comment: With cumulative factors considered (b) (4)

(b) (4) the shelf life for the commercial ADSTILADRIN DP should be 18 months at <-60°C. Accordingly, the rAd-IFN (b) (4) shelf life should be (b) (4) months as this is the duration of (b) (4) storage prior to use to make the DP used in the (b) (4) labeling study. The shelf-life assignment is based on the stability data from (b) (4). This is acceptable because extensive additional stability data (e.g., long-term stability below -60°C/-20°C for up to (b) (4) months, product stability after (b) (4) is available that provide reasonable assurance of product stability for the claimed shelf-life at the intended storage temperature (please also refer to the reviewer's comment in following section on post-approval commitment).

Post-approval commitment for collection of stability data

The post-approval stability protocol was reviewed in the original submission. Ongoing stability studies with ADSTILADRIN will be continued out to the final timepoint (b) (4) months) as per protocol. (b) (4) batch of ADSTILADRIN will be placed on long term stability at below (b) (4) and subjected to (b) (4) testing.

This is not sufficient.

Reviewer's comment: The (b) (4)

because that will represent the worst-case scenario and commercial manufacturing process.

The Applicant was informed of our assessment of (b) (4)/DP shelf-life (comments dated Dec 7, 2022), which is less than claimed. The Applicant responded on Dec 9, 2022 in Amd #94:

- The Applicant agrees to the assigned DP shelf-life of 18 months.
- The Applicant confirms that post-approval DP stability will form batches manufactured according to the commercial manufacturing process, which includes the (b) (4) Sponsor also agrees to generate DP stability data from the aged (b) (4) (i.e., stored for intended (b) (4) shelf-life duration).
- To support that they provided the data from their phase 3 (b) (4) product. (b) (4)

The (b) (4) is similar to current DP (with Syn3 also), but the vector concentration and container closure are different. This data also did not consider (b) (4).

The Applicant's concern is that limiting the DS shelf-life to (b) (4) months will make (b) (4) batches of current DS inventory unavailable (as they exceed the (b) (4) months of shelf-life). This can cause product shortage and have a direct impact on product availability to patients.

The Applicant's submitted supportive data for (b) (4) shelf-life of (b) (4) months is strong, but it is not fully representative of the intended manufacturing process and DS/DP storage. Therefore, we will agree to the (b) (4) shelf-life of (b) (4) months that is based on the real-time stability data derived from the (b) (4)/DP lots manufactured using the intended commercial manufacturing process, stored in the intended container closure, and at intended formulation (including vector concentration). However, the Applicant was advised (dated Dec 12, 2022) that the Applicant may request to release the (b) (4) batches that currently exceeds (b) (4) months of shelf-life (but within (b) (4) months of storage) to manufacture the DP after submitting a supplement to FDA that should include a risk analysis based on currently available stability data and providing justification for use in DP manufacturing.

The Applicant responded (December 14, 2022; Amd #99) and agreed to the (b) (4) shelf life of (b) (4) months below (b) (4). The Applicant also updated the (b) (4)/DP post-approval stability protocol in the BLA for future stability studies on DP batches produced according to the commercial manufacturing process, and to generate additional DP stability data with (b) (4) stored at below (b) (4).

(b) (4) months (intended extension to (b) (4) shelf-life; cumulative stability for storage) prior being formulated to DP (including the (b) (4)). This is acceptable.

Potency assay (PLI re-inspection feedback)

The product manufacturing facility (FinVector Oy, Kuopio, Finland) was reinspected in September 18-27, 2022 (as part of pre-license inspection). The CMC reviewers from the product office did not participate in-person for the inspection but provided remote support to the DMPQ inspection team. Overall, six 483 observations were made by the inspection team that were satisfactorily resolved and classified as VAI (voluntary action indicated). Please refer to DMPQ review memo for additional details.

Here is the feedback provided by the CMC reviewers regarding the potency assay:

The potency assay for (b) (4)

The re-inspection team found that the Applicant initiated a CAPA for the potency assay. (b) (4)

Reviewer's comment: (b) (4)

. There is no concern about the batch quality consistency due to the potency CAPA.

(b) (4)

6 pages have been determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

Addition of a new testing site: (b) (4)

In the response to information request dated October 25, 2022, the Applicant confirmed (response dated November 2, 2022) that only (b) (4)

(b) (4). The assay has been successfully validated at the site (See the above (b) (4) validation).

Reviewer's comment: There is no concern with the assay transfer.

Label Review

(reviewed by AS)

Full Prescribing Information (PI):

The following sections were reviewed: Highlights; Sections 2 (Dose and Administration) and 3 (Dosage Forms and Strengths); Section 11 (Description); Section 12 (Clinical Pharmacology); Section 16 (How supplied / storage and handling)

There were multiple mistakes, incomplete or misleading information in the PI that were communicated to the Applicant on November 29, 2022, and December 7, 2022. The Applicant submitted the revised PI on December 2, 2022 (Amd # 89). After few additional rounds of edits, the final updated PI was submitted on December 14, 2022 (Amd #100). All issues are satisfactorily addressed.

Reviewer's comment: The information provided in the PI is consistent with the information in the BLA. This product is provided in a carton containing four (4) vials. All vials have a nominal concentration of 3×10^{11} viral particles (vp)/mL. Each vial of ADSTILADRIN contains an extractable volume of not less than 20 mL.

The PI contains adequate instructions for dose preparation and administration - the storage of the product in freezer, with appropriate instructions to use the thawed product within 24 h.

Carton and Vial Label:

(reviewed by AS)

The product is in 30 mL vials with 20 mL fill volume. The initial container label was not acceptable because there were several mistakes. The container labels were updated in

amendment 89 (December 2, 2022) to correct several issues that were not in compliance with 21 CFR 610.62. The Applicant revised the labels to correct proper name to be at least as prominent as the tradename, added suffix to and positioned the proper name above the trade name, added NDC number and “single-use vial” on the vial label, added “No U.S. standard of potency” to the carton label, removed certain ‘intervening material’ from the labels. The Applicant confirmed that one dose is 4 vials of the same batch. Multiple drug product lots cannot be supplied in one carton. The Applicant also confirmed that sufficient area of the vial remains uncovered from the label for its full length or circumference to permit inspection of the contents (a photo of labeled vial was provided). The final carton and vial labels were submitted in Amd #100 dated December 14, 2022.

The vial and carton labels (**Figure 1** and **Figure 2**) contain all required text.

Reviewer’s comment: The vial and carton labels are acceptable.

Figure 1: Vial label

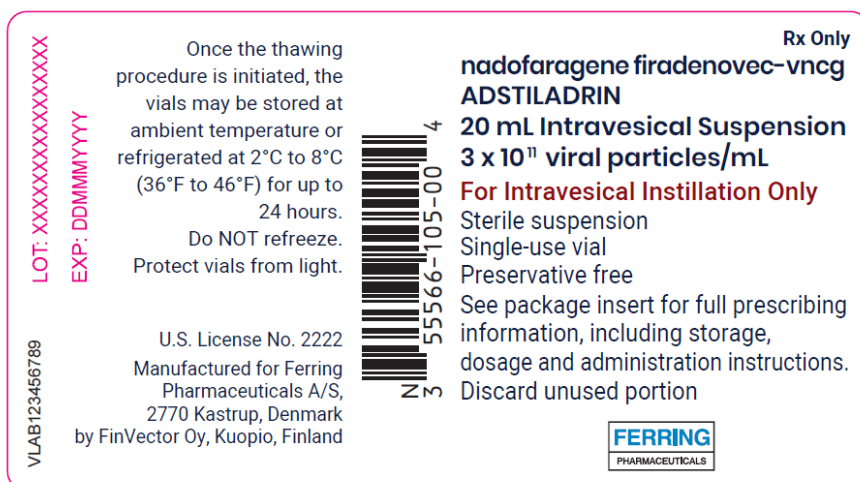



Figure 2: Carton label

53 mm
38 mm
93 mm
38 mm
53 mm



CLABE123456789

Discard unused portion.
See package insert for full prescribing information,
including dosage and administration instructions.
for up to 24 hours. Do NOT freeze. Protect vials from light.
Once the thawing procedure is initiated, the vials may be stored at
ambient temperature or refrigerated at 2°C to 8°C (36°F to 46°F).
Contents: Single dose carton containing 4 x 20 mL vials for a
recommended total dose of 75 mL.


Ingredients: Each vial contains 20 mL extractable
volume of 3 x 10¹¹ vp/mL of nadofaragene
firadenovec, and the following excipients:
[N-(3-chloroamino)propyl]-N-(3-iodoamino)propyl-
carbamate (Spr3), citric acid monohydrate,
sodium citrate dihydrate, polysorbate 80 (Tween 80),
phosphorylcholine-cyclodextrin, sodium hydrogen
phosphate dihydrate, tromethamine, sucrose,
magnesium chloride hexahydrate, glycerol, and Water
for injection, USP.

NDC 55566-105-01

Rx Only

nadofaragene firadenovec-vnccg
ADSTILADRIN
75 mL Intravesical Suspension
Each carton contains 4 x 20 mL vials
Each vial contains 3 x 10¹¹ viral particles/mL
No U.S. standard of potency
For Intravesical Instillation Only

Sterile suspension
 Preservative free
 Discard unused portion
 U.S. Licence No. 2222
 Manufactured for Ferring Pharmaceuticals A/S,
 2770 Kastrup, Denmark
 by FinVector Oy, Kuopio, Finland




NDC 55566-105-01

Rx Only

nadofaragene firadenovec-vnccg
ADSTILADRIN
75 mL Intravesical Suspension
Each carton contains 4 x 20 mL vials
Each vial contains 3 x 10¹¹ viral particles/mL
No U.S. standard of potency
For Intravesical Instillation Only

Store the product in this carton and use by original
expiry date if stored ≤ -60°C. This carton can be stored
at -25°C to -15°C up to 3 months, but not exceeding
the original expiry date.

Write start date for storage at -25°C to -15°C: ____/____/____	Write the discard by date (maximum 3 months): ____/____/____
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GTIN: 00374045100019
S/N: xxxxxxxxxxxxxxxxx
LOT: xxxxxxxxxxxxxxxxx
EXP: DDMMYYYY

