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Applicant	FKD Therapeutics Oy
Established Name	Nadofaragene firadenovec
(Proposed) Trade Name	ADSTILADRIN
Pharmacologic Class	TBD
Formulation(s), including Adjuvants, etc	
Dosage Form(s) and Route(s) of Administration	Administered by intravesical instillation every three months.
Dosing Regimen	2.25×10^{13} virus particles (vp) /mL in a total volume of 75 mL
Indication(s) and Intended Population(s)	Treatment of high-grade, Bacillus Calmette- Guérin (BCG) unresponsive non-muscle invasive bladder cancer.

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GLOSSARY

AC	advisory committee
AE	adverse event
AESI	Adverse Event of Special Interest
BCG	Bacillus Calmette-Guérin
BLA	biologics license application
CBER	Center for Biologics Evaluation and Research
CI	Confidence Interval
CIS	carcinoma in situ
CR	Complete response
CRT	clinical review template
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	electronic common technical document
FDA	Food and Drug Administration
HGRF	High-grade recurrence free
ICH	International Conference on Harmonization
IND	Investigational New Drug
ITT	intent to treat
MIBC	muscle invasive bladder cancer
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NMIBC	Non-muscle invasive bladder cancer
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PP	per protocol
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
TEAE	treatment emergent adverse event
TURBT	transurethral resection of bladder tumor

1. EXECUTIVE SUMMARY

This original Biologics License Application (BLA) is submitted for ADSTILADRIN (recombinant adenovirus vector containing the interferon- α 2b gene) [INN: nadofaragene firadenovec] for the treatment of subjects with high-grade, Bacillus Calmette-Guérin (BCG) unresponsive non-muscle invasive bladder cancer (NMIBC).

Two clinical studies were included in the application: the completed phase 2 study, rAd-IFN-CS-002, and the ongoing phase 3 pivotal study, rAd-IFN-CS-003.

Study rAd-IFN-CS-002 is a completed phase 2, multi-center, randomized, open label study that evaluated 40 patients with BCG-relapsed or refractory, high-grade NMIBC. Subjects received up to 4 doses of ADSTILADRIN, at 3 monthly intervals. Overall, 14/40 patients (35.0%; 95% CI: 20.6%, 51.7%) were high-grade recurrence free at 12 months, including 7 patents in the 7.5×10^{12} vp/mL dose group (33.3%, 95% CI: 14.6%, 57.0%) and 7 patents in 2.25×10^{13} vp/mL dose group (36.8%, 95% CI: 16.3%, 61.6%).

Study rAd-IFN-CS-003 is a pivotal Phase 3, multi-center, open-label, safety and efficacy study that enrolled 157 patients with BCG-unresponsive, high-grade NMIBC, of whom 107 had carcinoma *in situ* (CIS) and 50 had papillary disease. The dosage is 2.25×10^{13} vp/mL. The primary efficacy endpoint, the complete response (CR) rate, was observed as 53.4% (55/103) with a 95% CI (43.3%, 63.3%). Therefore, the null hypothesis of a true response rate of less than 27% is rejected and the study met its pre-specified success criterion. Among the 55 patients in the CIS cohort who achieved CR, the median durability of CR (a key secondary endpoint) is 9.69 months (95% CI: 9.2, 14.7). All 55 patients with CIS who achieved CR did so by the Month 3 Efficacy Assessment Visit, with 76.4%, 67.3% and 45.5% of these patients remaining HGRF at the Month 6, 9, and 12 Efficacy Assessment Visits, respectively. The study is still ongoing and at the long-term follow up stage. The primary efficacy analysis was based on the primary database lock on 24 May 2019, the date of the Month 12 Efficacy Assessment Visit for the last patient. Other statistical analyses were based on the latest datasets received by CBER under the amendment 125700/0024, in which the data cut was 15 November 2019.

There were no significant safety issues in studies rAd-IFN-CS-002 and rAd-IFN-CS-003.

Overall, the statistical analysis results from studies rAd-IFN-CS-003 and rAd-IFN-CS-002 support the safety and effectiveness of ADSTILADRIN in the proposed indication.

2. CLINICAL AND REGULATORY BACKGROUND

ADSTILADRIN is a non-replicating adenovirus vector containing the human IFN α 2b transgene.

2.1 Disease or Health-Related Condition(s) Studied

Bladder cancer is the fifth most common malignancy in the USA. It can be divided into metastatic, locally advanced, and non-muscle invasive disease subgroups. Non-muscle invasive bladder cancer (NMIBC) can be further subdivided into low and high risk NMIBC. Approximately 75-85% of patients with bladder cancer present with NMIBC, which includes papillary disease (Ta and T1

tumors) and CIS. The majority of cases of NMIBC are low risk; however, 7% of NMIBC are highly aggressive, high-grade papillary disease or CIS.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Treatment of NMIBC is directed at eliminating recurrences and preventing progression to muscle invasive bladder cancer (MIBC) and subsequent metastases. Bacillus Calmette-Guerin (BCG) immunotherapy following transurethral resection of bladder tumor (TURBT) is the standard frontline therapy for the treatment of NMIBC bladder cancer and has been used since the 1970s. BCG treatment fails up to 50% patients, including unresponsive patients and patients who respond but experience recurrence and progression. There are no approved drugs available for subjects who have no response to BCG therapy or therapy failure, and cystectomy is the standard of care in these subjects, which is a complex surgical procedure associated with surgical complications and risk of mortality.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

ADSTILADRIN has been studied in 221 subjects enrolled in four clinical trials in USA. These studies include a Phase 1 dose-escalating single-dose study (P03816), a Phase 1b study (2009-0938), a Phase 2 multi-center, randomized, parallel arm, open label study (rAd-IFN-CS-002), as well as a pivotal Phase 3 multi-center, open label, repeat dose study (rAd-IFN-CS-003).

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Schering Plough Corporation's Investigational New Drug (IND) application, Reference number IND12547, was cleared by the FDA in August 2005. The transfer of IND ownership from Schering Plough, now known as Merck and Co. (Merck), to FKD Therapies Oy took place in November 2011.

An End of Phase 1 meeting was held between FKD and FDA in February 2012 to discuss protocol design issues, including study design, inclusion/exclusion criteria, dose levels, criteria for evaluation, and endpoints for a Phase 2 clinical study (rAd-IFN-CS-002) in patients with BCG-refractory and relapsed NMIBC (CRMTS8327, IND 12547/37). Following the successful completion of this study, an End of Phase 2 meeting was held with FDA in July 2015 (CRMTS9851, IND 12547/71) to discuss the design of the pivotal Phase 3 clinical study (rAd-IFN-CS-003) in patients with BCG-unresponsive NMIBC, and the non-clinical data for the excipient, Syn3, that would be available to support a BLA.

Fast Track Designation was granted for ADSTILADRIN for the treatment of high-grade BCG refractory or relapsed NMIBC on June 27, 2013, and Breakthrough

Therapy Designation for such product was granted for the treatment of transitional cell carcinoma of the bladder on December 13, 2016, respectively.

An Initial Comprehensive Multidisciplinary Breakthrough Therapy teleconference was held on June 29, 2017 (CRMTS 10712) and two subsequent teleconferences held on September 14, 2017 and December 5, 2017. Based on “Guidance for Industry on BCG-Unresponsive Non-Muscle Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment” issued by FDA in February 2018, the primary endpoint for the Phase 3 study (rAd-IFN-CS-003) was amended from the incidence of Event-Free Survival at 12 months in all subjects to the incidence of complete response at any time after the first administration of ADSTILADRIN in subjects with CIS with or without concomitant high-grade Ta/T1 disease, with the key secondary endpoint defined as the durability of complete response. Efficacy in patients with Ta/T1 disease without concomitant CIS, among others, was evaluated as a secondary endpoint (specifically, incidence and durability of high-grade recurrence-free survival).

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

This submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

Two clinical studies, aAD-IFNCS-002 and aAD-IFNCS-003, were reviewed to evaluate the efficacy and safety of ADSTILADRIN for the treatment of high-grade, BCG unresponsive, NMIBC subjects.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

The following documents in the original BLA submission (125700/0003) were reviewed:

- Module 1.6: Meetings
- Module 1.14: Labeling
- Module 2.2: Introduction
- Module 2.5: Clinical Overview
- Module 2.7: Clinical Summary
- Module 5.3.5.2/rad-ifn-cs-002:
 - Study Report Body
 - Protocol
 - Statistical Analysis Plan
 - ADaM Datasets

- Module 5.3.5.2/rad-ifn-cs-003:
 - Study Report Body
 - Protocol
 - Statistical Analysis Plan
 - ADaM Datasets

The first ADaM datasets were submitted in amendments 125700/0003 on 7/5/2019. The applicant submitted the Month 12 clinical study report as well as AdaM datasets under amendments 125700/0007 on 10/22/2019. A 4-Monty Safety Update (4MSU) report for the study aAD-IFNCS-003 was submitted in 125700/0024 on 1/3/2020. The data cut for this 4MSU was 15 November 2019 which includes safety data reported through the Month 15 Efficacy Assessment Visit for all patients, as well as additional safety data for patients whose study participation is beyond the Month 15 visit. This memo reviews ADaM datasets based on datasets submitted under both amendments 125700/0007 and 125700/0024.

5.3 Table of Studies/Clinical Trials

Table 1 summarizes all clinical studies for the develop of ADSTILADRIN.

Table 1: Listing of clinical studies for ADSTILADRIN

Study ID / Centers / Status/ Phase / Type	Population / Age / Sex	Test Product, Regimen, and Duration of Treatment	ADSTILADRIN Treatment (vp/mL)	No. of Patients	Efficacy criteria and conclusion
P03816 2 centers (USA) Completed Phase 1 Safety, PD, PK	BCG-refractory superficial TCC of the Bladder Age: 37-85 16 M / 1 F	ADSTILADRIN Single administration (Part 1) If CR, patient able to receive 2nd administration (Part 2)	2.25 x 10 ¹¹ 7.5 x 10 ¹¹ 2.25 x 10 ¹² 7.5 x 10 ¹² 2.25 x 10 ¹³	17	CR: 7/17 (41.1%) 5/7 patients received a 2nd
2009-0938 1 Center (USA) Completed Phase 1b Tolerability, PD, Efficacy	BCG-refractory NMIBC who refused radical cystectomy Age: 68 - 83 7 M / 0 F	ADSTILADRIN Days 1 and 4	2.25 x 10 ¹³	7	CR: 2/7 (28.6%) No impact on efficacy observed with a second administration at Day 4
rAd-IFN-CS-002, 14 Centers (USA, NCT01687244) Phase 2 Efficacy/Safety	High-grade BCG-refractory or relapsed NMIBC Age: 52 – 91 33 M / 7 F	ADSTILADRIN every 3 months (max 4 administrations in 12 months)	7.5 x 10 ¹² 2.25 x 10 ¹³	40	HGRF survival n=14/40 (35.0%); incidences comparable between dose groups
rAd-IFN-CS-003, 34 Centers (USA) NCT02773849 Phase 3 Efficacy/Safety	High-grade BCG unresponsive NMIBC Age: 39 – 89 129 M / 28 F	ADSTILADRIN every 3 months (max 4 administrations in 12 months)	2.25 x 10 ¹³	157	CR at any time point After 1 administration: 55/103 (53.4%) patients

Source: Adapted from BLA125700/0003/m2/27-clin-sum, summary-clin-efficacy bladdercancer.pdf, Section 2, Table 2, page 9-12.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: rAd-IFN-CS-003

Study rAd-IFN-CS-003 is an open-label, phase III study to evaluate the safety and efficacy of ADSTILADRIN for high-grade, BCG unresponsive NMIBC patients.

6.1.1 Objectives

The primary objective of this study is to evaluate the complete response (CR) rate in patients with CIS (with or without concomitant high-grade Ta or T1 papillary disease).

The secondary objectives of this study are:

- To evaluate the durability of CR in patients with CIS who achieve CR.
- To evaluate the rate of event-free survival, where event-free survival is defined as HGRF survival in patients with high-grade Ta or T1 papillary disease (without concomitant CIS).
- To evaluate the durability of event-free survival in patients with high-grade Ta or T1 papillary disease (without concomitant CIS), who have no recurrence of high-grade Ta or T1 papillary disease. For comparison purposes, this is evaluated in patients with CIS.
- To determine the incidence of and time to cystectomy.
- To determine the overall survival in all patients.
- To determine the anti-adenoviral antibody levels for correlation to response rate.
- To evaluate the safety of ADSTILADRIN.
- To monitor the durability of response during the long-term follow-up period.

6.1.2 Design Overview

This is an ongoing Phase III, multi-center, open-label, repeat-dose study to investigate the safety and efficacy of ADSTILADRIN administered intravesically to BCG unresponsive patients with high-grade NMIBC.

There are two cohorts defined in this study:

- CIS cohort - patients with CIS (with or without concomitant high-grade Ta or T1 papillary disease)
- Papillary disease cohort - patients with high-grade Ta or T1 papillary disease (without concomitant CIS)

The duration of this study is up to 4 years.

There is an initial 12-month treatment period. The first dose of ADSTILADRIN was administered intravesically on Day 1 (Month 1). All subjects were evaluated for evidence of high-grade disease recurrence with cytology and cystoscopy to determine accurate staging. Biopsies were performed if clinically indicated. If no evidence of high-grade disease recurrence was detected at any Efficacy Assessment Visit, a further dose of ADSTILADRIN was administered at Day 90

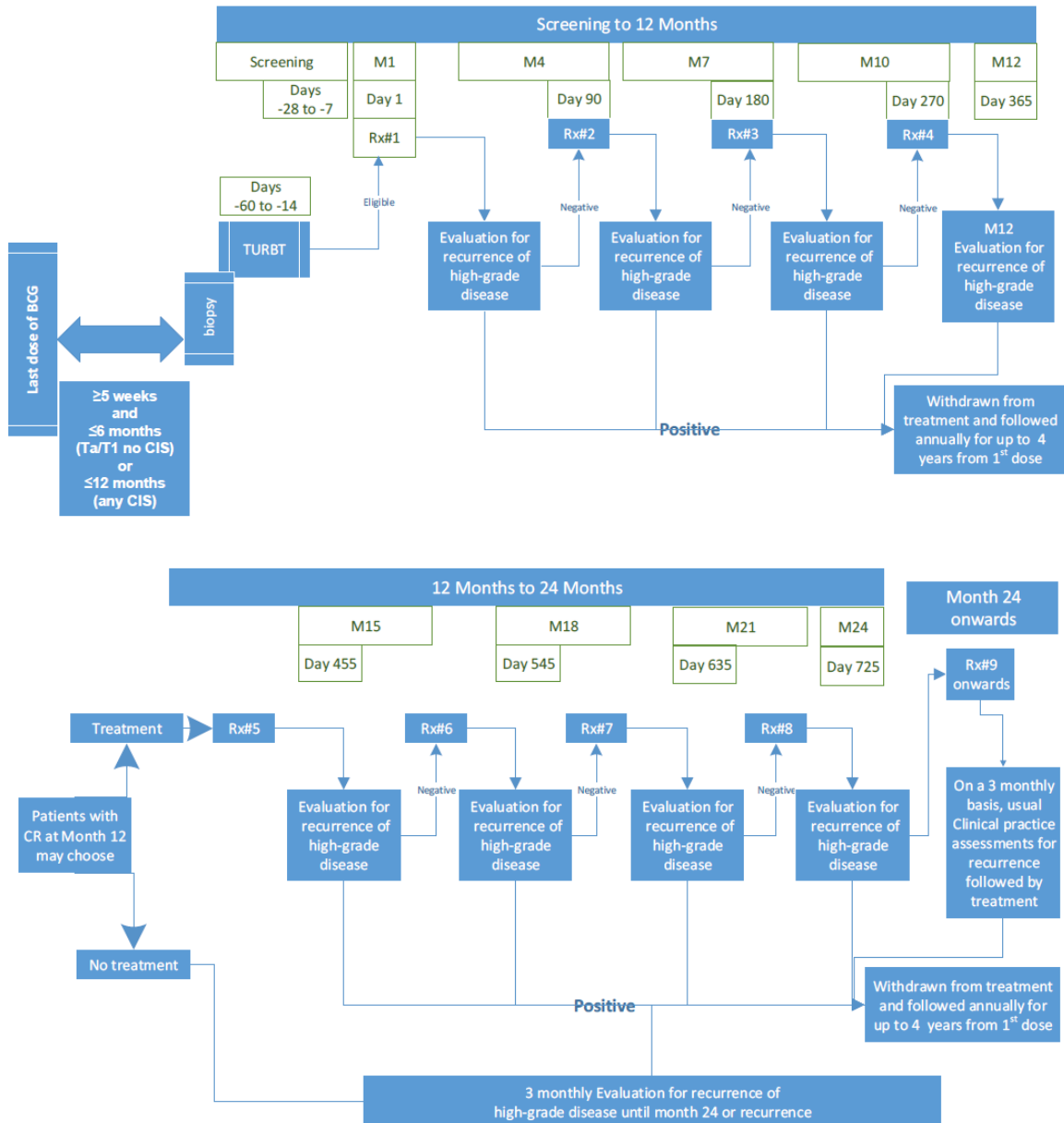
(Month 4), Day 180 (Month 7), and Day 270 (Month 10). Subjects who do not withdraw from treatment will have an efficacy assessment at Month 12 (i.e., Day 1 [Month 1] +365 days) after the first dose of ADSTILADRIN.

Following the initial 12-month treatment period, subjects could enter a 3-year follow-up period. Subjects with no evidence of high-grade disease recurrence at Month 12 will be offered continued treatment, if considered appropriate by their treating physician. ADSTILADRIN will be administered every 3 months for a maximum of 4 doses. Further assessments at Months 15, 18, 21, and 24 will be performed by cytology, cystoscopy, and biopsy, if clinically indicated.

Subjects with no evidence of high-grade disease recurrence at Month 12, but who declined continued treatment, will have further assessments at Months 15, 18, 21, and 24 performed by cytology, cystoscopy, and biopsy, if clinically indicated.

The final analysis of the study was performed after all subjects either completed the Month 12 Assessment or withdrew from the study before that point. A follow-up analysis will be performed after the last patient completes the long-term follow-up. No formal interim analyses were planned for this study.

Figure 1: Study Design Schematic - rAd-IFN-CS-003



Source: Copied from BLA125700/0007, rad-ifn-cs-003 report body-m12, Section 9.1, figure 1, page 28.

6.1.3 Population

Subjects who met all of the following criteria were eligible to participate in the study:

- Aged 18 years or older at the time of consent.
- Able to give written informed consent.
- Had at entry, confirmed by a pathology report:

- CIS only
- Ta/T1 high-grade disease with concomitant CIS or
- Ta/T1 high-grade disease without concomitant CIS.
- Were “BCG unresponsive” which referred to patients with high-grade NMIBC who were unlikely to benefit from and who did not receive further intravesical BCG. The term “BCG unresponsive” included patients who did not respond to BCG treatment and had a persistent high-grade recurrence within 12 months after BCG was initiated, and those who, despite an initial CR to BCG, relapsed with CIS within 12 months of their last intravesical treatment with BCG or relapsed with high-grade Ta/T1 NMIBC within 6 months of their last intravesical treatment with BCG. The following criteria defined the patients who were eligible for inclusion in the study:
 - Had received at least 2 previous courses of BCG within a 12-month period. This was defined as at least 5 out of 6 induction BCG instillations and at least 2 out of 3 instillations of maintenance BCG, or at least 2 out of 6 instillations of a second induction course, where maintenance BCG was not given. Exception: Those who had T1 high-grade disease at the first evaluation after induction BCG alone (at least 5 out of 6 doses) qualified in the absence of disease progression.
 - At the time of tumor recurrence, patients with CIS alone or high-grade Ta/T1 with CIS were within 12 months of last exposure to BCG and patients with high-grade Ta/T1 without CIS were within 6 months of last exposure to BCG.
 - No maximum limit to the amount of BCG administered.
 - All visible papillary tumors were required to be resected and those with persistent T1 disease on transurethral resection of bladder tumor (TURBT) undergone an additional re-TURBT within 14 to 60 days prior to beginning study treatment. Obvious areas of CIS were also fulgurated.
- Available for the whole duration of the study.
- Life expectancy > 2 years, in the opinion of the Investigator.
- Eastern Cooperative Oncology Group (ECOG) status 2 or less.
- Absence of concomitant upper tract urothelial carcinoma or urothelial carcinoma within the prostatic urethra. Freedom from upper tract disease (if clinically indicated) as indicated by no evidence of upper tract tumor by either intravenous pyelogram, retrograde pyelogram computed tomography scan with or without urogram, or magnetic resonance imaging with or without urogram performed within 6 months of enrollment.
- Patients with prostate cancer on active surveillance at a low risk for progression, defined as prostate-specific antigen <10 ng/dL, Gleason Score 6 and cT1 were permitted to be included into the study at the discretion of the Investigator (see exclusion criterion 10).
- Female patients of childbearing potential were required to use maximally effective birth control during the period of therapy, were required to use contraception for 1 month following the last study drug infusion and were required to have a negative urine or serum pregnancy test upon entry into

- this study. Otherwise, female patients were required to be postmenopausal (no menstrual period for a minimum of 12 months) or surgically sterile. Maximally effective birth control meant that the patient, if sexually active, used a combination of 2 methods of birth control that were approved and recognized to be effective by regulatory agencies.
- Male patients were required to be surgically sterile or were required to use a double barrier contraception method upon enrollment, during the course of the study, and for 1 month following the last study drug infusion.
 - Adequate laboratory values:
 - Hemoglobin ≥ 10 g/dL.
 - White blood cells $\geq 4000/\mu\text{L}$.
 - Absolute neutrophil count $\geq 2000/\mu\text{L}$.
 - Platelet count $\geq 100,000/\mu\text{L}$.
 - International normalized ratio below institutional upper limit of normal (ULN).
 - Activated partial thromboplastin time below institutional ULN.
 - Aspartate aminotransferase $\leq 1.5 \times \text{ULN}$.
 - Alanine aminotransferase $\leq 1.5 \times \text{ULN}$.
 - Total bilirubin $\leq 1.5 \times \text{ULN}$.
 - Estimated glomerular filtration rate $\geq 30 \text{ mL/min/1.73 m}^2$.

Patients who met any of the following criteria were excluded from participation in the study:

- Current or previous evidence of muscle invasive (muscularis propria) or metastatic disease presented at Screening. Examples of increased risk of metastatic disease included, but were not limited to:
 - Presence of lymphovascular invasion and/or micropapillary disease as shown in the histology of the biopsy sample.
 - Patients with T1 disease accompanied by the presence of hydronephrosis secondary to the primary tumor.
- Current systemic therapy for bladder cancer.
- Current or prior pelvic external beam radiotherapy within 5 years of entry.
- Prior treatment with adenovirus-based drugs.
- Suspected hypersensitivity to INTRON A.
- Symptomatic urinary tract infection or bacterial cystitis (once satisfactorily treated, patients could have entered the study).
- Clinically significant and unexplained elevated liver or renal function tests.
- Women who were pregnant or lactating or refused to commit to use contraception throughout the study.
- Any other significant disease or other clinical findings which, in the opinion of the Investigator, prevented study entry.
- History of malignancy of another organ system within the past 5 years, except treated basal cell carcinoma or squamous cell carcinoma of the skin and $\leq \text{pT2}$ upper tract urothelial carcinoma at least 24 months after nephroureterectomy. Also, patients with genitourinary cancers other than

- urothelial cancer or prostate cancer that were under active surveillance were excluded (see inclusion criterion 9).
- Patients who could not hold instillation for 1 hour.
 - Patients who could not tolerate intravesical dosing or intravesical surgical manipulation.
 - Intravesical therapy within 8 weeks prior to beginning study treatment with the exception of:
 - Cytotoxic agents (e.g., Mitomycin C, doxorubicin, and epirubicin) when administered as a single instillation immediately following a TURBT procedure which was permitted between 14 to 60 days prior to beginning study treatment.
 - Previous intravesical BCG therapy, which could be given at least 5 weeks before the diagnostic biopsy required for entry into the study.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Patients receive ADSTILADRIN at a dose of 2.25×10^{13} vp on each treatment day. It was administered into the bladder through a urinary catheter. If no evidence of high-grade disease recurrence was detected at any Efficacy Assessment Visit, a further dose of ADSTILADRIN was administered at Day 90 (Month 4), Day 180 (Month 7), and Day 270 (Month 10). Patients received up to 4 intravesical administrations of ADSTILADRIN over the initial 12-month observed period.

6.1.6 Sites and Centers

This study was conducted at 33 centers in the U.S.

6.1.7 Surveillance/Monitoring

The Safety Management Committee was responsible for monitoring safety throughout the study. It included the FKD Medical Monitor, an independent reviewer selected by the Sponsor, and other FKD representatives. It met at regular intervals to review emerging safety data; they specifically reviewed Month 1 safety data from the first 20 patients treated in the study, Month 1 safety data from the first 40 patients treated in the study, and Month 1 safety data from the first 60 patients treated in the study.

6.1.8 Endpoints and Criteria for Study Success

Primary efficacy endpoint

The primary efficacy variable is complete response (CR) at any time in subjects in the CIS (with or without concomitant high-grade Ta or T1 papillary disease) cohort after the first administration of ADSTILADRIN. In this study, a subject with CIS is defined to achieve a complete response (CR) if cystoscopy, cytology and biopsy (if clinically indicated) show no evidence of CIS.

Key secondary efficacy endpoint

The key secondary efficacy variable is the durability of CR in patients in the CIS cohort who show CR at any time after the first administration of ADSTILADRIN.

Other secondary endpoints:

- Incidence of HGRF survival at Months 3, 6, 9, and 12
- HGRF survival for all patients
- Incidence of cystectomy
- Cystectomy-free survival
- Overall survival

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample Size Determination

This study was designed to test whether the true CR rate is higher than 27% after discussion between the applicant and FDA in 2018. One-hundred CIS subjects provide 90% power to reject a null hypothesis that $CR \leq 27\%$, assuming a true CR rate of 43.75%.

Analysis populations

The Safety Analysis Set was defined as all patients who receive at least 1 dose of ADSTILADRIN. This set was used for all safety analyses.

The Efficacy Analysis Set was defined as all patients in the Safety Analysis Set with a diagnosis of high-grade, BCG unresponsive NMIBC. This set was used as the primary analysis set for the analyses of efficacy data.

The Per-Protocol Analysis Set was defined as all patients in the Efficacy Analysis Set who have no major protocol violation and either:

- Complete the Month 12 Assessment at earliest Day + 357 and at latest Day + 396 or
- Withdraw before the Month 12 Assessment because of disease recurrence or progression, death, an adverse event related to the disease or treatment, or lack of tolerability

The Per-Protocol Analysis Set was not determined for this analysis. Analyses based on the Per-Protocol Analysis Set were not performed for this clinical study report.

Blinding

This is an open-label study and no blinding is performed.

Missing Data Handling

A subject is treated as not to have achieved a CR if there are insufficient data to determine whether or not a CR has occurred.

A patient is treated as not to have achieved high-grade-recurrence-free survival at an evaluation visit if there are insufficient data to determine whether or not high-grade recurrence-free survival has occurred. It is considered sufficient

evidence for HGRF survival if a subsequent assessment shows HGRF survival and there has been no intermediate treatment for bladder cancer other than ADSTILADRIN.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

In total, 157 subjects were enrolled and treated with ADSTILADRIN at Month 1 Day 1, including 107 subjects in the CIS cohort and 50 subjects in the papillary disease cohort. All enrolled patients were included in the Safety Analysis Set.

The Efficacy Analysis Set included 151 patients: 103 patients in the CIS cohort and 48 patients in the papillary disease cohort.

The Per-Protocol Analysis Set included 147 patients: 100 patients in the CIS cohort and 47 patients in the papillary disease cohort.

Table 2 summarizes the number of patients in each analysis set.

Table 2: Analysis Populations			
	<i>CIS</i>	<i>Papillary</i>	<i>Total</i>
Enrolled	107 (100%)	50 (100%)	157 (100%)
Safety Analysis	107 (100%)	50 (100%)	157 (100%)
Efficacy Analysis	103 (96.3%)	48 (96.0%)	151 (96.2%)
Per-Protocol Analysis	100 (93.5%)	47 (94.0%)	147 (93.6%)

6.1.10.1.1 Demographics

The mean age for the Efficacy Analysis Set is 71.2 years, with 76.6% of patients being ≥ 65 years old. Overall, the majority of patients are male (129 [82.2%] patients), White (146 [93.0%] patients), and not Hispanic or Latino (148 [94.3%] patients). In total, 140 (89.2%), 13 (8.3%) and 4 (2.5%) patients had a baseline ECOG (Eastern Cooperative Oncology Group) status of 0, 1 and 2, respectively. This patient population is representative of the proposed indicated patient population proposed.

Table 3 summarizes demographic baseline characteristics for the Safety Analysis Set. The demographic baseline characteristics for the Efficacy Analysis Set, which are provided by the applicant in Tables 14.1.2 of the clinical study report in 125700/0007, are similar.

Table 3: Demographic and Baseline Characteristics – Safety Analysis Set

Demographic/Baseline Characteristics	CIS (N=107)	Papillary Disease (N=50)	Total (N=157)
Age at informed consent			
N	107	50	157
Mean (SD)	71.2 (8.88)	70.1 (9.78)	70.8 (9.16)
Age group			
< 65 years	25 (23.4)	13 (26.0)	38 (24.2)
≥ 65 years	82 (76.6)	37 (74.0)	119 (75.8)
Sex (n, %)			
Male	95 (88.8)	34 (68.0)	129 (82.2)
Female	12 (11.2)	16 (32.0)	28 (17.8)
Race (n, %)			
White	99 (92.5)	47 (94.0)	146 (93.0)
Black or African American	6 (5.6)	2 (4.0)	8 (5.1)
Asian	2 (1.9)	1 (2.0)	3 (1.9)
Ethnicity (n, %)			
Hispanic or Latino	3 (2.8)	1 (2.0)	4 (2.5)
Not Hispanic or Latino	99 (92.5)	49 (98.0)	148 (94.3)
Not reported	1 (0.9)	0 (0.0)	1 (0.6)
Unknown	4 (3.7)	0 (0.0)	4 (2.5)
Height (cm)			
N	107	50	157
Mean (SD)	174.7 (9.89)	170.9 (10.27)	173.5 (10.14)
Baseline weight (kg)			
N	107	50	157
Mean (SD)	90.14 (20.919)	85.88 (18.639)	88.78 (20.259)
Baseline BMI (kg/m2)			
N	107	50	157
Mean (SD)	29.38 (5.716)	29.28 (5.121)	29.34 (5.517)
Baseline ECOG status (n, %)			
0	97 (90.7)	43 (86.0)	140 (89.2)
1	7 (6.5)	6 (12.0)	13 (8.3)
2	3 (2.8)	1 (2.0)	4 (2.5)

Source: Adapted from BLA125700/0007, rad-ifn-cs-003 report body-m12, Section 10.4, Table 5, page 61.

6.1.10.1.2 Medical Characterization of the Enrolled Population

Table 4 summarizes the medical characteristics for the Safety Analysis Set.

Table 4: Medical Characteristics – Safety Analysis Set

Demographic/Baseline Characteristics	CIS (N=107)	Papillary Disease (N=50)	Total (N=157)
Time from initial diagnosis of bladder cancer (months)			
N	107	50	157
Mean (SD)	30.64 (31.194)	24.24 (35.449)	28.60 (32.632)
Disease classification at initial diagnosis (n, %)			
CIS only	24 (22.4)	1 (2.0)	25 (15.9)
Ta	35 (32.0)	18 (36)	53 (33.8)
Ta + CIS	11 (10.3)	4 (8.0)	15 (9.6)
T1	23 (21.5)	24 (48.0)	47 (29.9)
T1 + CIS	9 (8.4)	1 (2.0)	10 (6.4)
Unknown	5 (4.7)	2 (4.0)	7 (4.5)
Current status at entry (n, %)			
Refractory	58 (54.2)	35 (70.0)	93 (59.2)
Relapsed	49 (45.8)	15 (30.0)	64 (40.8)
Current stage at entry (n, %)			
CIS only	81 (75.7)	0 (0.0)	81 (51.6)
Ta	0 (0.0)	35 (70.0)	35 (22.3)
Ta + CIS	21 (19.6)	0 (0.0)	21 (13.4)
T1	0 (0.0)	15 (30.0)	15 (9.6)
T1 + CIS	5 (4.7)	0 (0.0)	5 (3.2)
Grade at initial diagnosis (n, %)			
High	94 (87.9)	44 (88.0)	138 (87.9)
Low	10 (9.3)	4 (8.0)	14 (8.9)
Unknown	3 (2.8)	2 (4.0)	5 (3.2)

Source: Adapted from BLA125700/0007, rad-ifn-cs-003 report body-m12, Section 10.4, Table 6, page 62.

6.1.10.1.3 Subject Disposition

There are 157 patients enrolled in this study with 107 of them in the CIS cohort and 50 of them in the papillary disease cohort. All 157 patients are included in the Safety Analysis Set.

Six patients (Patients (b) (6)) are not included in the Efficacy Analysis Set because they do not meet the protocol definition of high-grade, BCG unresponsive NMIBC.

Ten patients from the Safety Analysis Set (Patients (b) (6)) are not included in the Per-Protocol Analysis Set because they do not meet the criteria described above.

Overall, 58 (36.9%) patients completed the 12-month treatment period. A total of 99 (63.1%) patients did not complete the 12-month treatment period, consisting of 74 (69.2%) patients in the CIS cohort and 25 (50.0%) patients in the papillary disease cohort. Disease recurrence is the most common reason for incompleteness, which causes 71 (66.4%) patients in the CIS cohort and 23 (46.0%) patients in the papillary disease cohort to discontinue the study.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

Among 103 patients in the CIS cohort of Efficacy Analysis Set, 55 (53.4%) patients (95% CI: [43.3, 63.3]) in the CIS cohort achieve CR. The lower bound (43.3%) of the 95% CI of the incidence of CR at any time in patients with CIS exceeds 27%, therefore, the null hypothesis specified in the protocol of a true response rate of 27% is rejected.

Each of the 55 CIS patients who achieved CR did so by the Month 3 Efficacy Assessment Visit. Table 5 reports the CR rate during different time windows in CIS cohort of Efficacy Analysis Set.

Table 5: Incidence of CR at Any Time in CIS Patients – Efficacy Analysis Set

	CIS (N=103)
Patients who achieved CR	
By Month 3 (n, %)	55 (53.4)
95% CI	(43.3, 63.3)
During Month 4 to 6 (n, %)	0 (0.0)
95% CI	(0.0, 3.5)
During Month 7 to 9 (n, %)	0 (0.0)
95% CI	(0.0, 3.5)
During Month 10 to 12 (n, %)	0 (0.0)
95% CI	(0.0, 3.5)
Total (n, %)	55 (53.4)
95% CI	(43.3, 63.3)

Source: Adapted from BLA125700/0007, rad-ifn-cs-003 report body-m12, Section 11.1, Table 9, page 67.

6.1.11.2 Analyses of Secondary Endpoints

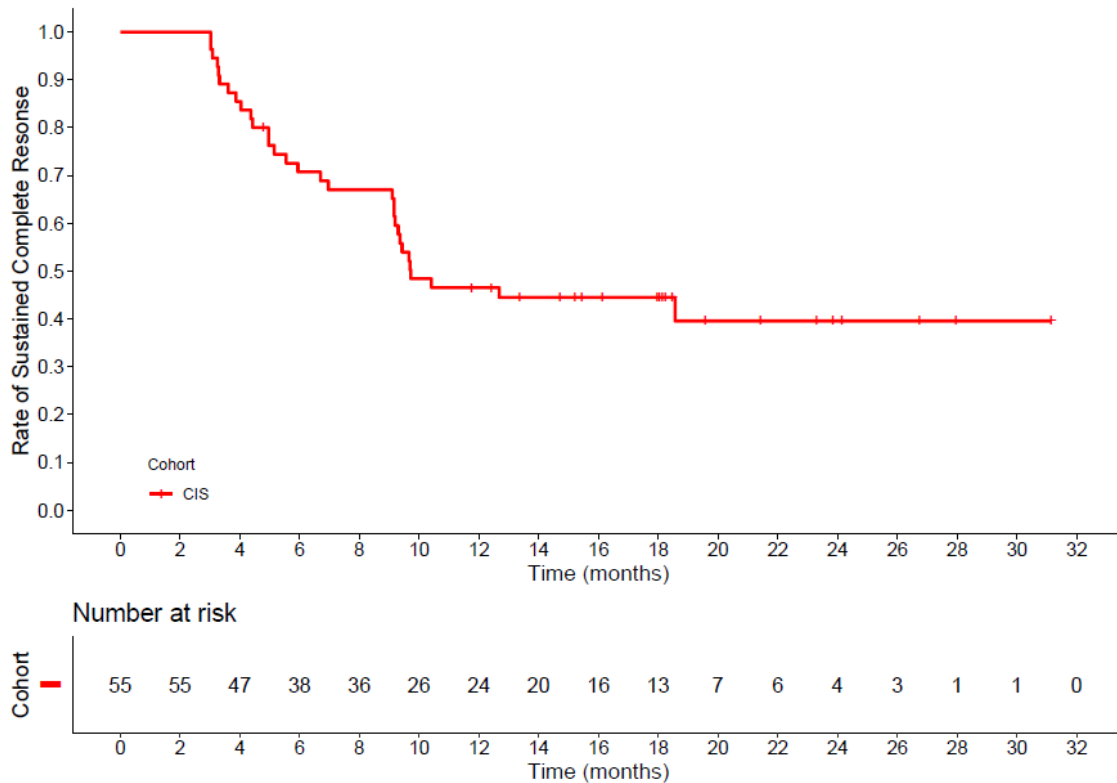
Durability of Complete Response

By the cut-off day on November 15, 2019, the median duration of CR by Kaplan-Meier estimate is 9.69 months for the 55 patients with CIS who achieved CR. Twenty-four patients were censored. The 95% CIs of the median duration of CR

are (9.9, 13.6) with normality assumption and (9.2, 14.7) with the nonparametric method, respectively.

Figure 2 shows the Kaplan-Meier plot of durability of CR in patients with CIS based on the Efficacy Analysis Set.

Figure 2: Kaplan-Meier plot of durability of CR in patients with CIS



Source: FDA Efficacy analysis performed by the clinical reviewer and the statistical reviewer.

HGRF survival

Of the 55 patients with CIS who achieved CR by the Month 3 Efficacy Assessment Visit, 42 (76.4%), 37 (67.3%) and 25 (45.5%) patients remained HGRF survival at the Month 6, 9 and 12 Efficacy Assessment Visit, respectively.

Table 6 presents HGRF survival in the patients with CIS who achieved a CR.

Table 6: Summary of HGRF survival in CIS Patients Who Achieve CR – Efficacy Analysis Set

	CIS (N=55)
Month 3 (n, %)	55 (100)
95% CI	(93.5, 100.0)
Month 6 (n, %)	42 (76.4)
95% CI	(63.0, 86.8)
Month 9 (n, %)	37 (67.3)
95% CI	(53.3, 79.3)
Month 12 (n, %)	25 (45.5)
95% CI	(32.0, 59.4)

Source: FDA Efficacy analysis performed by the statistical reviewer.

6.1.11.3 Subpopulation Analyses

The incidence of CR in the CIS cohort for subgroups defined by sex, age, race, time from initial diagnosis of bladder cancer, and tumor type at study entry are reported in Table 7.

Table 7: Subgroup analyses of Complete Response in CIS Patients – Efficacy Analysis Set

Subgroup	n/N (%)	95% CI
Sex		
Male	48/91 (52.7)	(42.0, 63.3)
Female	7/12 (58.3)	(27.7, 84.8)
Age group		
< 65 years	13/24 (54.2)	(32.8, 74.4)
≥ 65 years	42/79 (53.2)	(41.6, 64.5)
Race group		
White	52/95 (54.7)	(44.2, 65.0)
Non-White	3/8 (37.5)	(8.5, 75.5)
Time from initial diagnosis of bladder cancer		
< Median*	26/44 (59.1)	(43.2, 73.7)
≥ Median	29/59 (49.2)	(35.9, 62.5)
Tumor type at study entry		
CIS only	43/79 (54.4)	(42.8, 65.7)
CIS with Ta/T1	12/24 (50.0)	(29.1, 70.9)
Positive immunogenic response in anti-adenoviral antibodies at postbaseline		
Yes	43/62 (69.4)	(56.3, 80.4)
No	8/24 (33.3)	(15.6, 55.3)
Unknown	4/17 (23.5)	(6.8, 49.9)

*: The median time from initial diagnosis of bladder cancer was 19.4 months in the Efficacy Analysis Set.

Source: Adapted from BLA125700/0007, rad-ifn-cs-003 report body-m12, Section 11.1, Table 10, page 68.

6.1.12 Safety Analyses

6.1.12.3 Deaths

Eight patient deaths were reported as of November 15, 2019. No deaths occurred before the end of 12-month treatment period. All patients who died were in the long-term follow-up period and had been withdrawn from study treatment. All 8 deaths occurred at least 4 months after the last administration of the study drug.

6.1.12.4 Nonfatal Serious Adverse Events

As of November 15, 2019, 31 (19.7%) patients had an NCI-CTCAE Grade 3/4/5 Treatment-emergent adverse event (TEAE) with 20 (18.7%) patients in the CIS cohort and 11 (22.0%) patients in the papillary disease cohort. The most common NCI-CTCAE Grade 3/4/5 TEAE was hypertension (4 patients). Overall, 2 patients had an NCI-CTCAE Grade 4 TEAE and no patient had an NCI-CTCAE Grade 5 TEAE. The 2 NCI-CTCAE Grade 4 TEAEs of sepsis and anaphylactic reaction are considered to be study drug-unrelated, although sepsis is considered study procedure-related.

In total, 6 (3.8%) patients had a study drug-related NCI-CTCAE Grade 3/4/5 TEAE. Among those, 3 (2.8%) patients in the CIS cohort and 3 (6.0%) patients in the papillary disease cohort. The most common study drug-related NCI-CTCAE Grade 3/4/5 TEAE was micturition urgency (2 [1.3%] patients).

6.1.12.5 Adverse Events of Special Interest (AESI)

Not applicable.

6.2 Trial #2: rAd-IFN-CS-002

A phase II, randomized, open label, parallel arm study to evaluate the safety and efficacy of ADSTILADRIN for high-grade, BCG unresponsive NMIBC patients.

6.2.1 Objectives

The primary objective is to evaluate the incidence of high-grade recurrence-free survival at 12 months.

Secondary objectives include the following:

- To evaluate the incidence of high-grade recurrence-free survival at 3, 6 and 9 months.
- To determine the time to progression to muscle-invasive disease.
- To determine the cystectomy rate.
- To determine the overall survival in all patients.
- To determine the biodistribution of the viral vector.
- To determine the levels of anti-IFNalpha2b and anti-adenoviral antibodies.
- To quantify the concentration of IFNalpha2b in the urine.

- To evaluate the safety of ADSTILADRIN.

6.2.2 Design Overview

This is a multi-center, randomized, open label, parallel arm, phase II study to investigate the safety and efficacy of ADSTILADRIN administered intravesically in patients with high-grade BCG or refractory or relapsed NMIBC.

Patients in the ADSTILADRIN treatment groups were randomized to receive a 75 mL intravesical administration of ADSTILADRIN at a treatment dose of either 7.5×10^{12} vp/ml or 2.25×10^{13} vp/ml on Day 1 of the study. Following the initial treatment, patients could be re-treated with the same dose at Months 4, 7 and 10. Therefore, patients could receive up to 4 intravesical administrations of ADSTILADRIN over the 12 month treatment phase of the study.

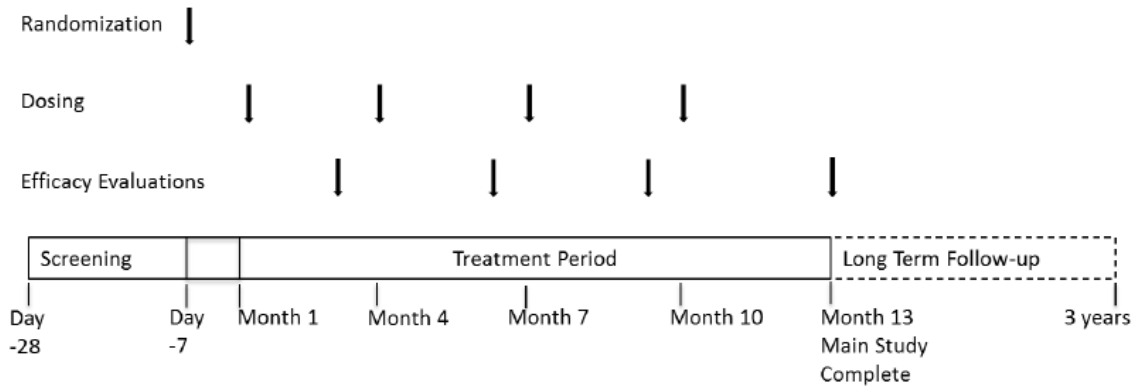
All patients were evaluated for recurrence of high-grade disease after 3, 6 and 9 months of treatment. Cystoscopy, cytology, and, if clinically indicated, biopsies were performed to obtain accurate staging. If no evidence of recurrence of high-grade disease was detected then a further dose of ADSTILADRIN was administered as maintenance therapy. Patients who had recurrence of high-grade disease were withdrawn from treatment but were followed for survival and time to cystectomy.

At 12 months, a final efficacy evaluation was performed. This included cystoscopy, cytology, and biopsies.

The study was complete when all patients had either completed the Month 13 assessment or had been withdrawn from treatment and undergone a safety assessment. Survival data and information regarding invasive disease and cystectomy will be collected from all patients for 3 years after completion of the study. This long-term follow-up data will be reported separately.

Figure 3 describes the timeline of study rAd-IFN-CS-002.

Figure 3: Flow Chart



Source: Copied from BLA125700/0003, rad-ifn-cs-002 clinical report body.pdf, Section 9.5.1, Figure 9.5.1, page 34.

6.2.3 Population

Patients who met the following criteria were eligible to be included in the study:

- Aged 18 years or older at the time of consent.
- Able to give informed consent.
- Patients with high-grade BCG-refractory or relapsed NMIBC defined as: High grade non-invasive papillary carcinomas (Ta) and patients with high-grade tumors that invade sub-epithelial connective tissue (T1), or CIS only, or CIS and Ta or T1 tumors.
- Complete resection of visible papillary lesions or CIS by transurethral resection of bladder tumor (TURBT) or endoscopic resection between 14 and 60 days prior to beginning study treatment.
- Available for the whole duration of the study.
- Life expectancy >2 years, in the opinion of the Investigator.
- ECOG status 2 or less.
- Absence of upper tract urothelial carcinoma.
- Female patients of childbearing potential were to use maximally effective birth control during the period of therapy, be willing to use contraception for 1 month following the last study drug infusion and have a negative urine or serum pregnancy test upon entry into this study. Otherwise, female patients were to be postmenopausal (no menstrual period for a minimum of 12 months) or surgically sterile.
- Male patients were to be surgically sterile or willing to use a double barrier contraception method upon enrolment, during the course of the study, and for 1 month following the last study drug infusion.
- Adequate laboratory values:
 - Hemoglobin ≥ 10 g/dL.
 - White blood cell count (WBC) $\geq 4000/\mu\text{L}$.
 - Absolute neutrophil count (ANC) $\geq 2000/\mu\text{L}$.
 - Platelet count $\geq 100,000/\mu\text{L}$.

- International normalized ratio (INR)* within institutional normal limits.
- Activated partial thromboplastin time (aPTT)* within institutional normal limits.
- Aspartate aminotransferase (AST) ≤ 1.5 x upper limit of normal (ULN).
- Alanine aminotransferase (ALT) ≤ 1.5 x ULN.
- Total bilirubin within institutional normal limits.
- Creatinine ≤ 1.5 x ULN.

Patients who met the following criteria were to be excluded from the study:

- Current or previous evidence of muscle invasive (muscularis propria) or metastatic disease.
- Current systemic therapy for bladder cancer.
- Current or prior pelvic external beam radiotherapy.
- Prior treatment with adenovirus-based drugs.
- Suspected hypersensitivity to interferon alpha.
- Existing urinary tract infection or bacterial cystitis.
- Clinically significant and unexplained elevated liver or renal function tests.
- Women who were pregnant or lactating.
- Severe cardiovascular disease.
- History of malignancy of other organ system within past 5 years (except treated basal cell carcinoma or squamous cell carcinoma of the skin).
- Patients who could not hold instillation for 1 hour.
- Patients who could not tolerate intravesical dosing or intravesical surgical manipulation.
- Intravesical therapy within 3 months prior to beginning study treatment with the exception of cytotoxic agents (e.g. mitomycin C, doxorubicin and epirubicin) when administered as a single instillation immediately following a TURBT procedure which is permitted up to 14-60 days prior to beginning study treatment.

6.2.4 Study Treatments or Agents Mandated by the Protocol ADSTILADRIN.

6.2.6 Sites and Centers

The study was conducted in 14 centers in the United States.

6.2.7 Surveillance/Monitoring

The Safety Monitoring Committee was responsible for monitoring safety throughout the study. The members of the committee were the principal investigators and their representatives.

6.2.8 Endpoints and Criteria for Study Success

The primary efficacy response was the HGRF survival rate at 12 months defined as survival at 12 months without evidence of recurrence of a high-grade tumor by cystoscopy, cytology or, biopsy. This HGRF survival rate at 12 months as well as the exact binomial 90% CI were reported for each dose group and for the overall population.

The primary endpoint for safety analysis is the incidence of TEAEs, including:

- Common Terminology Criteria for Adverse Events (CTCAEs) all grades (including new events post-screening and changes from baseline).
- Clinical chemistry, hematology, urinalysis results out of range and considered clinically significant in the opinion of the Investigator. Any out of range clinical chemistry, hematology and urinalysis results not considered clinically significant (in the opinion of the Investigator) were not be reported as AEs.
- Abnormal findings during clinical assessments, including physical examination (including neurological examination) and vital signs.
- Abnormal ECG readings.
- Spontaneous patient reports.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Sample Size Determination

Approximately 40 patients were planned to be enrolled. Each dose group size of 20 subjects was sufficient to give an 80% probability of rejecting a reference HGRF survival rate of 10% with an exact 5% one-sided test when the true HGRF survival rate is 35%.

Analysis populations

The safety analysis set was defined to include all subjects who received at least one dose of ADSTILADRIN. This analysis set were used for the safety analyses.

The efficacy analysis set was defined to include all randomized subjects who received study medication which should be identical to the safety analysis set. The efficacy analysis set was be used in the analysis of primary and secondary efficacy endpoints. All subjects in this analysis set were analyzed according to the dose they were randomized to receive

Blinding

This is an open-label study and no blinding is performed.

6.2.10 Study Population and Disposition

6.2.10.1 Population Enrolled/Analyzed

Overall, 43 patients were randomized into the study; 22 patients in the 7.5x10¹²

vp/mL dose group and 21 patients in the 2.25×10^{13} vp/mL dose group. Three patients were not dosed.

Table 8: Analysis Populations

	<i>Number of Subjects</i>
Enrolled subjects	43
Safety analysis	40
Efficacy analysis	40

6.2.10.1.1 Demographics

The mean age was 71.1 years (SD: 9.42) ranging from 52 to 91 years. There were more male patients (N=33 [82.5%]) than female patients (N=7 [17.5%]) in the study. The majority of patients were white (N=38 ([95.0%]) and were not Hispanic or Latino (N>32 [80.0%]).

Table 9 summarizes demographic and baseline characteristics for the Safety Analysis Set.

Table 9: Demographic and Baseline Characteristics – Safety Analysis Set

	7.5×10^{12} vp/mL (N=21)	2.25×10^{13} vp/mL (N=19)	Total (N=40)
Age at informed consent			
N	21	19	40
Mean (SD)	71.6 (8.07)	70.6 (10.94)	71.1 (9.42)
Median (quartiles)	70.0 (67.0, 74.0)	73.0 (62.0, 81.0)	70.5 (64.5, 77.5)
Min, Max	59, 91	52, 86	52, 91
Sex (n, %)			
Male	19 (90.5)	14 (73.7)	33 (82.5)
Female	2 (9.5)	5 (26.3)	7 (17.5)
Race (n, %)			
Asian	0	1 (5.3)	1 (2.5)
Black or African American	1 (4.8)	0	1 (2.5)
White	20 (95.2)	18 (94.7)	38 (95.0)
Ethnicity (n, %)			
Hispanic or Latino	0	1 (5.3)	1 (2.5)
Not Hispanic or Latino	17 (81.0)	15 (78.9)	32 (80.0)
Not reported	0	2 (10.5)	2 (5.0)
Unknown	4 (19.0)	1 (5.3)	5 (12.5)

Source: Adapted from BLA125700/0007, rad-ifn-cs-002 clinical report body, Section 11.2.1, Table 11.2.1, page 54-56.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Most patients had an ECOG performance status of 0 (N=34 [85.0%]); 6 patients (15.0%) had a status of 1. Assessment of urinary symptoms at baseline showed that 13 patients (32.5%) had urinary frequency and 13 patients (32.5%) showed presence of urinary urgency. The majority of patients (N=31 [77.5%]) did not have dysuria. Nocturia was present in 29 patients (72.5%) with a mean number of nocturnal voids of 3.0 (SD: 1.83).

Table 10 summarizes medical baseline characteristics for the Safety Analysis Set.

Table 10: Medical Baseline Characteristics – Safety Analysis Set

	7.5×10^{12} vp/mL (N=21)	2.25×10^{13} vp/mL (N=19)	Total (N=40)
ECOG PS (n, %)			
0	16 (76.2)	18 (94.7)	34 (85.0)
1	5 (23.8)	1 (5.3)	6 (15.0)
Urinary frequency (n [%])			
Yes	7 (33.3)	6 (31.6)	13 (32.5)
No	14 (66.7)	13 (68.4)	27 (67.5)
Presence of urgency (n [%])			
Yes	7 (33.3)	6 (31.6)	13 (32.5)
No	14 (66.7)	13 (68.4)	27 (67.5)
Severity of dysuria (n [%])			
None	16 (76.2)	15 (78.9)	31 (77.5)
Mild	5 (23.8)	1 (5.3)	6 (15.0)
Moderate	0	2 (10.5)	2 (5.0)
Severe	0	1 (5.3)	1 (2.5)
Presence of nocturia (n [%])			
Yes	14 (66.7)	15 (78.9)	29 (72.5)
No	7 (33.3)	4 (21.1)	11 (27.5)
If Yes, number of nocturnal voids			
N	14	15	29
Mean (SD)	3.2 (1.72)	2.8 (1.97)	3.0 (1.83)
Median (quartiles)	3.0 (2.0, 4.0)	2.0 (1.0, 4.0)	3.0 (2.0, 4.0)
Min, Max	1, 7	1, 8	1, 8

Source: Adapted from BLA125700/0007, rad-ifn-cs-002 clinical report body, Section 11.2.1, Table 11.2.1, page 54-56.

6.2.10.1.3 Subject Disposition

Overall, 43 patients were randomized into the study with 22 patients in the 7.5×10^{12} vp/mL dose group and 21 patients in the 2.25×10^{13} vp/mL dose group. There were 3 patients (7.0%) who were not dosed:

- Patient (b) (6) was withdrawn prior to dosing due to events of pulmonary edema.
- Patient (b) (6) had a wrongly reported creatinine level at screening. The actual value was outside of the inclusion range and so the patient did not qualify for study.
- Patient (b) (6) did not meet inclusion criterion no 3; the patient did not have high grade bladder cancer.

A total of 17 patients (42.5%) completed the 12 months treatment period. Overall 23 patients (57.5%) did not complete the treatment period. The most common reason for study discontinuation was disease recurrence in 21 patients (52.5%); 1 patient (2.5%) discontinued study participation on their own request and 1 patient (2.5%) discontinued due to safety reasons (i.e. due to an AE which was subsequently shown to be disease progression). There were no study discontinuations due to death, noncompliance, protocol violations, or losses to follow-up.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint

Overall, 14/40 patients (35.0%; 90% CI: 22.6, 49.2) were HGRF and alive at 12 months. The rate was comparable between dose groups with 7/21 patients (33.3%) in the 7.5×10^{12} vp/mL dose group and 7/19 patients (36.8%) in the 2.25×10^{13} vp/mL dose group. The applicant reported the two-sided 90% CIs in the CSR. The lower bounds of the two-sided 90% CIs of the HGRF survival rate in the 7.5×10^{12} vp/mL dose group and the 2.25×10^{13} vp/mL dose group each exceed 10%. The null hypothesis specified in the protocol of a true response rate of 10% is therefore rejected at a one-sided .05 significance level. Table 11 summarizes the incidence of HGRF survival at 12 months as well as 90% and 95% CIs.

Table 11: HGRF survival at 12 months
(Efficacy Analysis Set)

	7.5×10^{12} vp/mL (N=21)	2.25×10^{13} vp/mL (N=19)	Total (N=40)
High-grade recurrence-free at 12 months	7 (33.3%)	7 (36.8%)	14 (35.0%)
90% CI*	(16.8%, 53.6%)	(18.8%, 58.2%)	(22.6%, 49.2%)
95% CI**	(14.6%, 57.0%)	(16.3%, 61.6%)	(20.6%, 51.7%)

*: The 90% CIs were provided by the applicant.

**: The 95% CIs were provided by this statistical reviewer.

Source: Adapted from BLA125700/0007, rad-ifn-cs-002 report body, Section 10.4, Table 5, page 61.

6.2.11.2 Analyses of Secondary Endpoints

6.2.11.2.1 High-Grade Recurrence-Free Survival at 3, 6 and 9 Months

Overall, 23/40 patients (57.5%) were HGRF at 3 months, which was greater than that at 6 and 9 months (N=17/40 [42.5%]). At each time point, the rate of HGRF survival was higher in the 2.25×10^{13} vp/mL dose group compared to the 7.5×10^{12} vp/mL dose group. Table 12 summarizes the HGRF results.

Table 12: HGRF survival at 3, 6, and 9 months
(Efficacy Analysis Set)

	7.5×10^{12} vp/mL (N=21)	2.25×10^{13} vp/mL (N=19)	Total (N=40)
High-grade recurrence-free			
3 months	10 (47.6%)	13 (68.4%)	23 (57.5%)
90% CI	(28.6%, 67.2%)	(47.0%, 85.3%)	(43.3%, 70.8%)
6 months	8 (38.1%)	9 (47.4%)	17 (42.5%)
90% CI	(20.6%, 58.3%)	(27.4%, 68.0%)	(29.2%, 56.7%)
9 months	8 (38.1%)	9 (47.4%)	17 (42.5%)
90% CI	(20.6%, 58.3%)	(27.4%, 68.0%)	(29.2%, 56.7%)
Incidence of cystectomy	0	0	0
90% CI	(0.0%, 13.3%)	(0.0%, 13.3%)	(0.0%, 13.3%)

Source: Adapted from BLA125700/0007, rad-ifn-cs-002 report body, Section 10.4, Table 5, page 61.

6.2.11.2.2 Duration of High-Grade Recurrence-Free Survival

Overall, 25 patients had high-grade recurrence of disease during the study, with 15 patients (37.5%) censored. The overall median time to high-grade recurrence was 6.51 months (90% CI: 3.52, 12.78). The individual maximum time to high-grade recurrence was 12.78 months. The median time to recurrence was higher in the 2.25×10^{13} vp/mL dose group with a median of 11.73 months (90% CI: 5.88, NE) compared to the 7.5×10^{12} vp/mL dose group with a median of 3.52 months (90% CI: 3.02, 12.78).

Table 13: Duration of HGRF survival at 3, 6, and 9 months
(Efficacy Analysis Set)

	7.5×10^{12} vp/mL (N=21)	2.25×10^{13} vp/mL (N=19)	Total (N=40)
Number of patients with high-grade recurrence	14	11	25
Number of patients censored (%)	7 (33.3)	8 (42.1)	15 (37.5)
Time to high-grade recurrence (months)			
Q1	2.92	4.07	3.12
Median (90% CI)	3.52 (3.02, 12.78)	11.73 (5.88, NE)	6.51 (3.52, 12.78)
Q3	NE	NE	NE
Min, Max	2.6, 16.9	1.5, 12.5	1.5, 16.9

Source: Adapted from BLA125700/0007, rad-ifn-cs-002 report body, Section 11.4.1.2.2, Table 11.4.3, page 62.

6.2.11.2.3 Cystectomy at 12 Months

No cystectomies were performed on-study on patients up to 12 months.

6.2.11.2.4 Time to Cystectomy

As no patient had a cystectomy performed until 12 months on study, time to cystectomy could not be evaluated.

6.2.11.2.5 Duration of High-Grade Recurrence-Free Survival

Overall survival was defined as the time from first dose of ADSTILADRIN to death. As death did not occur before the end of follow up for any patient, all patients were censored in the evaluation of overall survival endpoint.

6.2.11.3 Subpopulation Analyses

Not applicable.

6.2.12 Safety Analyses

6.2.12.3 Deaths

No patient died during this study.

6.2.12.4 Nonfatal Serious Adverse Events

Overall, 5 patients experienced a total of 10 SAEs during the study. Of those, 3 patients had a total of 8 SAEs in the 7.5×10^{12} vp/mL dose group and 2 patients had a total of 2 SAEs in the 2.25×10^{13} vp/mL dose group.

The events by PT included syncope, sepsis, diarrhea, coronary artery occlusion, carotid artery occlusion, renal neoplasm, nephroureterectomy, functional gastrointestinal disorder, back pain, and renal failure acute. Of these, diarrhea (7.5×10^{12} vp/mL dose group) and renal failure acute (2.25×10^{13} vp/mL dose group) were considered by the Investigator to be related to the study drug.

6.2.12.5 Adverse Event of Special Interest (AESI)

Not applicable.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

This original BLA includes study results from two clinical trials: rAd-IFN-CS-002 and rAd-IFN-CS-003.

Study rAd-IFN-CS-002 was a phase 2, randomized, open-label, parallel arm study to evaluate the safety and efficacy of ADSTILADRIN for high-grade, BCG unresponsive NMIBC patients. Forty patients were enrolled in this study, with 21 patients in the 7.5×10^{12} vp/mL dose group and 19 patients (36.8%) in the 2.25×10^{13} vp/mL dose group. Subjects received up to 4 doses of ADSTILADRIN,

at 3 monthly intervals. Overall, 14/40 patients (35.0%; 95% CI: 20.6%, 51.7%) were high-grade recurrence free at 12 months, including 7 patents in the 7.5×10^{12} vp/mL dose group (33.3%, 95% CI: 14.6%, 57.0%) and 7 patents in 2.25×10^{13} vp/mL dose group (36.8%, 95% CI: 16.3%, 61.6%).

Study rAd-IFN-CS-003 is an ongoing Phase 3, multi-center, open-label, safety and efficacy study that enrolled 157 patients with BCG-unresponsive, high-grade NMIBC, of whom 107 had CIS and 50 had papillary disease. The dosage is 2.25×10^{13} vp/mL. The primary efficacy endpoint, the CR rate within 12 months, was observed as 53.4% (55/103) with a 95% CI (43.3%, 63.3%). As the lower bound (43.3%) of the 95% CI of the incidence of CR exceeds 27%, the null hypothesis of a true response rate of 27% was rejected and the study met its pre-specified success criteria. The results for two key secondary endpoints were as follows:

- The median duration of CR was 9.69 months (95% CI: 9.2, 14.7) for the 55 patients with CIS who achieved CR.
- All 55 patients who achieved CR did so by the Month 3 Efficacy Assessment Visit. Of those, 42 (76.4%), 37 (67.3%) and 25 (45.5%) patients remained HGRF at the Month 6, 9 and 12 Efficacy Assessment Visits, respectively.

This study is still ongoing and at the long-term follow up stage. The primary efficacy analysis was based on the primary database lock on 24 May 2019, the date of the Month 12 Efficacy Assessment Visit for the last patient. Other statistical analyses were based on the data cut on 15 November 2019 (submitted in 125700/0024, with 4-Month Safety Update), including safety data through the Month 15 Efficacy Assessment Visit for all patients, as well as additional safety data for patients whose study participation is beyond Month 15 visit.

There were no significant safety issues in studies rAd-IFN-CS-002 and rAd-IFN-CS-003.

10.2 Conclusions and Recommendations

Overall, the statistical analysis results from studies rAd-IFN-CS-003 and rAd-IFN-CS-002 support the safety and effectiveness of ADSTILADRIN in the proposed indication.