

**CBER CMC BLA
Review Memorandum**

BLA STN 125700

Product Name: nadofaragene firadenovec

(Proposed proprietary name: ADSTILADRIN)

Reviewer/Title/Affiliation

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1. BLA#: STN 125700

2. APPLICANT NAME AND LICENSE NUMBER

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License Number # TBD

3. PRODUCT NAME/PRODUCT TYPE

Nadofaragene firadenovec, a gene therapy product expressing human interferon alpha-2b (IFN α 2b) gene using non-replicating Adenovirus Type 5 (Ad5) gene vector. The product acts by inducing direct cytotoxicity to tumors.

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

The active ingredient is a recombinant replication defective type 5 adenovirus vector containing the human interferon alpha-2b (IFN α 2b) gene. The recombinant virus (b) (4) containing a novel excipient called Syn3, that helps in virus infection.

5. MAJOR MILESTONES

Pre BLA meeting:July 11th 2019
Rolling BLA submitted on:September 3rd 2019
First Module (Pharmacology/Toxicology) submitted on: February 27th 2019
Clinical module submitted on:July 3rd 2019
Final module (CMC) submitted on:September 3rd 2019
Filing Meeting:October 22nd 2019
Midcycle meeting:December 19th 2019
Pre license Inspection:January 20th 2020 to 28th January 2020
Late cycle meeting:February 19th 2020

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Ramjay Vatsan	Manufacturing process DS and DP, Lot Release tests for DS and DP, Batch Records, etc
Anurag Sharma	Cell and Viral Banks, Virus derivation, Shedding, Environmental Assessment
Zhili Xu	Test methods and Assay Validations
Robert Aksamit	Stability, Comparability studies

7. INTER-CENTER CONSULTS REQUESTED

Reviewer/Affiliation	Section/Topic	In agreement with consult recommendations (Yes/No)
Rajiv Agarwal	Syn3 Excipient	Yes

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
9/3/2019	Amendment #3 CMC module	Reviewed
10/9/2019	Amendment #5 Response to IR related to manufacturing suites	Reviewed
10/22/2019	Amendment #7 manufacturing process response to IR/batch carton label	Reviewed
10/22/2019	Amendment #8 USPI	Reviewed
11/7/2019	Amendment # 11 Response to CMC IR information on DP vials	Reviewed
11/19/2019	Amendment # 15 Response to IR Lot Release Protocol, DP COA etc	Reviewed
11/20/2019	Amendment # 16 Response to IR Batch size	Reviewed
11/22/2019	Amendment # 17 Shipping container information	Reviewed
12/23/2019	Amendment # 22 Syn3 structure information	Reviewed
1/14/2020	Amendment # 26 Response to IR on RCA tests, (b) (4), Animal origin statement, RTU risk assessment, Thawing process etc.	Reviewed
1/16/2020	Amendment # 27, Response to IR Shedding studies assay methods	Reviewed
1/30/2020	Amendment # 30 Response to IR shedding data	Reviewed
1/31/2020	Amendment # 31 Response to IR Leachables and Extractables	Reviewed
2/10/2020	Amendment # 33 Response to IR on (b) (4) assay	Reviewed
2/12/2020	Amendment # 34 Response to IR Stability update for Syn3	Reviewed
2/13/2020	Amendment # 35 Response to 483 observations	Reviewed
2/14/2020	Amendment # 36 Response to Midcycle communications – pending Leachables and Extractables study	Reviewed
2/26/2020	Amendment # 38 Response 483 Remedial plans to address 483 issues	Reviewed

2/28/2020	Amendment # 39 Response to midcycle meeting requests Revisions to Lot release specifications, Justification for specifications	Reviewed
3/2/2020 This is the review cut off Date- Amendments received after this date are not reviewed in this review cycle.	Amendment # 40 Response to 483, Rationale for sample storage, batch records review	Reviewed
3/13/2020	Amendment # 41 Response to IR on sterility Test method qualifications	Not Reviewed
3/31/2020	Amendment # 42- Responses to Late-Cycle Meeting dated February 10, 2020 (questions #2b and #2c) and the assessment of drug substance lots information request received via email on February 24, 2020.	Not Reviewed
4/15/2020	Amendment # 43 - Response to the Form FDA 483 associated with the pre-licensing inspection of the manufacturing facility FinVector Oy, conducted January 20-24, 27 and 28, 2020.	Not Reviewed

Note: All the reviewed updated CMC information is included in the BLA review.

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

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
NA	NA	NA	NA	NA

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

The product: rAd-IFN is a non-replicating Ad5-based gene therapy product containing human interferon alpha-2b (IFN α 2b) gene and is (b) (4) Syn3, a novel excipient used to improve infectivity. The rAd-IFN has been assigned a USAN name nadofaragene firadenovec and the formulated product has been assigned a proprietary name ADSTILADRIN®. Nadofaragene firadenovec encodes the human IFN α 2b (b) (4)

Expression of recombinant IFN α 2b by the recombinant rAd-IFN is driven by the (b) (4)

(b) (4)

Syn3: Syn3NODA is a novel excipient that is utilized to enhance the delivery of SCH 721015 substance.

(b) (4)

The Syn3® NODA is manufactured by (b) (4)

During the clinical trials, Syn3NODA was provided as a lyophilized formulation, which was reconstituted with sterile water for injection and combined with rAd-IFN injection to produce an (b) (4) (on-site) for intravesical administration. The to-be-marketed product, ADSTILDRIN, however, is a mixture of the drug substance (rAD-IFN α 2b) and syn3NODA, in a “ready-to-use” (RTU) formulation. The BLA contains comparability studies conducted to show that the RTU formulation is comparable to the product used in the clinical studies. The comparability data are acceptable.

Mode of action: Transduction of urothelial cells with rAd-IFN vector results in over-expression of IFN α 2b protein. The urothelium thus functions as a (b) (4)

The excipient Syn3 is included in the formulation to facilitate transduction of the urothelium by the adenoviral vector. Intravesical administration of ADSTILADRIN® takes advantage of the ‘contained’ nature of the bladder allowing local delivery by catheter instillation. Consequent sustained exposure of the urothelium and bladder tumor cells (directly or by the ‘bystander effect’) to very high local concentrations of expressed IFN α 2b is expected to result in durable therapeutic responses in NMIBC.

Pharmacology/Toxicology studies in laboratory and animal models support the hypothesis that intracellular expression and prolonged local exposure of IFN α 2b protein in NMIBC leads to significantly improved anti-tumor activity.

Proposed clinical use: The applicant’s proposed indication is: “ADSTILADRIN® is indicated for the treatment of high grade, BCG unresponsive, non-muscle invasive bladder cancer.” The final decision on the indication is pending as the labeling meetings have not been held due to unresolved GMP and CMC issues that need to be addressed by the applicant. It is anticipated that the final label indication will be decided after the applicant addresses all the unresolved GMP and CMC issues.

CMC information: ADSTILADRIN® is a suspension for intravesical instillation, supplied as ready to use product (RTU) in a 20 mL extractable volume in 4 single-dose 30 mL vials for a single administration. The supplied concentration is 3.0×10^{11} viral particles (vp)/mL. The dose (content) of nadofaragene firadenovec is defined by the viral particle concentration in the ADSTILADRIN® Drug Product. The RTU formulation contains (b) (4) mg/mL of Syn3. Patients will receive individual instillations into the bladder of 75 mL ADSTILADRIN® at a dose of 3×10^{11} vp/mL (total dose per administration is therefore 2.25×10^{13} viral particles).

The (b) (4) Drug product (DP) are manufactured by a contract research organization (CRO) called FinVector Oy (located at Mikrokatu 1 S, FI-70210 Kuopio, FINLAND). Both FKD (the applicant) and FinVector Oy are sister organizations owned by an entity called Trizell Ltd., (Sanderum House Oakley Road, Chinnor, Oxfordshire OX39 4TW, UK). A majority of the (b) (4) DP lot release tests are done in house by FinVector Oy.

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

The Drug Substance may be stored for (b) (4)

The drug product is manufactured by (b) (4)

(b) (4) Syn3 (the novel excipient that acts as surfactant and enhances viral infectivity in the urinary bladder), filter sterilized and filled into the final container in 20 mL volumes. ADSTILADRIN® is stored at manufacturing and distribution sites below -60°C and shipped frozen below -60°C. It may be stored in pharmacy frozen below -20°C. The drug product has a proposed shelf life of 12 months and the BLA contains supporting data for storage for 12 months based on (b) (4) commercial lots. However, they have provided stability data for the RTU formulation for only 9 months, and it is not clear if prior storage of the DS for the maximum proposed storage period of (b) (4) months will impact further storage of the DP. Stability data for the Syn3 component in the RTU is available for (b) (4) months of storage at (b) (4). However, there is no Syn3 stability data for storage at (b) (4). This is a pending information request as of the date of this review.

There are several pending CMC issues that have not been fully addressed by the applicant. These are part of the reasons for a complete response (CR). (CMC Note: this is also highlighted at appropriate places in the text of this review)

1. The applicant has yet to submit shipping validation data to show that the DP can be shipped to their destinations without loss of container integrity or deviation from the recommended storage temperature.
2. The applicant has provide supporting data to show that the DP can be stored for the proposed durations (they have proposed different acceptable storage periods and conditions for different tests) prior to shipping. However a corrective and preventive action (CAPA) plan in the event of a deviation from the scheduled hold times has not been provided.
3. The applicant has yet to provide data supporting stability of (b) (4) that are being used as a (b) (4). The applicant was also requested to provide comparability data to show that the (b) (4) when (b) (4) to support up to (b) (4) commercial lots continue to maintain their quality attributes, including limits on the number of (b) (4). This information request is still pending as of the date of this review. The stability data for the DP includes an ongoing stability study that has data for 9 months. The applicant has claimed a 12 month shelf life for the DP. Additional stability data should be included in the BLA. This data should also support storage of the DP manufactured from previously stored DS.
4. The applicant has yet to fully address the concerns with four of the proposed DP lot release tests: (a) Endotoxin test: this test does not include (b) (4) and so is not

capable to detecting (b) (4) of endotoxin in the context of the DP formulation containing Syn3. Though this may not be a safety issue, the assay needs to be reverified with a (b) (4) and the reverification test results are pending. (b) The calculation for (b) (4) . While the calculation of (b) (4) the tests do not consistently provide this result. This makes the (b) (4) for this test. Due to this error in calculation, the (b) (4) should be listed as (b) (4) as proposed by the applicant. Given this difference in the assay sensitivity, the applicant will also have to re-justify based on a revised risk assessment for RCA in the final product. (c) The calculation for (b) (4) assay needs to be revised. The (b) (4) assay has a (b) (4) . However, the assay requires the (b) (4) prior to performing the assay. Given this (b) (4) , the final results should be (b) (4) . Thus, the (b) (4) should be set as (b) (4) , and the acceptance criteria be revised from (b) (4) . Given this is not a safety issue a minor revision of the acceptance criterion would suffice. (d) A robustness study of the (b) (4) assay used to (b) (4) in the DP has not been done and should be done to verify the assay performance.

5. There are multiple GMP, quality assurance (QA) oversight, manufacturing facility maintenance, facility record-keeping and employee training issues that were a part of pre-license inspection (PLI) citations (483 observations). These issues are yet to be fully resolved.

Device comments:

6. 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 (b) (4) ”, in which you (b) (4)

Please address the following:

- a. 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.
- 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 four (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 drug product. 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.
- 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 drug product (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.
- c. According to Section 2.2 Preparation and Handling of the draft labeling in Module 1.14.1.3, submitted in Amendment 25 dated January 10, 2020, the drug product 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 drug product in the compatibility testing was (b) (4) withdrawal into syringes, (b) (4), and administration via catheter. It is not clear how representative the dose preparation steps are of the 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.

Clinical data: ADSTILADRIN has been studied in 221 patients enrolled in four clinical trials (Phase 1 through Phase 3). The Phase 3, multi-center (33 centers in the US), open-label, safety and efficacy study enrolled 157 patients with BCG-unresponsive, high-grade NMIBC, of whom 107 had CIS and 50 had papillary disease. In this study, patients receive an initial dose of 2.25×10^{13} vp per administration, followed by up to 4 doses of ADSTILADRIN, at 3 monthly intervals or in the second part of the trial redosing is continued until disease recurrence. In the Phase 3 study, ADSTILADRIN has met the protocol-defined primary endpoint, with 53.4% of patients with CIS demonstrating a complete response to treatment. For commercial use, it is proposed that treatment may continue indefinitely at the physician's discretion, provided that the patient remains free from recurrence of high-grade disease.

Shedding Studies: The shedding of the vector rAd-IFN was assessed in the Phase 1 (4 subjects at the highest dose of 3×10^{11} vp/mL) and Phase 2 studies (19 subjects at the 2.25×10^{13} vp). All together (including lower dose levels) the shedding studies include data from 57 subjects (17 phase 1 and 40 phase 2). Vector shedding was evaluated only in the urine samples (and not in other secretions/excretions). Considering the route of administration of the vector and limited systemic exposure, vector shedding analyses of only urine samples is acceptable. The data from phase 1 and phase 2 studies indicate that rAd-IFN-derived DNA (not necessarily intact viral particles) is likely to be excreted in urine in gradually declining numbers of patients for up to approximately 14 days. In phase 2 study, at 1 day after administration, rAd-IFN-derived DNA was detected in urine of all (n=19) subjects at the median levels of 1.5×10^6 copies/ml, which shows a continuous decline with time. At 12 day, 16 out of 19 subjects (84.2%) subjects had detectable levels of rAd-IFN-derived DNA with a median level of 2.5×10^4 copies/ml urine. The maximum amount of virus DNA was in 1 subject (b) (4) who shed 8.9×10^5 copies detected on day 4, followed by 1.5×10^6 copies of DNA on day 12. The same subject also had a high level of virus shedding on day 2 after the second cycle (4.8×10^7 copies). However, the viral genomic copy numbers were close to the level of detection by day 12 of the second cycle. These results showed that the virus is not retained long and is normally shed by 2 weeks after administration.

The vector DNA was measured in urine using a validated (b) (4) assay and a (b) (4) [REDACTED]. The extraction efficiency assessment for urine indicated there was individual (b) (4) effect on the recovery of rAD-IFN DNA. Due to these issues, it was deemed that the assay has a variability of (b) (4), making the effective (b) (4) of rAd-IFN at (b) (4) [REDACTED].

Environmental Assessment:

- The active component product is a replication defective adenovirus type 5. The human adenovirus is highly specific to its natural host (humans) and has a restricted host range for productive infections. Wild-type Ad5 is known to replicate only in a very limited species of animals other than humans, when infected experimentally: essentially Syrian hamster, and to some extent in cotton rat. The virus does not infect plants or other microbes and is not known to be involved in environmental processes. The potential concern from this product to the environment is also reduced due to (b) (4) [REDACTED] human adenoviruses and thus more sensitive to (b) (4) and less capable to survival in the environment. However, there may be limited (b) (4) [REDACTED] generated during the manufacturing process. (b) (4) [REDACTED]

[REDACTED] The applicant has proposed mitigation strategies that include the use of bleach in the toilet bowl after urination, and cleaning the manufacturing areas after any spillage. The applicant has assessed that the potential impact of the nadofaragene firadenovec on the environment, given the nature of the product and the mitigation strategies are adequate. We agree.

B. RECOMMENDATION

I. APPROVAL

Approval not recommended at this time.

II. COMPLETE RESPONSE (CR)

Complete response recommended due to GMP and CMC issues that have not been fully addressed by the applicant.

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Ramjay Vatsan PhD BLA Review Chair, CMC Reviewer GTB/DCGT/OTAT	Concurred	
Anurag Sharma PhD CMC Reviewer, GTB/DCGT/OTAT	Concurred	
Zhili Xu PhD CMC Reviewer, GTIB/DCGT/OTAT	Concurred	
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Steven Oh PhD Deputy Div. Director, DCGT/OTAT	Concurred	
Raj Puri MD PhD Division Director, DCGT/OTAT	Concurred	

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Module 3

3.2.S DRUG SUBSTANCE

3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties

3.2.S.1.1 Nomenclature

Nadofaragene firadenovec is a recombinant type 5 adenovirus vector containing the human interferon alpha-2b (IFN α 2b) gene. Nadofaragene firadenovec is designed to deliver the human IFN α 2b gene into the bladder urothelium. (b) (4)

(b) (4) excipient, Syn3, is included in the formulation. Intravesical administration of nadofaragene firadenovec with Syn3 takes advantage of the localized nature of the bladder to allow exposure of tumor cells to very high concentrations of IFN α 2b. The nomenclature applied to the vector is presented in the table below:

Table 1: Nomenclature of the Drug Substance

Recommended International Nonproprietary Name (INN)	Nadofaragene firadenovec
Compendial name	Not applicable
Chemical name(s)	Not applicable
Company or laboratory code	rAd-IFN, rAd-IFN α 2b, SCH 721015
Other non-proprietary name(s):	
United States Adopted Name (USAN)	Nadofaragene firadenovec
Chemical Abstracts Service (CAS) number	(b) (4)

Nadofaragene firadenovec (b) (4)

(b) (4) The Company codes rAd-IFN and rAd-IFN α 2b were used interchangeably by FKD Therapies Oy during the Phase 2 and Phase 3 clinical trials. The Company code SCH 721015 was assigned by Schering-Plough Corporation.

Drug product: The instillation administered to subjects in the clinical trials was freshly prepared by combining the vector concentrate with appropriate volumes of diluent and reconstituted excipient Syn3 Powder for Irrigation to form 80 mL of diluted (b) (4) for instillation into the bladder. This combination of components is termed (b) (4). The instillation volume was 75 mL at a concentration of 3×10^{11} vp/mL. The three-component presentation was termed rAd-IFN/Syn3 in the Phase 1 and 2 clinical trials, and Instiladrin during the Phase 3 clinical trial.

The Drug Product for commercial use is a fully constituted Ready to Use (RTU) presentation for administration directly to the patient after thawing. Four vials of Drug Product are required for a single treatment. The Proprietary Name for the product accepted by FDA on 3 December 2018 is ADSTILADRIN. It contains the identical constituents in the same proportions as the (b) (4) made-up in the pharmacy and used in clinical trials and is termed 'Drug Product'

3.2.S.1.2 Structure

(b) (4)

(b) (4)

(b) (4)

3.2.S.1.3 General Properties

The parental organism is Human adenovirus type 5, the taxonomy of which is as follows:

Scientific Name: Human adenovirus Type 5 (Ad5); Group: Group III, Subgroup C;

Family: Adenoviridae; Genus: Mastadenovirus; Species: Human adenovirus; Strain name: Serotype 5

The modifications made are listed below:

(b) (4)

Table 2: Major Features of Nadofaragene Firadenovec (b) (4)

(b) (4)					
---------	--	--	--	--	--

(b) (4)

Mechanism of action: Nadofaragene firadenovec is designed to deliver the human IFN α 2b gene into the bladder urothelium. (b) (4)

(b) (4) excipient, Syn3, is included in the formulation. Intravesical administration of nadofaragene firadenovec with Syn3 takes advantage of the localized nature of the bladder to allow exposure of tumor cells to very high concentrations of IFN α 2b. Prolonged exposure to high local concentrations or the (b) (4) of IFN α 2b is expected to potentiate durable therapeutic responses of (b) (4) bladder cancer cells.

The dose (content) of nadofaragene firadenovec is defined by the viral particle concentration in the ADSTILADRIN® Drug Product. Patients will receive individual instillations into the bladder of 75 mL ADSTILADRIN® at a dose of 3×10^{11} vp/mL (total dose per administration is therefore 2.25×10^{13} viral particles).

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

The following is a list of manufacturers for nadofaragene firadenovec

Table 3: Sites involved in the manufacture and testing of the Drug Substance

(b) (4)

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

(b) (4)

(b) (4)

3.2.P DRUG PRODUCT

The drug product is the (b) (4) and contains an excipient (Syn3) that acts as a surfactant (see table 50 below for the composition of the Drug Product). The Drug product (DP) has a propriety name “ADSTILADRIN®”. It is a sterile, clear to opalescent suspension. It is filled in 20mL volumes into Type (b) (4) glass (b) (4) vials, closed with a polymer-faced rubber stopper, and sealed with a crimped aluminum seal with flip-off cap. A total of four vials are to be used for a single clinical dose (one dose unit of 75 mL), and these are supplied in a secondary container. ADSTILADRIN® is stored at manufacturing and distribution sites below -60°C and shipped frozen below -60°C. It may be stored in pharmacy frozen below -20°C (please refer to stability information in section 3.2.P.8.3).

3.2.P.1 Description and Composition of the Drug Product

ADSTILADRIN® for commercial use is a fully constituted Ready to Use (RTU) presentation for administration to the patient. It is formulated at an approximate (b) (4). The composition of the DP is given below:

CMC analysis and comments: The RTU (ready to use) formulation is not the product that was evaluated in the Phase 3 clinical studies. The applicant has done a comparability study to show that the RTU formulation is comparable to the clinical study material. Additional stability study is in progress (please refer to the section on stability studies). Stability study results for the Syn3 component is as yet incomplete (refer to the consult review for Syn3). Other than these specific limitations due to absence of sufficient stability data, the composition of the DP is acceptable.

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

The DP consists of the (b) (4) (see below for composition of the (b) (4) and a functional excipient called Syn3 (reviewed by CDER), that acts as a surfactant and helps in virus infectivity.

3.2.P.2.1.1 Drug Substance

(b) (4)

3.2.P.2.1.2 Excipients

The drug product contains Syn3 [N-(3-cholamidopropyl)-N-(3- lactobionamidopropyl)]-cholamide, as a surfactant. It is a novel excipient, and is reviewed in detail by the CDER consult reviewer. Additional information on the Syn3 structure was submitted to the BLA on 12/23/2019 (amendment # 22) in response to an IR and is reviewed as a part of the novel excipient review. (please refer to the attached CDER Consult review for details).

3.2.P.2.2 Drug Product

The drug product is the formulated active ingredient nadofaragene firadenovec from the drug substance. The Drug product (DP) has a propriety name “ADSTILADRIN®”.

3.2.P.2.2.1 Formulation Development

For the Phase 1/2 and Phase 3 clinical trials, the vector Drug Product was supplied as a (b) (4) vials, which was combined with Diluent and mixed with reconstituted Syn3 Powder for Irrigation in the hospital pharmacy to (b) (4) for instillation to the patient.

For commercial supply, it was decided to develop a Ready to Use (RTU) presentation (ADSTILADRIN®) where the components of the (b) (4) are already mixed in the correct concentrations, providing more convenient preparation by the urologist and reducing the possibility of pharmacy errors during preparation step. In addition, the product distribution and storage is simplified as the (b) (4) components were stored in different storage temperatures and therefore stored separately.

The strength and composition of the final prepared product the patient receives is unchanged between commercial product ADSTILADRIN® and the (b) (4) administered to subjects in the clinical trials.

3.2.P.2.2.2 Overages

There are no overages in the formulation of ADSTILADRIN®. The vials contain a (b) (4) /vial (b) (4) to enable extraction of 75 mL from four (b) (4) vials (forming a single dose).

CMC Note: the fill volume is calculated by (b) (4) with an acceptable range of (b) (4)

3.2.P.2.2.3 Physicochemical and Biological Properties

The active ingredient in the Drug product is the non-replicating virus nadofaragene firadenovec virus at a concentration of 3×10^{11} vp/mL. It is expected that the virus vector will be voided during urinations in (b) (4) (please see a summary of the shedding study results in section 3.2.A.2).

3.2.P.2.3 Manufacturing Process Development

For the Phase 1/2 and Phase 3 clinical trials, the vector Drug Product was supplied as a (b) (4) vials, which was combined with Diluent and mixed with reconstituted Syn3 Powder for Irrigation in the hospital pharmacy to (b) (4) for instillation to the patient, as described in Table 46 (below).

Table 46: Components of Phase 3 Admixture instillation

Component	Volume
rAd-IFNα2b Injection or ‘Vector Concentrate’	(b) (4)
rAd-IFNα2b Diluent	
Syn3 Powder for Irrigation*	
Total	

* Syn3 Powder for Irrigation (reconstituted in 20 mL of WFI).

**Of which 75 mL is drawn up at the point of administration and delivered via the catheter.

For commercial supply, a Ready to Use (RTU) presentation (ADSTILADRIN®) is used. In the RTU formulation the components of the (b) (4) are already mixed in the correct concentrations. The reasoning for this change was to (1) provide a convenient preparation for administration, (2) reduce the possibility of pharmacy errors during preparation step and (3) To simplify the product distribution and storage as the (b) (4) components were stored in different storage temperatures and therefore stored separately.

In the Phase 3 production process, (b) (4)

In the commercial process, the Drug Substance is (b) (4)

The filled vials are transferred to visual inspection, labelling, secondary packaging to a 4-vial cardboard box, and finally to storage below -60°C.

Comparison of clinical trial and commercial presentations:

Figure 16: Formulation and filling process flow in Phase 3 and commercial processes

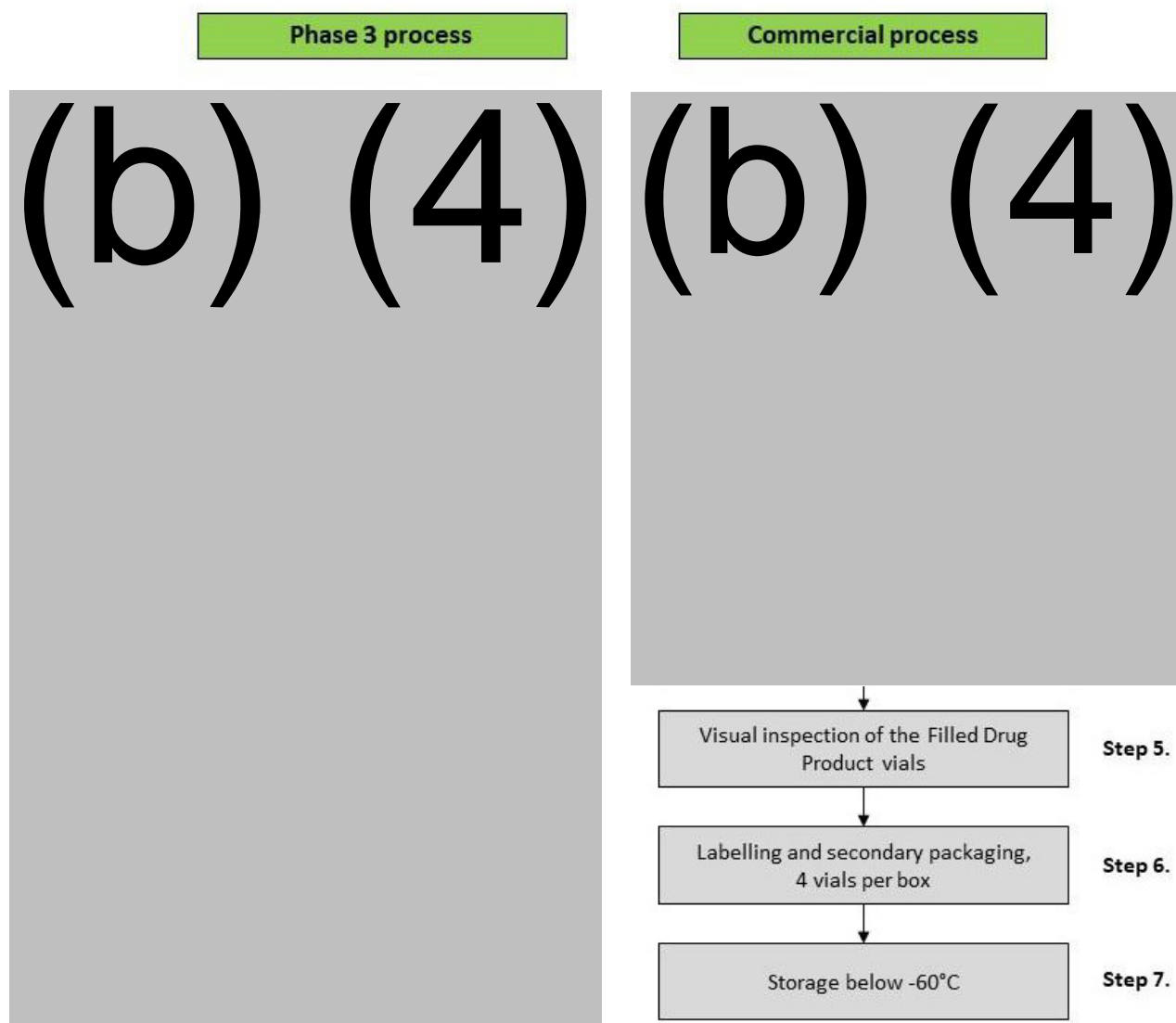


Figure legend: Phase 3 process is described on the left while the commercial process is described to the right. The DP (b) (4) process starts with the (b) (4) DS (obtained (b) (4) step). Note that the terminologies are slightly different as explained in the text.

Table 47: Comparison of excipients of ADSTILADRIN® (b) (4)

Component	Raw material	mg/mL	Component volume[mL]	mg/dose prepared (b) (4)	(b) (4)	ADSTILADRIN® concentration[mg/mL]
rAd-IFN diluent +	Sodium dihydrogen phosphate dihydrate	(b) (4)				
	Tromethamine	(b) (4)				
	Glycerol (b) (4)	(b) (4)				

<div>Syn3**</div> <div>(b) (4)</div>	Sucrose	(b) (4)					
	Magnesium chloride hexahydrate	(b) (4)					0.34
	Syn3 [N-(3-cholamidopropyl)-N-(3-lactobionamidopropyl)]	(b) (4)					
	Hydroxypropyl-beta-cyclodextrin	(b) (4)					
	Citric acid	(b) (4)					0.01
	Tri-Sodium citrate dihydrate	(b) (4)					0.04
	Polysorbate 80	(b) (4)					
	Water for Injections	N/A	N/A	N/A	(b) (4)		

* Of which 75 mL is drawn up at the point of administration and delivered via the catheter.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

CMC comments on the comparability studies: The applicant has conducted robust comparability studies to show that the product manufactured by the commercial process is substantially equivalent to the product manufactured for the Phase 3 clinical studies. Given that the commercial process is the RTU process, there are substantial differences. However the data included shows that the final product that was administered to the patient is similar in their physicochemical and biological properties and is acceptable. Agree with the applicant that the two products are substantially equivalent.

3.2.P.2.4 Container Closure System

ADSTILADRIN® is aseptically filled into (b) (4) Type (b) (4) glass vials (b) (4) and sealed using (b) (4) stoppers. The stoppers are secured with tamper evident aluminum crimps. Details of the container closure system are reviewed in Section 3.2.P.7.

3.2.P.2.6 Compatibility

Compatibility with administration devices:

A study was performed with Phase 3 (b) (4), and the stability for (b) (4) and for (b) (4) was confirmed (CM-FKD003-SUM-15-035) following preparation/contact with preparation and representative administration devices. As ADSTILADRIN® Drug Product is identical in composition to (b) (4) administered to subjects in clinical trials this study is considered entirely supportive of the ADSTILADRIN® Drug Product compatibility.

The drug product is administered into the urinary bladder by instillation. In this device compatibility study, (b) (4) different representative instillation devices were evaluated, along with, various specified delivery components used during Admixture preparation and administration.

(b) (4)

An additional study was also performed, in which (b) (4) needles were used in the preparation of the (b) (4). This approach was studied in order to make the use of the syringes easier. All the assays described above were performed also for the (b) (4) prepared with (b) (4) needles, but only (b) (4) time point was studied and no catheter was used.

Catheter types used in this study:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Conclusions of the device compatibility study:

The (b) (4) different catheters analyzed were observed to produce similar results. Thus, there does not appear to be differences between the tested catheters, for CV% between the catheters were (b) (4) at all time points. Moreover, in the additional study, the (b) (4) prepared using the (b) (4) needles was observed to also produce similar results than obtained for the catheters. In addition, when using the (b) (4) needles, the withdrawal of the components of the (b) (4) from their vials into a syringe was easier and as a result the total volume of the (b) (4) was quite exactly the expected (b) (4) ml, whereas without the (b) (4) needles the total volume of the prepared (b) (4) was often higher than the expected. Formation of (b) (4) in glass vial may interfere with accuracy of syringe withdrawal. In conclusion, this study shows that the rAd-IFN in (b) (4) can be used after (b) (4)

administration via catheter.

CMC analysis and comments on the device compatibility studies:

The applicant has shown that the delivery of the drug product using any one of the regularly used catheter types is acceptable and does not reduce any of the critical quality attributes of the drug product (potency, infectivity, (b) (4)). Though the applicant has shown these results using the (b) (4) formulation and not the RTU formulation, there is no difference in the composition between the (b) (4) and the RTU formulations and so the results are supportive of the applicant's position that the device does not alter with the product potency. These results are acceptable.

Additional comments from the device consult reviewer (Steven Oh, Andrea Gray, and the Device review team CTB DCGT: (also included at the beginning of this review).

1. 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)”, in which you (b) (4)

Please address the following:

- a. 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.
- 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 four (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 drug product. 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.
 - 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 drug product (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.
- c. According to Section 2.2 Preparation and Handling of the draft labeling in Module 1.14.1.3, submitted in Amendment 25 dated January 10, 2020, the drug product 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 drug product in the compatibility testing was (b) (4)

It is not clear how representative the dose preparation steps are of the 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.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

The drug product is manufactured, vialled, labeled, and packaged prior to shipment at the FinVector Oy manufacturing facility in Kuopio, Finland. Most of the Drug product release testing is also done at the FinVector site. The DP is shipped to other facilities (described below) in (b) (4)

Table 49: Sites Involved in ADSTILADRIN® Manufacturing, Packaging and Testing

Testing place and address	Service	Quality standard
FinVector Oy Microkatu 1 S FI-70210 Kuopio FINLAND	Drug Product manufacture, packaging and release testing Excipient release testing	GMP (Fimea licensed facility), FEI 3010227150
(b) (4)	Drug Product release testing	GMP (MHRA licensed and FDA registered facility, FEI (b) (4))
(b) (4)	Drug Product and Excipient release testing Primary packaging testing	GMP (Fimea licensed and FDA registered facility, FEI (b) (4))
(b) (4)	Excipient release testing (b) (4) environmental monitoring (b) (4) Drug Product in-process testing	GMP (Fimea licensed facility)
(b) (4)	Excipient release testing	GMP (Fimea licensed and FDA registered facility, FEI (b) (4))
(b) (4)	Excipient release testing	GMP (Fimea licensed facility)
(b) (4)	Excipient release testing	GMP (MHRA licensed and FDA registered facility, FEI (b) (4))

(b) (4)	Excipient release testing	ISO certified (EN ISO (b) (4)
(b) (4)	Excipient release testing	GMP (MHRA licensed and FDA registered facility, FEI (b) (4)

Testing place and address	Service	Quality standard
(b) (4)	Excipient release testing	GMP (MHRA licensed and FDA registered facility, FEI (b) (4)
(b) (4)	Primary packaging testing	FDA registered, FEI (b) (4), and MHRA inspected facility
(b) (4)	Statistical analysis of potency and (b) (4) assay results	n/a
(b) (4)	(b) (4)	ISO certified (EN ISO (b) (4)

CMC Comments on the shipping and testing of the DP: The applicant has been shipping the drug product in (b) (4) to the testing facility for all tests including sterility tests. A mock shipping study report was submitted in response to FDA's IR received on 11/22/2019 (amendment # 17). FDA recommends that the Drug product be shipped in (b) (4) to enable the detection of any microbial contaminants, as (b) (4) the sample may reduce the assay sensitivity. During the pre-license inspection of the manufacturing facility, it was also noticed that the samples were also stored at (b) (4) for an unspecified period of time prior to shipment. These observations lead to some 483 observation citations that were issued to the manufacturer. In response to the observations, the manufacturer has promised to address the issues and ship sterility test materials at (b) (4) in future (FKD responses to 483 observations received on 2/13/2020). Please refer to FDA's Establishment Inspection Report (EIR) for additional details.

3.2.P.3.2 Batch Formula

Table 50: Composition of ADSTILADRIN®

Component	Reference to Quality Standard	Function	Target Concentration (per mL)
rAd-IFNα2b vector	In House	Active	3.0 x 10 ¹¹ virus particles
Sodium dihydrogen phosphate dihydrate	(b) (4)	Buffer agent	(b) (4)

Tromethamine	(b) (4)	Buffer agent	(b) (4)
Glycerol (b) (4)	(b) (4)	Stabilizer	(b) (4)
Sucrose	(b) (4)	Stabilizer	(b) (4)
Magnesium chloride hexahydrate	(b) (4)	Stabilizer	0.34 mg
Syn3 [N-(3-cholamidopropyl)-N-(3-lactobionamidopropyl)]-cholamide	In House	Surfactant	(b) (4)
Hydroxypropyl-beta-cyclodextrin	(b) (4)	(b) (4)	(b) (4)
Citric acid monohydrate	(b) (4)	Buffer agent	0.01 mg
Tri-Sodium citrate dihydrate	(b) (4)	Buffer agent	0.04 mg
Polysorbate 80	(b) (4)	Surfactant	(b) (4)
Water for Injections	(b) (4)	Solvent	q.s. 1 mL

3.2.P.3.3 Description of Manufacturing Process

The Drug product (DP) manufacturing process involves (b) (4) followed by sterile filtration, filling of the vials, and labeling. The manufacturing process is detailed in the following flow chart (Figure 18). All product contact materials are single use materials that come sterilized from the manufacturer. The vials in which the DP is filled is sterilized (b) (4) (please see filling description below).

(b) (4)

[Redacted text block]

[Redacted text block]

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

(b) (4)

Visual Inspection, Labelling and Secondary Packaging:

Visual inspection, labelling and final packaging/secondary packaging are performed in the Grade (b) (4) area.

- The vials are 100% visually inspected, involving (b) (4)
- The vials are inspected for (b) (4). Vials with (b) (4) rejected immediately.
- The vials are inspected for (b) (4) are rejected.

CMC analysis and comment on the visual inspection: (b) (4)

This was cited as an observation in the PLI (please refer to the 483 citations issued during the PLI). I agree that the applicant's plan to have 100% visual inspection is appropriate and required. They should however address the issues raised by the PLI team. According to the applicant's proposed plan to

implement remedial action plan (submitted on 2/26/2020), this will be completed in March 2020. Part of the issues for CR.

Labeling: The vial labelling is carried out with manual or automatic application of the pre-printed and QA released label. The labelled vials are 100% QA inspected before proceeding to secondary packaging. The vials are packed in sets of four into a secondary cardboard box, one box containing one patient dose. The box is closed with the secondary box label, which secures the lid on the box.

The vials in the secondary packages are frozen in freezers below -60°C, (b) (4) freezing of the filled vials (b) (4)

CMC Note: stability data included and reviewed in the DP stability section. Please refer to section under Module 1 vial and carton labeling for label information. Carton labeling is a part of pending review issues leading up to CR, as the carton is not capable to maintaining the specified temperature without the (b) (4).

3.2.P.3.4 Controls of Critical Steps and Intermediates

The manufacturing process for the Drug Product is controlled by following set of In-process specifications. In-process specifications contain the physical, chemical, biological or microbiological properties or characteristics (i.e. quality attributes) of a product or product intermediate that should be within an appropriate range to ensure the desired product quality is achieved. The in-process testing results are reviewed as part of the Batch review process.

- The quality attributes which impact the product quality have been defined based on criticality assessment using Failure Mode and Effects Analysis (FMEA) approach.
- The limits have been set based on data collected in (b) (4) development batches used for setting up the RTU formulation and filling process (b) (4) and re-evaluated based on process performance qualification manufacturing data in (b) (4) of the process validation.
- The limits for each in-process specification quality attribute have been set as Normal Operating Range (NOR). The NORs are based on minimum and maximum values seen in process validation.

Table 51: Quality attributes for formulation/fill of ADSTILADRIN® Drug Product

Quality attribute type	Description	Impact for batch release
Critical quality attribute	A physical, chemical, biological or microbiological property or characteristic of a product or product intermediate that should be within an appropriate range to ensure the desired product quality. A critical quality attribute has major impact to release specification.	The critical, key and general quality attributes NOR is set as a specification range in the in-process specification. Any result outside the specification limits is investigated according to an Out of Specification procedure.
Key quality attribute	A physical, chemical, biological or microbiological property or characteristic of a product or product intermediate that should be within an appropriate range to ensure the desired product quality. A key quality attribute has potential impact to release specification.	The failure of any of the in-process specifications may not necessarily result in the failure of the batch, if the cause and effect are understood and justified. General quality attributes may be excluded from the in-process

General quality attribute	A physical, chemical, biological or microbiological property or characteristic of a product or product intermediate that does not have impact to release	specification when data from an adequate amount of batches have been collected and evaluated for variance.
---------------------------	--	--

CMC analysis and comment on setting the Normal operating range (NOR) for the critical, key and general quality attributes (part of the pending PLI 483 observations that the firm has agreed to address): The applicant has not really set any rejection limits, and states that “Any result outside the specification limits is investigated according to an Out of Specification procedure” and “may not result in failure of the batch”. As such, the NOR limits seems to be more of a suggested limit with no real acceptance criteria, though the in process tests have specified acceptance limits. The acceptance limits are also listed as NOR. This apparent contradiction in calling an attribute a critical attribute but having an option to accept any deviations from this set limit is not acceptable. The NOR was set based on the results of the process validation runs. Though the NOR should be based on the clinical lots manufactured during the Phase 3 efficacy studies, the applicant has shown comparability of the Phase 3 lots and the commercial lots, and as such this is acceptable. The issue with reference to the process for acting on deviations from pre-set acceptance criteria for critical parameters was discussed with the applicant during the Midcycle meeting, and the applicant’s response dated 1/31/2020 states “Exceeding of NOR or where available PAR of a critical parameter will result in a major deviation and the cause and effect of the failure will be thoroughly investigated.” It is not a clear rejection of the lot because of a process deviation but they will take additional steps to investigate the deviation. It would be good to have a clear rejection limit for any ‘major deviations’. The applicant has not filled many commercial drug product lots, and many of the lots that were filled (see batch analysis for additional details) have deviations and unaddressed out of specifications (OOS) results (please refer to 483 observations from the PLI). The applicant must clearly address all the OOS, implement rectifying action for all the 483 observations, prior to resuming filling operations. The final filled DP will have to be reviewed by the applicant’s QA team prior to deciding on the acceptability of the DP lot. This is an outstanding 483 observation made during the PLI, and the need for QA oversight is a part of the CR letter comments.

Table 52: In-process specifications for ADSTILADRIN® Drug Product manufacture

(b) (4)

(b) (4)

CMC analysis and comment on the in-process specifications for the DP: The in-process DP specification has appropriate controls in place. The major emphasis is placed on freedom from microbial contaminants (b) (4). These parameters are acceptable, considering that the (b) (4)

DP is the (b) (4)

. please also refer to comments on the container closure integrity testing below.

3.2.P.3.5 Process Validation and/or Evaluation

To demonstrate the process design is capable of reproducible commercial manufacture, (b) (4) successful PPQ runs were done. (b) (4) batches was performed in the (b) (4) facility at FinVector Oy, while the (b) (4) batch was performed in the (b) (4) facility at FinVector Oy. All of the runs performed as expected, with no significant issues across the (b) (4) batches. All of the (b) (4), sterile filtration and filling process parameters passed, and/or were within the pre-set acceptance criteria (see Table 53). None of the tested quality attributes of the production process intermediates, or the Drug Product failed or were outside the proposed acceptance criteria range/limit (see Table 53).

Altogether seven deviations (listed in the process validation summary, Attachment CM-FKD007- SUM-18-007) were reported related to the (b) (4) PPQ runs. However, an assessment of these deviations has shown none were process related, with no process related corrective actions required, which confirms both process design and reliability.

Table 53: RTU Formulation, Sterile Filtration, and Filling Product Quality Attributes

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

(b) (4)

CMC analysis and comments on the PPQ manufacturing runs used for process validation studies: Agree with the applicant's assessment that the reported deviations were not directly related to the manufacturing process. The deviations were mostly related to the operator not fully trained prior to being fully trained in the operating process (4 of 7 deviations). The other three deviations relate to calculation error in (b) (4) used to sterilize the vials was not (b) (4). These issues were also noticed during the PLI and the firm was cited for staff training prior and for GMP failures during the PPQ runs. This has caused the firm to repeat the PPQ runs, and per the applicant's communication dated 2/26/20, site

wide employee training will be completed in the 2nd quarter 2020, and presumably additional PPQ runs will be done (post-LCM telecon with FKD on 3/6/2020).

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

The drug product contains the following (b) (4) excipients (Table 73). Excipients are released based on the confirmation of the manufacturer's Certificate of Analysis and in-house testing by either FinVector Oy or a contract test laboratory. All excipients comply with the applicable (b) (4) standards. There is a novel excipient: Syn3 (detailed in section 3.2.P.4.6, below).

Table 54: List of Well-Established Excipients in ADSTILADRIN® Drug Product

Excipient	Reference Standard	to	Approved Supplier(s)
Citric acid monohydrate	(b) (4)		
Tri-sodium citrate dihydrate	(b) (4)		
Polysorbate 80	(b) (4)		
Hydroxypropyl-beta-cyclodextrin	(b) (4)		
Sodium dihydrogen phosphate dihydrate	(b) (4)		
Tromethamine	(b) (4)		
Sucrose	(b) (4)		
Magnesium chloride hexahydrate	(b) (4)		
Glycerol	(b) (4)		
Water for Injection	(b) (4)		In house system

3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures

All (b) (4) excipients are tested and released according to the respective (b) (4) requirements, using the methods described and qualified as defined by the respective (b) (4). The analytical procedures for the novel excipient Syn3 (N-(3-cholamidopropyl)-N-(3-lactobionamidopropyl)-cholamide), are described fully in Section 3.2.A.3, Novel Excipients. (b) (4)

3.2.P.4.4 Justification of Specifications

All (b) (4) excipients are tested and released according to the respective (b) (4) requirements. No further justification of specifications is required.

Please see below for details of the specification for Syn3 (N-(3-cholamidopropyl)-N-(3-lactobionamidopropyl)-cholamide). The release testing of Syn3 is verified by FinVector Oy (b) (4)

3.2.P.4.5 Excipients of Human or Animal Origin

The Excipients are not derived from or manufactured using materials of human or animal origin.

3.2.P.4.6 Novel Excipient

The DP contains a novel excipient, called Syn3. Syn 3 acts as a surfactant and also helps in viral infectivity. Please refer to section 3.2.A.3 for additional details about this novel excipient.

3.2.P.5 Control of Drug Product

3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

Table 55: ADSTILADRIN® Drug Product Release Specification




















Test	Method	Testing Facility	Acceptance Criteria
General Tests:			
Appearance	(b) (4)	FinVector Oy	Opalescent colorless solution, practically free of visible particles
Extractable volume	Determination of extractable volume by (b) (4)	FinVector Oy	≥ 20.0 mL
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Identity:			
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Concentration:			
Viral particle concentration	Determination of rAd-IFN total viral particle concentration by (b) (4)	FinVector Oy	3 x 10 ¹¹ vp/mL (b) (4)
Activity/potency:			

	(b) (4)		
	(b) (4)		
Potency assay	(b) (4)	FinVector Oy	(b) (4)
Purity:			
(b) (4)			
Safety:			
Endotoxin	(b) (4)	FinVector Oy (b) (4)	(b) (4)
Sterility	(b) (4)		Sterile

Justification for DP specifications:

Table 56: Justification of ADSTILADRIN® Specifications

Test	Specification	Justification
General Tests:		
Appearance	Opalescent colorless solution, practically free of visible particles	The appearance test is a general indicator that the manufacturing process has been performed successfully. The product is administered to the bladder via catheter. Some visible particles are therefore deemed acceptable.
Extractable volume	≥ 20.0 mL	The specification for extractable volume is based on the requirement to enable the clinical dose of Drug Product to be withdrawn from the vial.
		(b) (4)

		(b) (4) 
		
Identity:		
		(b) (4) 
Concentration:		
Viral particle concentration	3×10^{11} vp/mL  (b) (4) 	<p>The concentration of virus particles in the Drug Product reflects the safe and efficacious viral particle dose demonstrated in the clinical studies (target 3×10^{11} vp/mL instilled). The range is based on commercial batch data available to date using a 99% (95% confidence) tolerance interval and was calculated from the full dataset (190723 RTU tolerance interval report).</p>
Activity/potency:		
		(b) (4) 
		
Potency assay		(b) (4) 

Test	Specification	Justification
Purity:		
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Safety:		
Endotoxin	(b) (4)	(b) (4) The specification is based on the levels achieved in the current process and found to be safe in clinical studies.
Sterility	Sterile	The Drug Product is tested for sterility by (b) (4) in accordance with the requirements (including sampling requirements) of (b) (4). ADSTILADRIN® is administered as an instillation into the bladder, and must therefore pass the sterility test in order to assure patient safety.

CMC Comments on the DP specifications: DP Lot release specifications are acceptable, except for the endotoxin test. The endotoxin test needs to be reverified for its function in the DP (b) (4) (ability of the test to perform as expected in the presence of Syn3) and the data has to be submitted to the BLA. Note that the endotoxin limit is set at (b) (4). Given that the dose is 75 mls this would mean potentially up to (b) (4) of endotoxin per dose. However given the route of administration of the DP, this is not expected to be a major concern. A review of the batch records also show that the batches have routinely had (b) (4). It may be good to revise the endotoxin limit for product consistency. Assay verification for endotoxin is a part of the CR issues.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

In clinical trials Adstiladrin was prepared by combining the vector (rAd-IFN DP) with diluent and excipient Syn3 to form an (b) (4) for instillation into the bladder. To ease the handling in clinical setting, for commercial use it is now proposed that Adstiladrin (b) (4) will be filled in ready to use formulation (RTU).

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

(b) (4)

Endotoxin per (b) (4) (SOP-QC-158)

Reviewed by DBSQC. Briefly, verification is not acceptable. The communication is covered in CR letter.

Sterility per (b) (4)

Reviewed by DBSQC, Briefly, verification is acceptable.

Overall Reviewer's Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3:

In response to FDA's IR request on endotoxin testing procedures and assay qualification, additional information on assay qualification was submitted on 3/2/2020 (amendment # 40). However the endotoxin assay was not appropriately qualified (please refer to DBSQC review on endotoxin assay qualification for additional details). This is a part of the CR issues.

The other assays for release of DP (including rAd-IFN DP and Adstiladrin RTU) have been appropriately designed and validated. The only exception is the (b) (4), which still needs to be validated for robustness.

3.2.P.5.4 Batch Analyses

Table 60: Details of ADSTILADRIN® Batches (Drug product) Manufactured to Date

Batch number	Drug Substance batch	Number of vials for release(a) (b)	Theoretical number of vials that would be filled if all the (b) (4)	Batch use
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(b) (4)

(b) (4)

(b) (4)

CMC Comment: The above data is from the information included in the BLA and has not been updated since the time the BLA was submitted on 9/3/2019. The FinVector (the manufacturer for FKD, the applicant) has stored (b) (4) batches of Drug Substance batches at (b) (4) (as of 1/28/2020), ready to be used to manufacture the drug product. However, many of these DS batches may not be fully suitable for the DP manufacture due to various GMP failures at the manufacturing site (please refer to the PLI observations). The firm was asked to provide a list of DS batches that they would be able to fill once all the GMP issues are fully addressed (monthly CMC discussion held on 3/6/2020). The response to this IR will be reviewed, , along with the rest of the responses to the PLI observations, when submitted. This IR response is still outstanding and is not included in this BLA review. The review cut-off date is 3/2/2020 to enable completing of the review within the PDUFA clock.

Manufacturing scale/capacity:

The current commercial manufacturing process is capable of producing approximately (b) (4) vials of the DP per lot. Table 60 (above) provides an exact number vials that were manufactured per commercial manufacturing process and the number of vials from each lot that are ready for release (pending GMP qualifications). Below (Table 61) is the historical manufacturing capacity during Phase 3 clinical studies. *CMC note: The (b) (4) and the volumes are different (b) (4) vs 20mL for the Phase 3 clinical lots. The applicant has plans to (b) (4)*

but this will be a subject of a future supplement to the BLA).

(b) (4)

(b) (4)

(b) (4)

(b) (4)

CMC Note: Please refer to section 3.2.S.2.2 for batch numbering scheme. The manufacturing date of the Drug product batch is the date it is filled.

CMC Comments: The BLA contains the batch records for a batch of (b) (4), and product batches as described in Table 61, above. This data will be updated when additional information is submitted by the applicant (information pending on the new DP lots). For an analysis of data trends, please refer to the figures 9 in section 3.2.S.2.4. There is no trend analysis (explanation for any deviations/abnormal values) and this information is pending.

CMC Comment on the manufacturing date: The manufacturing date for the drug product is stated as the date the DP is filled in the final vial. This is acceptable for calculating the product stability and shelf life.

CMC comment on the Batch definition: The applicant uses the term Batch and lot interchangeably. This is acceptable for this product as (b) (4) batch and all the (b) (4).

3.2.P.5.5 Characterization of Impurities

The DP manufacturing process involves (b) (4). As such “there are no known impurities arising from the (b) (4) process of ADSTILADRIN®”

3.2.P.6 Reference Standards or Materials

No separate reference standard used for the DP qualifications. Please refer to the reference standards used to qualify the (b) (4) assay methods. (b) (4) are given in the following Table:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

3.2.P.7 Container Closure System

There are three elements to the primary packaging of Drug Product:

1. Clear Type (b) (4) glass (b) (4) vials (nominal volume 20 mL), supplied by (b) (4).
2. 20 mm (b) (4) stoppers based on bromobutyl rubber supplied by (b) (4). The inner face is sealed with a (b) (4) and the external non-contact face is (b) (4).
3. 20 mm aluminum crimps with flip-off seal supplied by (b) (4).

CMC Note: Though the BLA states this is a 20mL vial (bullet 1 above), the COA for this vial says its capacity is 30mL. So it is possible to load 20mL of the drug product in this vial.

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

1. Overview

- The shelf-life claim for Adstiladrin is based on a worst case scenario where storage is at (b) (4) from the date of manufacture (defined as date of filling).
- In practice, batches of Adstiladrin will be frozen and stored at below -60°C at the site of manufacture, shipped to the distributor below -60°C (for shipping validation see Section 3.2.P.2.4), and shipped to the clinical site from the distributor below -60°C. Storage at -20°C will only occur at the clinical site.
- Real-time stability data have been generated at both below -60°C and at -20°C. Data below -60°C is available for 18 months on (b) (4) development batches; for (b) (4) of these, the source of (b) (4) was manufactured according to Process 2.2 (see Section 3.2.S.2.6). The remaining (b) (4) development batches utilized (b) (4) manufactured according to the final commercial process (Process 2.3; see Section 3.2.S.2.6). However, these (b) (4) batches were (b) (4) and filled (b) (4), which will not be the case for commercial product.
- An additional (b) (4) batches of Adstiladrin manufactured according to the commercial process (b) (4) DP have been placed on stability at (b) (4) below -60°C (b) (4) and 12 months data are available. (b) (4) of these batches (Batch (b) (4)) was (b) (4) and filled (b) (4) which will not be the case for commercial product.

- Finally, supporting data on (b) (4) batches of rAd-IFNα2b (b) (4) used in the clinical trials (b) (4) manufactured according to Process 2.0) are available for (b) (4) years when stored below - (b) (4) (Batches (b) (4) was also monitored when stored at (b) (4) for (b) (4) years. These data are considered supportive of the inherent stability of the vector under these conditions, though the (b) (4) (b) (4) were different (see Section 3.2.P.2.2). The rAd-IFNα2b (b) (4) remains stable for (b) (4) years when stored below (b) (4).
- Batches of ADSTILADRIN® will be frozen and stored below -60°C at the site of manufacture, shipped to the distributor below -60°C, and shipped to the clinical site from the distributor below -60°C. Storage at -20°C will only occur at the clinical site.
- No photostability studies have been conducted. Storage in the secondary container (cardboard box) and the lack of light at the prescribed storage conditions (freezers at -20°C and below -60°C), as well as shipping conditions ensure that exposure of the product to light prior to use is negligible.

2. Primary Stability Studies

Primary stability studies on Adstiladrin are summarized below. Test procedures are summarized in Table 63 and are the same as described in Section 3.2.S.4.2 and Section 3.2.P.5.2 except for the Syn3 NODA assay which is described in Section 3.2.P.8.3.

The primary container closure system is the same as that described in Section 3.2.P.7.

Table 63: Test procedures for drug product stability testing

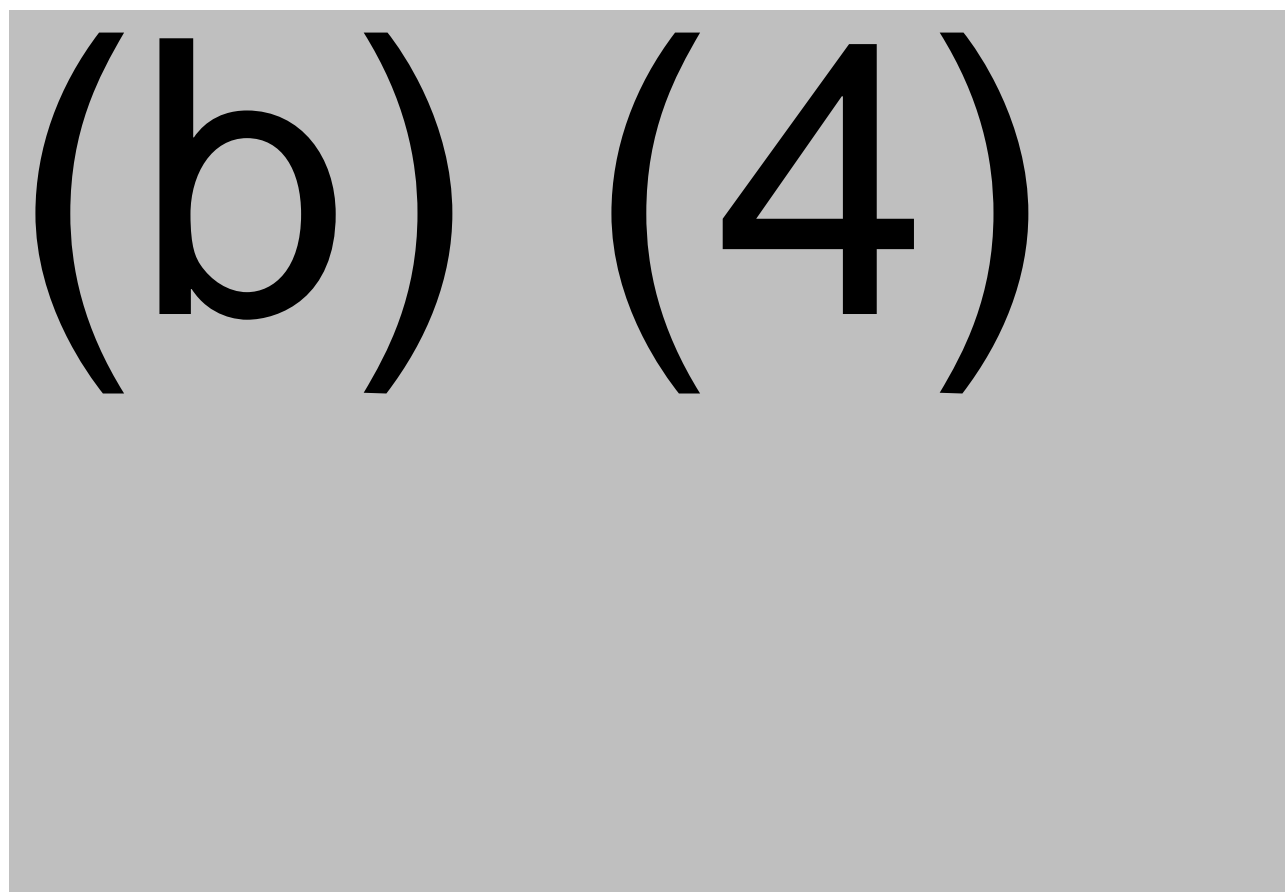
Parameter	Test	Drug Product specification	Relative acceptance criteria (a)
Appearance	Determination of clarity and degree of opalescence & degree of coloration (b) (4)	Opalescent colorless solution, practically free of visible particles	Comparable to (b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Viral particle concentration	Determination of rAd-IFN total viral particle concentration by (b) (4)	3x10 ¹¹ vp/mL (b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Potency assay	(b) (4)	(b) (4)	(b) (4)

(b) (4)			
Sterility	(b) (4)	Sterile	Sterile

CMC Comments: (a) Relative acceptance criteria are relative to the (b) (4) result and take into account assay variability. In order to be considered acceptable, the result of each test at each timepoint must pass both the Drug Product stability specification and the relative acceptance criteria. An updated stability information was submitted on 2/1/22020, amendment # 34, and is reviewed as a part of this stability review.

(b) The batches of Adstiladrin placed on stability are summarized below. All studies are ongoing as of the time of this review (3/19/2020).

(b) (4)



CMC Comments:

(a) All primary lots were manufactured according to the commercial ADSTILADRIN® manufacturing process, although (b) (4). The

(b) (4) process in parentheses refers to the process used to manufacture (b) (4) used in the (b) (4) Process 2.3 is the commercial process (see Section 3.2.S.2.6).

(b) These batches were (b) (4) and filled (b) (4) batch, which will not be the case for commercial product.

(c) For storage at -20°C, vials were initially frozen down to below -60°C, and then transferred to a -20°C freezer, which mimics the real-life situation.

Table 65: ADSTILADRIN® long term stability sampling schedule at below -60°C (b) (4)

Test	Timepoint (Months)					
	0	3	6	9	12	18
Appearance	x	x	x	x	X	x
(b) (4)						
(b) (4)						
Viral particle concentration	x	x	x	x	X	x
(b) (4)						
Potency	x	x	x	x	X	x
(b) (4)						
Sterility	x	-	-	-	-	-

(b) (4)

CMC Notes:

(a) (b) (4) was added after the start of the stability testing of the primary batches; therefore, it will be tested from the next available time point.

CMC comment: The data for the batches in section 3.2.S.8.3 indicate that the Adstiladrin is stable for 12 months at (b) (4) ≤-60°C. Because clinical trials were not performed with the RTU formulation, the expiry should correspond to the 12 month real time stability of the commercial (RTU) batches.

The (b) (4) storage period should be taken into consideration while calculating the stability of the DP. The proposed storage period of 12 months for the DP has not been fully demonstrated and is a part of the CR letter comments. The applicant should also address if the duration of (b) (4) storage prior to DP storage can impact the DP stability. This is also a part of the stability comments.

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

1. Post-Approval Stability Protocol

All existing long-term stability studies with ADSTILADRIN® as described in Section 3.2.S.8.1 will be continued to the final timepoint (b) (4) months) as per protocol.

2. Stability Commitment

(b) (4) [REDACTED] batch of (b) (4) [REDACTED] will be placed on long term stability at -20°C and below -60°C (b) (4) [REDACTED] according to the same protocol described above.

CMC Comments: The reviewer agrees that the stability studies should be continued. For the future, the applicant proposes placing (b) (4) batch on long term stability at -20°C and below -60°C (b) (4). This should depend on the utilization of batches. As more batches are used (b) (4), the number of lots on stability should increase.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

Facilities and equipment are described in detail in the BLA.

The facility has (b) (4) main GMP manufacturing suites called (b) (4). The (b) (4) is a multiproduct facility while the (b) (4) is a dedicated manufacturing facility to be used exclusively for the manufacture of Adstiladrin. The following new information was submitted to the BLA on 10/9/2019 (Amendment # 3) and additional information submitted on 11/7/2019 (amendment # 11) in response to IRs.: *(CMC comment: the (b) (4) manufacturing is not yet a validated manufacturing process and is not a part of this BLA review)*

- The (b) (4) batch in (b) (4) is the commercial scale manufacture.
- (b) (4) suites are capable of producing Adstiladrin at (b) (4) commercial scale at the same time.
- The company has piloted the (b) (4) and plans to manufacture using (b) (4) batch runs in due course, but this is not part of the current BLA application.
- (b) (4) for the process performance qualification of (b) (4) starts in January 2020. The difference between the (b) (4) batches is thus the possible (b) (4)
- (b) (4) (b) (4) produces (b) (4) vials, whereas a (b) (4) produces (b) (4).
- Commercial scale (b) (4) and is the subject of the BLA application with a lot size of (b) (4)

Please refer to DMPQ/OCBQ review for a detailed description of the facilities. *Lapses in the QA QC conditions and staff training are the also reasons for the CR letter.*

3.2.A.2 Adventitious Agents Safety Evaluation

(b) (4)

(b) (4)

Please refer to section on control of raw materials of biological origin (3.2.S.2.3) for information on (b) (4)

(b) (4)

Testing at appropriate stages of manufacture

(b) (4)

❑ Viral Shedding Studies

The shedding of the vector rAd-IFN was assessed in the Phase 1 and Phase 2 studies. The vector DNA was measured in urine using a (b) (4) assay (b) (4). Measurable amounts of rAd-IFN DNA in urine were detected in both the Phase 1 and Phase 2 studies. (partial Phase 1 study data submitted in amendment # 27, dated 1/16/2020 and in amendment 30 dated 1/30/2020).

Phase 1 study:

In the Phase 1 study, 17 patients received a single dose of ADSTILADRIN ranging from 2.25×10^{11} to 2.25×10^{13} vp. Urine samples for rAd-IFN DNA content were collected pre-dose and daily on Days 1 through 7 and on Day 14 (b) (4)

The presence of rAd-IFN DNA in urine was assessed by (b) (4). Generally, greater frequency of detection of samples positive for rAd-IFN derived DNA and persistence of presence correlated with increase in dose level with correspondingly more quantifiable samples at higher doses. At the highest dose concentration of 3×10^{11} particles/mL (Dose Level 5), quantifiable DNA was noted up to Day 3 in three of four subjects with detectable levels of DNA in urine persisting up to Day 14 in these subjects.

Detection of DNA by (b) (4) does not necessarily indicate the presence of intact rAd-IFN virus in urine. Infectivity assessment of (b) (4)-positive samples was not performed.

The (b) (4) assay used in shedding studies to measure vector DNA has been validated (validation report provided). (b) (4)

Phase 2 study:

In the Phase 2 study (rAd-IFN-CS-002), 40 patients with BCG-relapsed or refractory, high-grade NMIBC; patients received up to 4 doses of ADSTILADRIN, at 3 monthly intervals (7.5×10^{12} vp, n = 21; 2.25×10^{13} vp, n = 19). Urine vector DNA levels were measured pre-dose at months 1 and 4, and on Days 2, 4 and 12 following each dose, using a validated (b) (4) method. In urine, all patients had measurable amounts of rAd-IFN DNA at Month 1 Day 2. The number of patients with rAd-IFN DNA in urine slightly declined to 33 patients (84.6%) at Month 1 Day 12. Of 23 patients receiving dose 2, pre-dose levels of 20 patients (87.0%) were negative for rAd-IFN DNA and 3 patients (13.0%) had measurable rAd-IFN DNA in urine resulting from the first dose. At Month 4 Day 4, 19 patients (90.5%) receiving dose 2 had rAd-IFN DNA in urine but this dropped to 6 patients (28.6%) by Month 4 Day 12. Results for the 2 dose cohorts were comparable.

Taken together, data from phase 1 and phase 2 studies indicate that rAd-IFN-derived DNA (not necessarily intact viral particles) is likely to be excreted in urine in gradually declining numbers of patients for up to approximately 14 days. In phase 2 study, at 1 day after administration, rAd-IFN-derived DNA was detected in urine of all (n=19) subjects at the median levels of 1.5×10^6 copies/ml, which shows a continuous decline with time. At 12 day, 16 out of 19 subjects (84.2%) subjects had detectable levels of rAd-IFN-derived DNA with a median level of 2.5×10^4 copies/ml urine. Measures to minimize exposure of the environment to vector shed in urine are discussed (refer to *Environmental Analysis*).

To mitigate the risk of releasing vector in urine in the sewage water, in the USPI patient counseling information, patients and their caregivers are instructed to add 110 mL of bleach (sodium hypochlorite or hydrogen peroxide disinfectant) to the toilet bowl after each instillation prior to voiding and wait 15 minutes before flushing the toilet after each instillation and repeated for the first 2 days after each instillation during which transient shedding is expected.

CMC analysis and comment: Vector shedding was evaluated only in the urine samples (and not in other secretions/excretions). Considering the local administration of the vector and limited systemic exposure, vector shedding analysis only in the urine samples is acceptable. Only the rAd-IFN DNA was measured and not the intact infectious viral particles. The shedding of the vector rAd-IFN was assessed in the Phase 1 (4 subjects at the highest dose of 3×10^{11} vp/mL) and Phase 2 studies (19 subjects at the 2.25×10^{13} vp). All together (including lower dose levels) the shedding studies include data from 57 subjects (17 phase 1 and 40 phase 2). Vector shedding was evaluated only in the urine samples (and not in other secretions/excretions). The data from phase 1 and phase 2 studies (in a total of indicate that rAd-IFN-derived DNA (not necessarily intact viral particles) is likely to be excreted in urine in gradually declining numbers of patients for up to approximately 14 days. In phase 2 study, at 1 day after administration, rAd-IFN-derived DNA was detected in urine of all (n=19) subjects at the median levels of 1.5×10^6 copies/ml, which shows a continuous decline with time. At 12 day, 16 out of 19 subjects (84.2%) subjects had detectable levels of rAd-IFN-derived DNA with a median level of 2.5×10^4

copies/ml urine. Most of the viral DNA is detected between day 2 and day 4 of each cycle. The maximum amount of virus DNA was in 1 subject (b) (4) who shed 8.9×10^5 copies detected on day 4, followed by 1.5×10^6 copies of DNA on day 12. The same subject also had a high level of virus shedding on day 2 after the second cycle (4.8×10^7 copies). However the viral genomic copy numbers were close to the level of detection by day 12 of the second cycle. These results showed that the virus is not retained long and is normally shed by 2 weeks after administration. Most of the viral DNA is detected between day 2 and day 4 of each cycle. Because of the replication-incompetent nature of the vector and low environmental risk (refer to EA), evaluation of vector DNA and not the infectious viral particles is acceptable.

3.2.A.3 Novel Excipients

CMC Note: The drug product contains a novel excipient, called Syn3. It is a surfactant and is expected to help enhance viral infectivity. The CMC aspects of this novel functional excipient was evaluated by a CDER consult reviewer (Rajiv Agarwal). Summary of the consult reviewer is included here. For details of the submitted information, please refer to the consult review memo (to be included in the EDR).

Syn3NODA is a novel excipient that is utilized to “enhance” the delivery of SCH 721015 substance. For the commercial formulation, it is manufactured at (b) (4)

(b) (4)

The manufacture and control of (b) (4) including the rationale for starting materials is in line with (b) (4) guidelines and (b) (4). All raw materials, solvents, and reactants are tested upon receipt, and released for use according to the specifications developed for each material. No catalysts are employed in the (b) (4) process.

A reasonable approach is adopted to characterize this novel excipient using different (b) (4) techniques and studies. The structure of Syn3NODA is consistent with the (b) (4) route.

Certificate of Analysis of the batches manufactured at the (b) (4) sites (b) (4); Clinical) are provided and deemed adequate.

(b) (4), manufactures the batches for late phase clinical trials and for the to-be-marketed commercial product.

(b) (4) methods for the (b) (4) and related (b) (4) of this functional excipient (syn3NODA alone) are developed and validated. The validation of non-compendial analytical procedure is performed in accordance with (b) (4) guidance (b) (4)

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

(b) (4)

3.2.R Regional Information (USA)

❑ Executed Batch Records

CMC Note: The BLA contains examples of the executed batch records for Drug product lot (b) (4). Please see section 3.2.P.5.4 (batch analysis) for additional information. All the batch record information is not reproduced in this review.

❑ Leachables and Extractables:

CMC note: Below is the summary of a report for extractables that was submitted on 2/14/2020. (amendment # 36) An interim report was also submitted to the BLA on 1/31/2020 in response to FDA's IR.

All product contact materials are single use. These materials include the (b) (4)

. A screening exercise identified the extractables given in Table 66 as high priority for further investigation from a health perspective. A subsequent formal health risk assessment of these compounds/groups of compounds concluded that any potential exposure to these extractables (including the “unknowns”) is highly unlikely to pose any significant health risks to patients receiving treatment via the RTU process.

- A formal health risk assessment was done in line with ICH guidelines.
- The analytical studies detected (b) (4) organic leachables/groups of organic leachables from the RTU process.
- Worst-case patient exposures were estimated, both for a treatment day, and as averaged exposures over the one-year treatment period. Possible health risks were then assessed.

Assessment methods: The majority of the chemically-identified leachables lacked mutagenic character (i.e. were (b) (4)). As such, the health risk assessment was based on permitted daily exposures (PDEs) derived from key no-observed-adverse-effect levels (NOAELs) from appropriate high-quality subacute or subchronic toxicity studies where possible, using ICH PDE guidance. This process was supported by Expert Group derivations of tolerable exposure figures and health risk evaluations, and in a number of cases parenteral PDEs derived under ICH (b) (4) were employed directly. Expert Group reviews, together with REACH dossiers, served as valuable data sources on the identified compounds. Where necessary and appropriate, toxicity data on structurally-similar analogues were used (in a “read-across” approach). Where suitable data were lacking, the TTC approach was adopted. For chemically-identified extractables that are potentially mutagenic but were lacking substance-specific insights into cancer potency, the health risk assessment was based on default TTC values, adjusted to

reflect the brief exposure period (in line with (b) (4) principles). In all cases ICH principles (b) (4) were followed, and the patient exposures were compared with PDEs for each compound/group of compounds.

For the chemically-identified leachables/groups of leachables assessed (including the partially characterized (b) (4) and the (b) (4)

At such low concentrations, local irritation is not expected. Similarly, none of these compounds/groups of compounds were considered to pose a sensitization risk.

Turning to systemic toxicity, for all chemically-identified extractables, the relevant margin of safety (MoS) figures were greater than (b) (4) (in some cases markedly so), thus demonstrating toxicological acceptability.

The analyses also detected a number of unidentified organic compounds (“unknowns”, for which there was no chemical characterisation. These were evaluated assuming that they contain a structural alert for mutagenicity. They were additionally assessed as (b) (4), assuming them all to be (b) (4)

When assessed as mutagens, the estimated (hypothetical) maximum cancer risk was much less than (b) (4), indicating tolerability. When assessed as (b) (4), the MoS was lower than (b) (4) for acute exposure on a treatment day (b) (4). Taking into account both the intravesical route of administration and the short duration of treatment (a total of 4-8 hours, over just four days in a lifetime), these extractables are not expected to pose any significant thresholded toxicity risk. This assessment also does not evaluate any potential patient benefits of treatment with the RTU process, which may be considered to counterbalance this slight risk.

Overall it was concluded that the potential exposure to these leachables (including the “unknowns”) is highly unlikely to pose any significant health risks to patients receiving treatment via the RTU process.

Table 66: Health-critical extractables – a summary

Extractable/group of extractables	CAS RN ³	Daily patient exposure during a single treatment (µg/treatment day) ⁴	Averaged patient exposure over a one-year treatment period (µg/day) ⁵	Permitted daily exposure (PDE) used in the formal risk assessment (b) (4)	Health risk assessment (margin of safety ⁶) considering patient exposure during a single treatment	Health risk assessment (margin of safety ⁷) considering averaged patient exposure over a one-year treatment period
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(b) (4)

(b) (4)

(b) (4)

Extractable/group of extractables	CAS RN3	Daily patient exposure during a single treatment (µg/treatment day)4	Averaged patient exposure over a one-year treatment period (µg/day)5	Permitted daily exposure (PDE) used in the formal risk assessment (b) (4)	Health risk assessment (margin of safety6) considering patient exposure during a single treatment	Health risk assessment (margin of safety7) considering averaged patient exposure over a one-year treatment period

(b) (4)

(b) (4)



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(b) (4)



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CMC note: only a partial list of leachables identified in the drug product and evaluated in this study is reproduced here.

CMC Comment on the leachables and extractables studies: The leachables and extractables studies appear to be a comprehensive analysis of materials that could leach out of the product contact materials during the manufacturing and storage process steps. The vials used for DP storage have also been evaluated and the data included in the BLA. The data shows that though there are chemical leached out of the plastic tubing, I agree with the applicant's assessment that these chemicals do not pose a risk of toxic reaction in the patients. These study results are acceptable.

☐ **Combination Products**

Not a combination product.


Module 1

A. Environmental Assessment or Claim of Categorical Exclusion



Environmental assessment

Wild-type Ad5 (classified as Risk Group 2 category) is mainly associated with respiratory and gastrointestinal (including hepatic and urinary) infections. Most infections are mild and require no therapy or only symptomatic treatment. Although usually transient, infections in the newborns and immunocompromised individuals may be serious.

(b) (4)



(b) (4)

Vector shedding: There is a reduced risk of viral shedding via nasopharyngeal secretions, skin or stools when adenoviral vectors are administered into compartmentalized areas of the body. Nadofaragene firadenovec is administered to the patient by instillation into the bladder therefore shedding would most likely occur via the urine. Shedding in urine was assessed as part of the clinical development program by (b) (4) and measurable amounts of nadofaragene firadenovec-derived DNA in urine were detected in both phase1 and phase 2 studies. Measurements of nadofaragene firadenovec in urine by (b) (4) reflect the presence of DNA fragments in the biological sample but not necessarily intact viral particles. However, intact vector voided in urine may carry a risk of transducing human cells with the IFN gene. Based on calculations predicted by natural micturition metrics, intact vector particles in the bladder that

could be shed will have been reduced by (b) (4). To mitigate the risk of releasing vector in urine in the sewage water, patients and their caregivers are instructed to add 110 mL of bleach (sodium hypochlorite or hydrogen peroxide disinfectant) to the toilet bowl after each instillation prior to voiding and wait 15 minutes before flushing the toilet after each instillation (and repeated for the first 2 days after each instillation during which transient shedding is expected). Both substances have been shown to be effective in inactivating wild type adenovirus and have been shown to render nadofaragene firadenovec transduction-incompetent as part of the development program of ADSTILADRIN®.

Overall, in the case of unintended transfer of vector to a human recipient, the associated risks are expected to be very low, since the vector is not able to replicate and the dose, which may conceivably be transferred (from aerosol, splashing or fomites, for example) will be orders of magnitude lower than that received by patients. If vector were to get into the sewage water, it will be markedly diluted and the risk of exposure of the surrounding ecosystem is negligible. Further, due to the very restricted host range, the risk to other species (plants or animals) being exposed to the diluted virus is negligible.

(b) (4)

CMC comment: The acceptance limit of (b) (4) (and the proposed revised calculated limit of (b) (4)) exceeds FDA expectations. However, considering the localized administration and limited systemic exposure, the proposed acceptance limit is acceptable.

(b) (4)

The human adenovirus is highly specific to its natural host (humans) and has a restricted host range for productive infections. Wild-type Ad5 is known to replicate only in a very limited species of animals other than humans, when infected experimentally: essentially Syrian hamster, and to some extent in cotton rat. The virus does not infect plants or other microbes and is not known to be involved in environmental processes.

Only healthy, trained medical professionals are involved in the handling of nadofaragene firadenovec and these individuals will follow established routine practices for dealing with potentially biohazardous materials alongside using appropriate protective equipment and disinfectants. In case of a spill containing nadofaragene firadenovec, disinfectant will be present in the preparation area and patient room and will be used to inactivate the spill. Thus, the likelihood of occupational exposure is low. The likelihood of accidental release of the GTVV into the environment by handling errors is negligible. The proposed mitigation measures to minimize the potential risk associated with nadofaragene firadenovec are reasonable.

CMC comment: During the pre-license inspection, it was noticed that the disinfectant efficacy studies to inactivate adenovirus were not adequate. In particular, the SOPs to inactivate vector spillage did not reflect the results from the efficacy studies. In addition, applicant switched the disinfectants in the

November, 2019 and studies to demonstrate the efficacy of the new disinfectants to inactivate adenovirus has not been performed. These observations were cited in 483 form.

A risk estimation of potential environmental effects of nadofaragene firadenovec is summarized in the table below:

Table 67: Risk estimation based on potential hazards associated with nadofaragene firadenovec

Potential hazards associated with the GTVV nadofaragene firadenovec	Likelihood		Magnitude (consequence in case of)		Overall risk	
	Without mitigation	With mitigation	Without mitigation	With mitigation	Without mitigation	With mitigation

(b) (4)

(b) (4)

(b) (4)

CMC comments: The applicant's assessment of the potential impact of the nadofaragene firadenovec on the environment, and the mitigation strategies are adequate.

B. Labeling Review

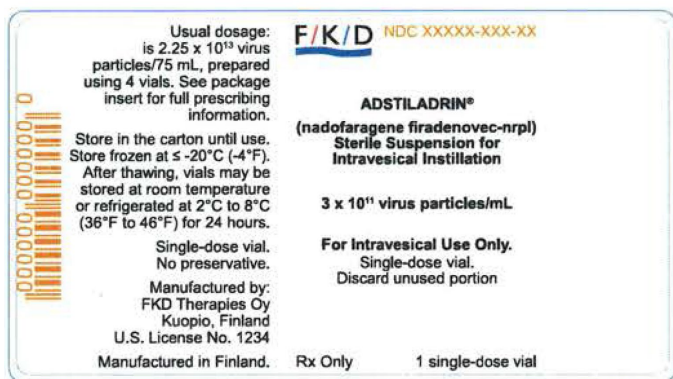
Full Prescribing Information (PI):

CMC Note: Labeling review is incomplete as of 3/11/2020 due to incomplete GMP standards for product manufacture. This section will be revised once the GMP issues are addressed and the manufacturing resumes.

Carton and Container Label:

Figure 19: Vial Label

Figure legend: Illustration of the actual vial label depicting the contents of the information

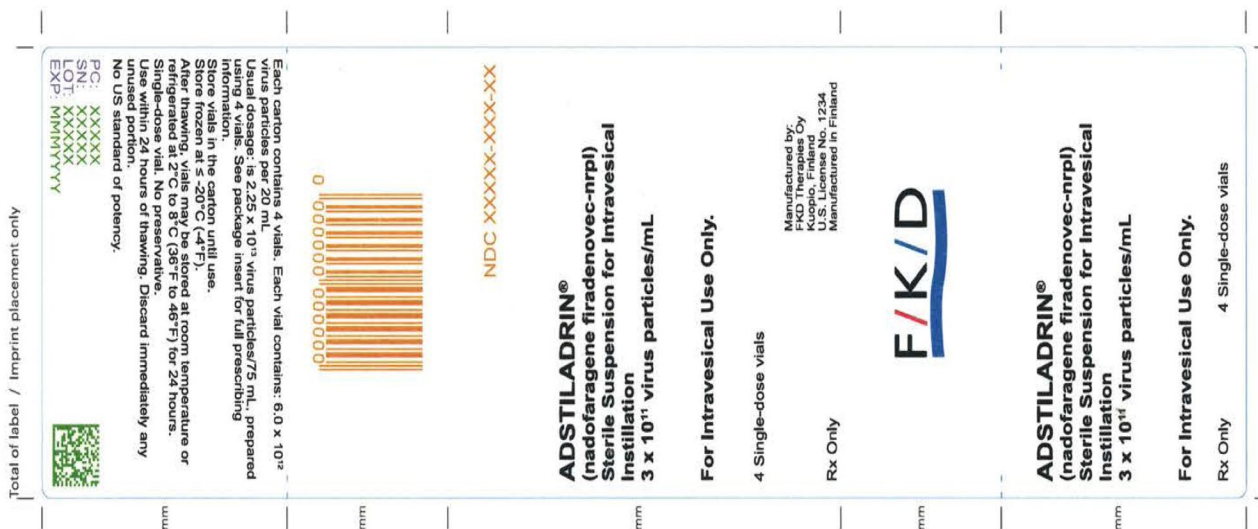


CMC Comment on the vial label: The requirement 610.60 (a)(4) expiration date is not on the vial but is on the secondary container and this is acceptable.

The BLA does not contain a picture of the vial with the label affixed on it, so it is not possible to confirm that the size of the label complies with the requirement of 610.60 (e) visual inspection. The carton and vial labels were submitted to the BLA on 10/22/2019 – amendment # 7, in response to a FDA IR. This will be reviewed again when the labeling review is undertaken. This part of the container label is as yet incomplete.

Figure 20: Carton Label: (secondary container)

Figure legend: Illustration of the actual carton label depicting the contents of the information



CMC comment on the carton label: Each carton will contain 4x20mL vials to enable withdrawing a total per dose volume of 75mL. The expiry date is included on the carton, in addition to the identifying name and address. However this label is not fully compliant with all the requirements of 610.60-62 (letter sizes are not appropriate- proprietary name) and will be reviewed and revised at the time of approval.





Modules 4 and 5

Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints






(b) (4)

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

(b) (4)



(b) (4)



Lot Release Testing:

This product is subject to CBER lot release testing. The lot release testing information (lot release protocol template) was submitted in amendments # 15 (dated 11/19/2019) and in amendment # 16 (11/20/2019) in response to FDA's IRs. The Lot Release template is being jointly reviewed by DBSQC and DCGT CMC reviewers. This review is incomplete.

Labeling: Labeling information including an unique product identifier (-nrpl) was proposed for nadofaragene firadenovec in amendment 7 (10/22/2019) and in amendment # 18 (12/6/2019). A set of 4 additional suffixs were submitted on 2/10/2020 (amendment # 37). This proprietary name extension is to be finalized prior to approval.