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Summary Basis for Regulatory Action

| | |
|---------------------------------|---|
| Date: | December 16, 2022 |
| From: | Anurag Sharma, PhD, Review Committee Chair, Office of Tissues and Advanced Therapies, Division of Cellular and Gene Therapies |
| BLA STN: | 125700/0 |
| Applicant: | Ferring Pharmaceuticals A/S |
| Submission Receipt Date: | Original submission: September 3, 2019 Resubmission: June 30, 2022 |
| PDUFA* Action Due Date: | December 30, 2022 |
| Proper Name: | nadofaragene firadenovec-vncg |
| Proprietary Name: | ADSTILADRIN |
| Indication: | For the treatment of adult patients with high-risk Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors |

* PDUFA=Prescription Drug User Fee Act

Recommended Action: The Review Committee recommends approval of this product.

Director, Office of Tissues and Advanced Therapies

Director, Office of Compliance and Biologics Quality

| Discipline Reviews | Reviewer / Consultant - Office/Division |
|--|--|
| <p>CMC</p> <ul style="list-style-type: none"> • CMC Product (Product Office and OCBQ/DBSQC) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ and Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC) | <p>Anurag Sharma, PhD (OTAT/DCGT) Zhili Xu, PhD (OTAT/DCGT) Ramjay Vatsan, PhD (OTAT/DCGT) Robert Aksamit, PhD (OTAT/DCGT)</p> <p>Bradley Dworak, PhD (OCBQ/DMPQ) Laura Fontan (OCBQ/DMPQ) Jared Greenleaf (OCBQ/DMPQ) Nicole Li (OCBQ/DMPQ) Cheryl Hulme (OCBQ/DMPQ) Maureen DeMar (OCBQ/DMPQ)</p> <p>Varsha Garnepudi (OCBQ/DBSQC) Jing Lin (OCBQ/DBSQC) Yen Phan (OCBQ/DBSQC) Tao Pan (OCBQ/DBSQC)</p> |
| <p>Clinical</p> <ul style="list-style-type: none"> • Clinical (Product Office) • Postmarketing safety Pharmacovigilance review (OBPV/DE) • BIMO | <p>Yuxia Jia, MD, PhD (OTAT/DCEPT) Laronna Colbert, MD (OTAT/DCEPT) Daniel Suzman, MD (OND/OOD)</p> <p>Adamma Mba-Jonas, MD, MPH (OBPV/DPV)</p> <p>Colonious King (OCBQ/DIS/BIMO) Christine Drabick (OCBQ/DIS/BIMO)</p> |
| <p>Statistical</p> <ul style="list-style-type: none"> • Clinical data (OBPV/DB) | <p>Jiang (Jessica) Hu, PhD (OBPV/DB)</p> |
| <p>Non-clinical/Pharmacology/Toxicology</p> <ul style="list-style-type: none"> • Toxicology (Product Office) • Developmental toxicology (Product Office) • Animal pharmacology | <p>Iwen Wu, PhD (OTAT/DCEPT) Allen Wensky, PhD (OTAT/DCEPT) Alyssa Galaro, PhD (OTAT/DCEPT) Ying Huang, PhD (OTAT/DCEPT)</p> |
| <p>Clinical Pharmacology</p> | <p>Xiaofei Wang, PhD (OTAT/DCEPT)</p> |
| <p>Labeling</p> <ul style="list-style-type: none"> • Promotional (OCBQ/APLB) | <p>Ben Cyge, PhD (OCBQ/DCM/APLB) Jun Lee, PharmD, PhD(OCBQ/DCM/APLB)</p> |
| <p>Other Review(s) not captured above categories, for example:</p> <ul style="list-style-type: none"> • Consults • Devices • Software | <p>Rajiv Agarwal (CDER/OPQ/ONDP)</p> |

| | |
|--|--|
| <ul style="list-style-type: none"> • Human Factors • FONSI | |
| Advisory Committee Summary | No advisory committee meeting was held |

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1. Introduction

Ferring Pharmaceuticals A/S submitted a Biologics License Application (BLA), STN 125700, for licensure of nadofaragene firadenovec-vncg, with the proprietary name of ADSTILADRIN. ADSTILADRIN is a non-replicating adenoviral vector-based gene therapy indicated for the treatment of adult patients with high-risk Bacillus

Calmette-Guérin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors.

ADSTILADRIN is designed to deliver a copy of a gene encoding human interferon-alfa 2b (IFN α 2b) to the bladder urothelium. The IFN α 2b has pleiotropic anti-tumor effects that include anti-proliferation, apoptosis, angiogenesis inhibition, and stimulation of immune responses. Intravesical instillation of ADSTILADRIN results in cell transduction and transient local expression of the IFN α 2b protein that is anticipated to have anti-tumor effects.

This document summarizes the basis for regular approval of ADSTILADRIN. An ongoing Phase 3 clinical trial provides the primary evidence of safety and effectiveness for the treatment of patients with high-risk BCG-unresponsive NMIBC with CIS, with or without papillary tumors. Our recommendation for approval is based on the clinically meaningful benefit of complete response (CR) rate and duration of response (DoR) demonstrated in the ongoing Phase 3 clinical trial. The more serious risks of ADSTILADRIN include muscle invasive or metastatic bladder cancer with delayed cystectomy and disseminated adenovirus infection in those who are immunocompromised or immunodeficient.

A complete response letter (CRL) was issued for the original BLA submission on April 24, 2020 due to the observations made during pre-license inspection of the product manufacturing facility that were not adequately addressed, and Chemistry, Manufacturing, and Controls (CMC) concerns. CMC concerns included the inadequate qualification of (b) (4), deficient analytical assays for release testing, product stability, and compatibility with the administration device. In response to FDA concerns, the Applicant implemented a comprehensive quality and compliance improvement program based on the quality systems approach at their product manufacturing facility, and specifically addressed the CRL deficiencies. All CRL items were satisfactorily addressed in the June 30, 2022 resubmission.

The Applicant has provided substantial evidence of effectiveness and safety based on a single, adequate, and well controlled single-arm clinical investigation providing compelling evidence of clinical benefit, supported by the initial clinical investigation and preclinical studies. The review team recommends regular approval of this BLA with the Clinical Postmarketing Commitment (PMC) listed in Section 11.c of this document.

2. Background

Disease background

High-risk non-muscle invasive bladder cancer (NMIBC) is defined as the presence of high-grade Ta (confined to urothelium), any T1 (invading lamina propria), or CIS (high-grade flat lesions). Standard treatment for high-risk NMIBC includes transurethral resection of bladder tumor (TURBT), followed by immunotherapy with intravesical BCG that includes induction and maintenance therapy for up to 3 years. BCG treatment fails in up to 50% of patients. In patients with BCG-unresponsive NMIBC, who are at high risk for progression to muscle-invasive or metastatic urothelial carcinoma, the standard of care is radical cystectomy. However, cystectomy is associated with high rates of 90-day post-operative mortality; generally, 1-7% in younger patients who have no comorbidities

seen at academic medical centers, and up to 15% in elderly patients in the SEER database. One intravesical therapy, valrubicin, is approved for patients who are ineligible for cystectomy, but has a low complete response rate (18%) and minimal use due to perceived lack of efficacy. A systemic PD-1 inhibitor, pembrolizumab, administered intravenously, was approved for this population in January 2020 based on a complete response (CR) rate of 41% and median duration of response (DoR) of 16 months.

Product description

ADSTILADRIN (nadofaragene firadenovec-vncg) is a suspension of adenoviral-vector based gene therapy for intravesical instillation. The active ingredient is recombinant, non-replicating adenovirus serotype 5 (Ad5) vector containing a transgene encoding the human interferon alfa-2b (IFNα2b). (b) (4)

. The expression of IFNα2b is driven by the (b) (4)

Intravesical instillation of ADSTILADRIN results in cell transduction and local expression of the IFNα2b protein that is anticipated to have anti-tumor effects.

Table 1. Regulatory History

| Regulatory Events / Milestones | Date |
|---|-------------------|
| 1. IND submission | June 30, 2005 |
| 2. Fast Track designation granted | June 27, 2013 |
| 3. Breakthrough Therapy designation granted | December 13, 2016 |
| 4. Pre-BLA meeting | July 11, 2019 |
| 5. BLA 125700/0 -final module of rolling BLA submission | September 3, 2019 |
| 6. BLA filed | November 1, 2019 |
| 7. Complete Response | April 24, 2020 |
| 8. Type A meeting | September 2, 2020 |
| 9. Re-submission | June 30, 2022 |
| 10. Action Due Date | December 30, 2022 |

3. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

The CMC review team concludes that the ADSTILADRIN manufacturing process and controls can yield a product with consistent quality attributes, and the CMC review team recommends approval.

Manufacturing summary

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

(b) (4)

The drug product (DP) is manufactured by (b) (4) formulation with Syn3NODA (a novel excipient that acts as surfactant and enhances viral infectivity in the urinary bladder), sterile filtration, filling into the final container in 20 mL volumes, visual inspection, labeling and packaging.

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

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

Manufacturing Control strategy

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

Process Validation

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

The validation for the DP manufacturing process was conducted by manufacturing (b) (4) PPQ DP lots at FinVector Oy. Subsequently, with additional gain in process knowledge, the process control strategy was further improved and (b) (4) PPQ batches were manufactured. The data demonstrate that the formulation, sterile

filtration, filling, and labeling steps of the manufacturing process are effectively controlled to produce DP that consistently meets the established product quality acceptance criteria. Additional validation studies, including aseptic process simulation and shipping validation studies, were also performed.

Impurity profile

Impurities can be classified into product-related and process-related impurities.

Product-related impurities include (b) (4)

impurities may include (b) (4)

impurities are (b) (4)

impurities are further controlled by lot release specifications.

Process-related

Most process-related

steps. The residual levels of

Manufacturing Risks

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

Stability

(b) (4)

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

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

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

Comparability

Throughout clinical trials the manufacturing process was optimized and scaled up. For the Phase 1-2 and Phase 3 clinical trials, the vector suspension was supplied as a concentrate, which was combined with a diluent and mixed with Syn3NODA at the hospital pharmacy to form an (b) (4) for instillation to the patient. For commercial supply, a ready-to-use (RTU) presentation (ADSTILADRIN), where the components of the (b) (4) are already mixed in the correct concentrations, was developed to provide a more convenient formulation. The comparability studies have demonstrated that the current manufacturing process produces the ADSTILADRIN DP with critical quality attributes that are comparable to those of the clinical (b) (4) used in Phase 3 studies.

b. Testing Specifications

The analytical methods and their validations and/or qualifications for the ADSTILADRIN DS and DP were found to be adequate for their intended purpose. The final lot release specifications for the DP are shown in the table below.

Table 2. Drug Product Specifications

| Test | Method | Acceptance Criteria |
|------------------------------|---|--|
| General Tests | | |
| Appearance | Determination of clarity and degree of opalescence & degree of coloration; (b) (4) visual method (b) (4) | Opalescent colorless solution, practically free of visible particles |
| Extractable volume | Determination of extractable volume (b) (4) | ≥ 20.0 mL |
| (b) (4) | (b) (4) | (b) (4) |
| (b) (4) | (b) (4) | (b) (4) |
| (b) (4) | (b) (4) | (b) (4) |
| Identity | | |
| Vector Identity | Identity assay by (b) (4) (target: IFNα2b transgene) | rAd-IFNα2b identity confirmed (b) (4) |
| Concentration | | |
| Viral particle concentration | Total viral particle concentration by (b) (4) | 3 x 10 ¹¹ vp/mL (b) (4) |
| Activity/potency | | |

| | | |
|---------------|------------|------------|
| [REDACTED] | [REDACTED] | (b) (4) |
| [REDACTED] | [REDACTED] | [REDACTED] |
| Potency assay | (b) (4) | [REDACTED] |
| Purity | | |
| (b) (4) | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] |
| Safety | | |
| Endotoxin | (b) (4) | [REDACTED] |
| Sterility | (b) (4) | Sterile |

c. CBER Lot Release

The lot release protocol template for ADSTILADRIN was submitted to CBER for review and found to be acceptable after revisions. A Laboratory Quality Product Testing Plan was developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of nadofaragene firadenovec-vncg (ADSTILADRIN) are listed in the table 3 below. The activities performed and inspectional histories are noted in the table and are further described in the paragraphs that follow.

Table 3. Manufacturing Facilities for nadofaragene firadenovec-vncg

| Name/address | FEI number | DUNS number | Inspection/waiver | Results/Justification |
|--------------|------------|-------------|-------------------|-----------------------|
|--------------|------------|-------------|-------------------|-----------------------|

| | | | | |
|---|------------|-----------|------------|-------------------------------|
| FinVector Oy Microkatu 1S 70210 Kuopio Finland (b) (4) drug product (DP) manufacturing including labeling and packaging DP release testing (general, chemical, and microbial) | 3010227150 | 540248820 | Inspection | CBER September 2022 VAI |
| (b) (4) DP sterility release testing | (b) (4) | | | ORA/OPQO (b) (4) VAI |
| (b) (4) DP release testing (sterility and endotoxin) | | | | (b) (4) |

(b) (4), CBER = Center for Biologics Evaluation and Research, ORA = Office of Regulatory Affairs, OPQO = Office of Pharmaceutical Quality Operations, VAI = Voluntary Action Indicated

CBER conducted a pre-license inspection (PLI) of FinVector Oy from September 19-27, 2022, for the (b) (4) DP activities for ADSTILADRIN. At the end of the inspection, CBER issued a Form FDA 483 listing inspectional observations. The firm responded to the observations and the corrective actions were reviewed and found to be adequate and the inspection was classified as VAI. All inspectional issues are considered to be satisfactorily resolved.

(b) (4) conducted a GMP inspection of (b) (4). The inspection report was made available to the FDA on November 30, 2022, via the Mutual Recognition Agreement (MRA) confidentiality commitment. The report included inspectional observations. The corrective and preventive measures in response to the observations were assessed by (b) (4) and the observations were deemed not critical, and a certificate of GMP compliance was issued by (b) (4).

OPQO conducted a surveillance inspection of (b) (4) from (b) (4). At the end of the inspection OPQO issued a Form FDA 483 with inspectional observations and the inspection was classified as VAI.

e. Container/Closure System

The drug product is filled into clear Type (b) (4) glass (b) (4) vials with a nominal volume of 20mL manufactured by (b) (4) with (b) (4) stoppers containing bromobutyl rubber manufactured by (b) (4). Specifically, the stopper inner face is sealed with a (b) (4), while the external non-contact face is (b) (4). Vials are sealed using 20-mm aluminum crimps with flip-off seal manufactured by (b) (4). Ferring Pharmaceuticals conducted the container closure integrity testing at FinVector Oy, employing the (b) (4) test method; all acceptance criteria were met.

f. Environmental Assessment

The Applicant submitted an environmental assessment (EA) pursuant to 21 CFR part 25. The EA provided an assessment of ADSTILADRIN environmental exposure based on known biology of parental virus (Adenovirus serotype 5; Ad5), genetic modifications made to the vector, data from biodistribution and shedding studies, waste disposal, lot release testing, and related nonclinical studies, and a worst-case assumption in each case. The Agency determined that approval of ADSTILADRIN will not result in any significant environmental impact. A Finding of No Significant Impact memorandum has been prepared.

4. Nonclinical Pharmacology/Toxicology

Intravesical administration of ADSTILADRIN was evaluated in an orthotopic mouse model of human bladder cancer (b) (4). Anti-tumor activity was observed following intravesical administration of ADSTILADRIN at 1×10^{10} viral particles (vp)/animal (1×10^{11} vp/mL). A dose-dependent increase in IFN α 2b concentration was observed in urine and bladder tissue of healthy animals. Urine IFN α 2b concentration declined more rapidly following repeat administrations as compared to a single administration in healthy (b) (4) rats, with concentrations sustained longest for a dosing interval of 90 days compared to shorter intervals.

Safety was assessed in cynomolgus monkeys receiving intravesical administration of ADSTILADRIN at dose levels of 2.5×10^{11} vp/animal (1×10^{11} vp/mL), 1.25×10^{13} vp/animal (5×10^{11} vp/mL), Syn3 alone (1 mg/mL), or placebo control on Days 1 and 91, followed by a two-month observation period in a GLP toxicology study. Histopathology changes in ADSTILADRIN and Syn3 groups were noted in the urethra, ureter, and urinary bladder at Days 8 and 98. Findings in the urethra and ureter included mononuclear cell infiltration, urothelial hyperplasia, cytoplasmic vacuolation, and were mostly mild in severity. Findings in the urinary bladder included mononuclear cell infiltration, inflammation, cytoplasmic vacuolation, urothelial hyperplasia, ulceration, and chronic inflammation, and were minimal to mild except for a few animals with moderate ulceration. Severity and incidence were increased at the higher ADSTILADRIN dose

level. Most of the changes were trending towards resolution after the two-month observation period following the second dose, with remaining findings of minimal cytoplasmic vacuolation and mononuclear cell infiltration observed in the urinary bladder and urethra, and minimal inflammation and fibrosis in the urinary bladder. Neutralizing antibodies to the adenovirus were detected in all animals in both the low- and high-dose groups after the second administration. Anti-IFN α 2b antibodies were detected in the majority of animals in the high-dose group (9/10 animals) and to a lesser extent in the low-dose group (7/10 animals) following the second administration and were more sustained in the high-dose group during the observation period.

Biodistribution analysis indicated the presence of vector DNA in the bladder on Days 8 and 98. Vector DNA was detected in the blood of most high-dose animals and a few low-dose animals within the 24-hour post-instillation period and was not detectable at subsequent time points evaluated starting at Day 8. In the urine, animals in both groups had detectable vector DNA for 2-3 days following dosing. In several animals, lower levels of vector DNA were also detected in the liver, kidney and gonads. No vector DNA was detected in the reproductive tissues at the end of the observation period. Human IFN α 2b was detected in serum and urine and declined by Day 15 post-dose, remaining detectable in only 2/10 animals in the low-dose group and 3/10 animals in the high-dose group.

Safety pharmacology, pharmacokinetics, toxicology, and genotoxicity studies were also conducted for the excipient Syn3. Carcinogenicity and reproductive and developmental toxicity studies were not performed for ADSTILADRIN. These studies are not warranted based on the product characteristics, results from the nonclinical studies, and target patient population.

5. Clinical Pharmacology

To support this BLA, the clinical pharmacology evaluation included three studies: one Phase 1 study (Study P03816), one Phase 2 study (Study rAd-IFN-CS-002), and one Phase 3 study (Study rAd-IFN-CS-003) to evaluate the pharmacokinetic, pharmacodynamic, and immunogenicity of ADSTILADRIN. ADSTILADRIN comprises a non-replicating adenovirus vector containing the human IFN α 2b transgene. ADSTILADRIN is administered via intravesical instillation. The proposed ADSTILADRIN dosing regimen is 2.25×10^{13} virus particles (vp) in a total volume of 75 mL administered by intravesical instillation every three months.

Following intravesical administration of ADSTILADRIN, only one subject (2.25 x 10¹³ vp dose group, second dose) had a measurable rAd-IFN-derived DNA in blood. All other subjects did not have any detectable systemic exposure of rAd-IFN-derived DNA. The excipient, Syn3 was detected in serum at the end of instillation for all subjects. The peak level ((b) (4)) was reached at one hour post-dose. The mean half-life was (b) (4) hours (range: (b) (4) hours).

rAd-IFN-derived DNA was detected in urine in all subjects after the first dose of intravesical administration of ADSTILADRIN. A higher frequency of detection of rAd-IFN-derived DNA in urine was associated with a higher dose level. The persistence of

rAd-IFN-derived DNA also correlated with increase in dose level: rAd-IFN-derived DNA was detected up to 14 days post-dose for the highest dose level (2.25×10^{13} vp).

Following intravesical administration of ADSTILADRIN, dose-dependent gene transfer and sustained expression of the human IFN α 2b gene in bladder urothelial cells were observed:

- After administration of the first dose of ADSTILADRIN, all except two subjects at the lowest dose level (2.25×10^{11} vp) had measurable IFN α 2b protein in urine up to Day 10 post-dose. The amount of IFN α 2b protein in urine increased with increasing dose of ADSTILADRIN. The peak concentration of IFN α 2b protein in urine increased from 201 IU/mL to 6640 IU/mL when dose increased from 7.5×10^{11} vp to 2.25×10^{13} vp. Compared to the first dose, the concentrations of the IFN α 2b protein in urine after the second dose were lower.
- IFN α 2b protein in serum was measurable in some subjects and the levels of IFN α 2b protein declined over a period of 10-12 days. In the Phase 2 Study, IFN α 2b protein in serum was detected after first dose in 33% of evaluable subjects on Day 1 post-dose, and in 8% of evaluable subjects on Day 12 post-dose.

The immune responses against ADSTILADRIN (anti-adenovirus type 5 antibody and anti-IFN α 2b antibody) did not have apparent impact on the safety and efficacy of ADSTILADRIN.

6. Clinical/Statistical

The clinical review team's recommendation for regular approval of ADSTILADRIN for the treatment of adult patients with high-risk Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors is based on Study rAd-IFN-CS-003 (CS-003) (Safety and Efficacy).

a. Clinical Program

The effectiveness claim of this original BLA is based on the Study rAd-IFN-CS-003 (CS-003), a single-arm trial that enrolled patients with high-grade, BCG-unresponsive non-muscle invasive bladder cancer (NMIBC). The study population included patients with CIS only, Ta/T1 high-grade disease with concomitant CIS, or Ta/T1 high-grade disease without concomitant CIS. Only patients with CIS with or without concomitant Ta/T1 tumors were considered evaluable for complete response (CR) at any time, which was the primary endpoint of the study. The key secondary endpoint was the durability of CR in patients in the CIS cohort who showed CR at any time after the first administration of ADSTILADRIN.

Study CS-003 enrolled a total of 107 subjects with CIS, of whom 103 were considered to have had adequate prior BCG therapy to be considered BCG-unresponsive per FDA guidance. FDA conducted analysis of response data as per the definition of CR put forth in FDA Guidance for Industry "BCG-Unresponsive Nonmuscle Invasive Bladder Cancer:

Developing Drugs and Biologics for Treatment,” (February 2018). The study protocol did not require a specific cystoscopy imaging technology to be used during screening at study entry; however, FDA considered subjects to be evaluable for response only if there was confirmation that there had been no change from a more sensitive (e.g., blue light or narrow band imaging) modality at screening to a less sensitive (white light) modality.

Of the 107 subjects with CIS who were enrolled onto Study CS-003, 98 subjects were considered to be evaluable for response. Reasons why subjects were considered unevaluable included: no confirmation of BCG unresponsiveness (n=4), unknown cystoscopy imaging modality at screening (n=2), and positive cytology at CR determination without adequate evaluation of the upper and lower urinary tracts (n=3). As these latter two factors were not protocol violations, but rather reflect FDA determination of the evaluable population subsequent to study initiation and conduct, these subjects were considered unevaluable for response and removed from the efficacy population.

Efficacy was based on fifty subjects [51% (95% CI: 41%, 61%)] who experienced a CR at the first disease assessment (three months after initial treatment). No subjects subsequently experienced a CR. The median duration of response was 9.7 months (range 3, 52+). Forty-six percent of subjects who achieved a CR remained in response for ≥12 months.

The Applicant agrees to a Postmarketing Commitment-Status Update to provide annual updates for duration of response for all subjects with CIS with ongoing complete response enrolled in Study CS-003. Annual reports should continue until all enrolled patients have experienced recurrence of high-grade non-muscle invasive bladder cancer, progression, death, or been lost to follow-up through 5 years of follow-up post-treatment. The final status report will be submitted as Postmarketing Commitment-Final Study Report by Jan 31, 2024.

The basis of FDA’s conclusion of substantial evidence of effectiveness comes from a single adequate and well controlled trial with highly persuasive results on the benefit of CR rates, along with duration of response, supported by the initial clinical investigation, clinical pharmacology, and preclinical studies. Therefore, the evidence supports regular approval for ADSTILADRIN.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

Eight Bioresearch Monitoring (BIMO) inspections: four inspections for Protocol rAD-IFN-CS-002 and four inspections for Protocol rAD-IFN-003, involving five Clinical Investigators (CI), were conducted in support of this original Biologics License Application (BLA). The inspections did not reveal substantive problems that impact the data submitted in the application.

BACKGROUND:

BIMO inspection assignments were issued for the following two protocols in support of this BLA:

Protocol rAd-IFN-CS-002: A Phase 2, Randomized, Open Label, Parallel Arm Study to Evaluate the Safety and Efficacy of rAd-IFN/Syn3 Following Intravesical Administration in Subjects with High Grade, BCG Refractory, Relapsed or Resistant Non-Muscle Invasive Bladder Cancer (NMIBC). (Referred to in this document as Protocol 002)

Protocol rAd-IFN-CS-003: A Phase 3, Open Label Study to Evaluate the Safety and Efficacy of INSTILADRIN® (rAd-IFN/Syn3) Administered Intravesically to Patients with High Grade, BCG Unresponsive Non-Muscle Invasive Bladder Cancer (NMIBC). (Referred to in this document as Protocol 003)

Protocol 002 was conducted at four centers in the United States. Forty-three subjects were screened, and 40 subjects enrolled in Protocol 002. The inspections covered 44% of the enrolled subjects.

Protocol 003 was conducted at 33 sites in the United States. 198 subjects were screened, and 157 subjects were enrolled at the time of the database cutoff March 8, 2019. This protocol was on-going at the time of the inspection. The inspections covered 25% of the enrolled subjects.

The inspections were conducted in accordance with FDA’s Compliance Program (CP) 7348.811, Inspection Program for CI. Information submitted in the BLA was compared to source documents at the site. The inspection assignment included specific questions concerning the clinical study.

BIMO INSPECTION SUMMARY:

Eight BIMO inspections were conducted at five CI sites: four inspections were conducted for Protocol 002 and four inspections were conducted for Protocol 003.

| Site Number | Protocol Number | Location | FDA Form 483 Issued | Final Classification |
|-------------|-----------------|--|---------------------|----------------------|
| 02 | 002 | Mayo Clinic | No | No Action Indicated |
| 100 | 003 | Rochester, Minnesota | No | No Action Indicated |
| 16 | 002 | Jefferson Urology Associates, Philadelphia, Pennsylvania | No | No Action Indicated |
| 105 | 003 | Emory University | No | No Action Indicated |
| 03 | 002 * | 1365 Clifton Road NE Atlanta, Georgia | No | No Action Indicated |
| 108 | 003 * | MD Anderson | No | No Action Indicated |
| 01 | 002 | Houston, Texas | No | No Action Indicated |
| 111 | 003 | | No | No Action Indicated |

* Two different Clinical Investigators conducted Protocols 002 and 003 at Emory University

SIGNIFICANT INSPECTIONAL FINDINGS: No significant inspectional findings were observed.

SPONSOR ISSUES: No sponsor issues were identified.

FINANCIAL DISCLOSURE:

The CI CP directs the FDA investigator to ask the CI if and when he/she disclosed information about his/her financial interests to the sponsor and/or interests of any sub-investigators, spouse(s) and dependent children, and if and when the information was last updated. The information submitted to the BLA was verified for each of the inspected clinical sites.

ADMINISTRATIVE FOLLOW-UP:

Information letters were issued to the inspected CI.

c. Pediatrics

A Pediatric Review Committee (PeRC) meeting was held on March 18, 2020, which concurred with the Applicant's request for a full waiver of pediatric studies.

Justification for granting the full waiver was that necessary studies were impossible or highly impracticable to conduct in any pediatric population.

d. Other Special Populations

The efficacy of ADSTILADRIN has not been studied in any other special populations.

7. Safety and Pharmacovigilance

The safety of ADSTILADRIN was also evaluated in Study CS-003, a multicenter, single-arm, open-label study in 157 adult U.S. subjects with high-grade (HG) BCG-unresponsive NMIBC, 103 of whom had BCG-unresponsive carcinoma in situ (CIS) with or without papillary tumors.

Serious adverse reactions occurred in 11% of subjects who received ADSTILADRIN. Serious adverse reactions occurring in >1% of subjects included coronary artery disease and blood in urine.

Permanent discontinuation of ADSTILADRIN due to an adverse reaction occurred in three (1.9%) subjects. Adverse reactions that resulted in permanent discontinuation of ADSTILADRIN included bladder spasm, bladder discharge, and benign neoplasm of the bladder.

Dosage interruptions of ADSTILADRIN due to an adverse reaction occurred in 54 (34%) subjects. Adverse reactions that required dosage interruption in >10% of subjects included bladder discharge (33%), bladder spasm (20%), and urinary urgency (19%).

The most common (>10%) adverse reactions, including laboratory abnormalities (>15%), were increased glucose (38%), bladder discharge (33%), increased triglycerides (30%), fatigue (24%), bladder spasm (20%), urinary urgency (19%), increased serum creatinine (17%), blood in urine (17%), decreased serum phosphate (16%), decreased hemoglobin (16%), chills 16%), pain/discomfort with urination (16%), and fever (15%).

Clinically relevant adverse reactions, each of which occurred in 1% of subjects who received ADSTILADRIN, included coronary artery disease, acute coronary syndrome, atrial fibrillation, dehydration, low blood sugar, fainting, heart failure, pericarditis, brain edema, transient ischemic attack, bile duct stone, anaphylactic reaction, and sepsis.

Two risks were included in the warnings and precautions:

1. Risk of Muscle Invasive or Metastatic Bladder Cancer with Delayed Cystectomy

Delaying cystectomy in patients with BCG-unresponsive CIS could lead to development of muscle invasive or metastatic bladder cancer, which can be lethal. The risk of developing muscle-invasive or metastatic bladder cancer increases the longer cystectomy is delayed in the presence of persisting CIS. Of the patients with CIS treated with ADSTILADRIN on Study CS-003 who underwent subsequent radical cystectomy and for whom pathologic data were available, 14% (n = 6) had muscle-invasive (T2 or greater) disease at cystectomy. Two additional patients who did not undergo cystectomy experienced progression to muscle-invasive disease during the treatment period. If patients with CIS do not have a complete response to treatment after 3 months or if CIS recurs, consider cystectomy.

2. Risk of Disseminated Adenovirus Infection

Dissemination risk in immunocompromised patients is theoretical; however, immunocompromised patients, including those receiving immunosuppressant therapy, may be at risk for disseminated adenovirus infection because of the possible presence of low levels of replication-competent adenovirus in ADSTILADRIN. Individuals who are immunosuppressed or immune-deficient should not come into contact with ADSTILADRIN.

There were no outstanding safety issues. FDA agrees with the Applicant that there is no need for additional risk mitigation measures, beyond appropriate labeling and routine pharmacovigilance activities. The safety profile of ADSTILADRIN, an intravesical therapy without apparent systemic toxicity, is acceptable for this patient population.

8. Labeling

The proposed proprietary name, ADSTILADRIN, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on July 21, 2022 and was found acceptable. CBER communicated the acceptability of the proprietary name to the Applicant on July 27, 2022.

APLB reviewed the proposed prescribing information, carton and container labels on November 29, 2022 and found the information acceptable from a promotional and comprehension perspective.

9. Advisory Committee Meeting

No advisory committee meeting was held because initial review of information submitted in the BLA did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

10. Other Relevant Regulatory Issues

ADSTILADRIN received a Fast Track Designation and Breakthrough Therapy Designation, and this submission was reviewed under priority review.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The Applicant has provided substantial evidence of effectiveness and reasonable assurance of safety based on a single adequate and well controlled single-arm clinical trial that enrolled adult patients with BCG-unresponsive NMIBC with CIS with or without papillary tumors, supported by the initial clinical investigation, clinical pharmacology, and preclinical studies. The compelling evidence of treatment effect in the single adequate and well controlled trial is based on a persuasive clinically meaningful benefit of complete response (CR) rate of 51% (41, 61%) and median duration of response (9.7 months) in a population of patients with BCG-unresponsive NMIBC and CIS with or without papillary tumors.

The Applicant has met the statutory requirements for regulatory approval and the review team recommends regular approval of ADSTILADRIN for the treatment of adult patients with high-risk Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors.

b. Benefit/Risk Assessment

The efficacy of ADSTILADRIN was demonstrated in Study CS-003, a single-arm trial that enrolled 98 evaluable patients with BCG-unresponsive NMIBC with CIS with or without papillary tumors. Results demonstrated a clinically meaningful complete response (CR) rate of 51% (41, 61%) and median duration of response (9.7 months). A total of 23% (n=23) of all evaluable treated patients maintained a complete response for at least 12 months.

The safety profile of ADSTILADRIN was generally limited to transient bladder-related events. The most common (>10%) adverse reactions, including laboratory abnormalities (>15%), were increased serum glucose, bladder discharge, increased serum

triglycerides, fatigue, bladder spasm, urinary urgency, increased serum creatinine, blood in urine, decreased serum phosphate, chills, pain/discomfort with urination, and fever. .

Considering the magnitude of the CR rate, duration of response, and the mild and localized nature of the treatment-emergent adverse events, the review team concluded that ADSTILADRIN has a favorable benefit-risk profile.

c. Recommendation for Postmarketing Activities

Post-marketing study agreed upon with the Applicant as a post-marketing commitment (PMC)

The Applicant commits to providing long-term data on the duration of treatment response for all subjects with carcinoma in situ (CIS) with ongoing complete responses enrolled in clinical trial CS-003. All enrolled subjects will be followed until they have experienced recurrence of high-grade non-muscle invasive bladder cancer, progression, death, or been lost to follow-up through 5 years of follow-up post-treatment.

Final Study Report Submission: Jan 31, 2024.

Risk Evaluation and Mitigation Strategy (REMS)

The review team determined that a REMS is not required for this product.