

OCE MORE Team BLA Clinical Review and Evaluation

Disclaimer: In this document, the sections labeled as “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	Original Application			
Application Number(s)	125700			
Priority or Standard	Priority			
Submit Date(s)	February 27, 2019			
Received Date(s)	September 3, 2019			
PDUFA Goal Date	May 1, 2020			
Division/Office	DCEPT/OTAT			
Review Completion Date	April 3, 2020			
Established Name	Nadofaragene firadenovec			
(Proposed) Trade Name	ADSTILADRIN			
Pharmacologic Class	TBD			
Code name	N/A			
Applicant	FKD Therapeutics Oy			
Formulation(s)	Component	Reference to Quality Standard	Function	Target Concentration (per mL)
	rAd-IFNα2b vector	In House	Active	3.0 x 10 ¹¹ virus particles
	Sodium dihydrogen phosphate dihydrate	(b) (4)	Buffer agent	(b) (4)
	Tromethamine	(b) (4)	Buffer agent	(b) (4)
	Glycerol (b) (4)	(b) (4)	Stabilizer	(b) (4)
	Sucrose	(b) (4)	Stabilizer	(b) (4)
	Magnesium chloride hexahydrate	(b) (4)	Stabilizer	0.34 mg
	Syn3 [N-(3-cholamidopropyl)-N-(3-lactobionamidopropyl)]-cholamide	In House	Surfactant	(b) (4)
	Hydroxypropyl-beta-cyclodextrin	(b) (4)	(b) (4)	(b) (4)

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ADSTILADRIN® (nadofaragene firadenovec)

	Citric acid monohydrate	(b) (4)	Buffer agent	0.01 mg
	Tri-Sodium citrate dihydrate	(b) (4)	Buffer agent	0.04 mg
	Polysorbate 80	(b) (4)	Surfactant	(b) (4)
	Water for Injections	(b) (4)	Solvent	q.s. 1 mL
Dosing Regimen	Patients will receive 75 mL intravesical administration of ADSTILADRIN at a dose of 2.25 x 10e13 vp/mL q3months			
Applicant Proposed Indication(s)/Population(s)	Treatment of high grade, Bacillus Calmette-Guérin (BCG) unresponsive non-muscle invasive bladder cancer			
Recommendation on Regulatory Action	OCE MORE Team Recommends a full approval. However, due to issues related to manufacturing and product quality, a complete response (CR) for this application will be issued.			
Recommended Indication(s)/Population(s) (if applicable)	Not Applicable due to CR			

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GLP	good laboratory practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

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OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

ADSTILADRIN® (rAd-IFN/Syn3) is a gene-based therapy designed to deliver the gene encoding interferon-alfa2b (IFN α 2b) to cells on the luminal surface of the bladder wall. rAd-IFN is a replication-deficient adenovirus-based gene transfer vector. Syn3 is a polyamide surfactant and a novel excipient. rAd-IFN and reconstituted Syn3 are combined with diluent to produce an admixture for intravesical administration. One dose of ADSTILADRIN (2.25×10^{13} vp) is comprised of 4 vials of ready-to-use (RTU) product. ADSTILADRIN is to be administered once every 3 months.

The applicant's proposed indication for this new molecular entity (NME) is:

ADSTILADRIN is indicated for the treatment of high-grade, Bacillus Calmette-Guérin (BCG) unresponsive non-muscle invasive bladder cancer (NMIBC).

1.2. Conclusions on the Substantial Evidence of Effectiveness

High-risk BCG-unresponsive NMIBC carries a poor prognosis with a high incidence (>20%) of progression to muscle-invasive bladder cancer and cancer-related mortality. Cystectomy is the standard of care; however, cystectomy is associated with morbidity and a 90-day mortality rate that may be as high as 10-15% in patients ≥ 70 years in the SEER population. Currently, there exists only one in FDA-approved intravesical therapy for this patient population, intravesical valrubicin, but it is not widely used or recommended in clinical guidelines due to a lack of sufficient efficacy.

Pembrolizumab, a systemic PD-1 inhibitor, was approved in January 2020 for the treatment of patients with BCG-unresponsive, high-risk, NMIBC with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy. Pembrolizumab demonstrated a complete response (CR) rate of 41% (95% CI: 31,51%), a median duration of complete response of 16.2 months (range: 0.0+, 30.4+), and 46% of responding patients maintaining response for at least 12 months. Per FDA guidance (BCG-Unresponsive Nonmuscle Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment; <https://www.fda.gov/media/101468/download>), due to the lack of acceptable non-cystectomy treatment options, a single-arm trial may be sufficient to demonstrate efficacy in patients with BCG-unresponsive NMIBC containing CIS with complete response (CR) rate, with associated durability of response, as the primary endpoint. A randomized trial would be required to demonstrate efficacy in patients with papillary-only disease as the preferred

primary endpoint would be disease-free survival (DFS), which is difficult to interpret in the setting of a single-arm trial.

The effectiveness claim of this original BLA is based on, rAd-IFN-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 at any time, 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 nadofaragene firadenovec.

A total of 107 patients with CIS were enrolled onto rAd-IFN-CS-003 of whom 103 were considered to have had adequate prior BCG therapy to be considered BCG-unresponsive per FDA guidance. Fifty-five patients had a CR at the first disease assessment (three months after the treatment start), leading to a CR rate of 53.4% (95% CI: 43,63%). No patients experienced a CR subsequently. The median duration of response was 9.7 months (95% CI: 9.9, 13.9 months). As of the November 15, 2019 data cutoff, the applicant reported that all study subjects had completed the Month 15 efficacy assessment visit and thus all patients in CR had been followed for at least 12 months following response. Of the 103 patients with BCG-unresponsive CIS who were treated with r-Ad-CS-003, 24 remained in CR for at least 12 months after the response was achieved. This corresponds to 44% of responding patients and 23% of all treated patients. Of note, random biopsies, which may capture occult CIS thereby improving the reliability of the durability results, were performed at the 12 month follow-up visit. Thirty-two patients with CIS with either no CR or CR followed by recurrent disease underwent subsequent cystectomy. Progression to muscle-invasive disease (T2) was seen in 3 of these 32 patients (9.3%), which is not higher than expected based on historical controls in the literature.

The most common ($\geq 10\%$) adverse events in rAd-IFN-CS-003 included instillation site discharge, fatigue, micturition urgency, bladder spasm, chills, pyrexia, and dysuria. Nineteen percent of patients experienced a Grade 3-4 event, of which hypertension (2.5%) was the most common. Nadofaragene firadenovec was discontinued due to an adverse event in 2.5% of patients due to bladder spasm, chills, instillation site discharge, and benign bladder neoplasm (urothelial hyperplasia). No patients died on study within 4 months of the last dose of the study drug. With a minimum follow-up of 7 months from last patient enrolled to data cut-off and a median follow-up of 24 months, two (1.9%) patients with CIS experienced progression to muscle-invasive or extra-vesical disease prior to cystectomy while on study.

The OCE MORE Team concludes that nadofaragene firadenovec has a favorable benefit/risk profile for patients with BCG-unresponsive NMIBC with CIS, based on the demonstration of a complete response rate and durability that provide meaningful clinical benefit to patients with CIS alone or high-grade Ta/T1 with CIS as an alternative to cystectomy, a surgical procedure

with high rates of morbidity and mortality. The safety profile of nadofaragene firadenovec, an intravesical therapy without apparently systemic toxicity, is acceptable for this patient population, particularly given the alternative of cystectomy. In the context of a clinically meaningful response rate and duration in patients with CIS, the OCE MORE Team determines that there is a favorable risk-benefit profile for the use of nadofaragene firadenovec in this patient population and recommends approval. However, due to issues related to manufacturing and product quality, a complete response for this application will be issued.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

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 without comorbidities seen at academic medical centers, but up to 15% in elderly patients in the SEER database. One intravesical therapy, intravesical 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, was approved for this population in January 2020 based on a complete response rate of 41% and median duration of response of 16 months.

rAd-IFN-CS-003 was a single-arm trial that enrolled 107 patients with BCG-unresponsive NMIBC with CIS with or without papillary tumors in addition to 50 patients with papillary-only tumors. Of these 107 patients with CIS, 103 were determined by the FDA to have BCG-unresponsive CIS per the criteria discussed in the FDA Guidance to Industry and constituted the primary efficacy population. Results demonstrated a clinically meaningful complete response (CR) rate of 53% (43, 63%) and median duration of response (9.7 months). The FDA considered responses lasting at least 12 months from initial response to be a clinically meaningful duration. A total of 23% (n=24) of all treated patients maintained a complete response for at least 12 months.

The most common (incidence >10%) adverse events in rAd-IFN-CS-003 included instillation site discharge, fatigue, micturition urgency, bladder spasm, chills, pyrexia, and dysuria. Nineteen percent of patients experienced a Grade 3-4 event, of which hypertension (2.5%) was the most common. A total of 2.5% of patients discontinued due to an adverse event, all of which were local events. There were eight deaths on study, all of which occurred at least four months following the last treatment administration and none of which was considered related to nadofarogene firadenovec. Three of thirty-two patients (9%) who went on to undergo radical cystectomy were pathologically upstaged to muscle-invasive disease, which is not higher than expected based on historical data. Two (1.9%) patients with CIS experienced progression to muscle-invasive or extra-vesical disease on study prior to cystectomy. Overall, there did not appear to be an increased risk of progression during nadofarogene

firadenovec therapy compared to undergoing immediate radical cystectomy. However, the duration of follow-up may be too short to adequately characterize this risk.

The OCE MORE Team considers the benefit-risk favorable for nadofarogene firadenovec for the treatment of patients with BCG-unresponsive NMIBC with CIS, as an alternative to cystectomy. However, the review team does not consider efficacy to have been demonstrated for the population of patients with papillary-only disease, as the endpoint of disease-free survival requires a randomized trial to allow interpretation. The OCE MORE Team thus concludes that the results of rAd-IFN-CS-003 supports the above indication and a full approval of this application. However, there are manufacturing and product quality issues with this application necessitating a complete response to be issued.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Following intravesical BCG therapy, patients with recurrence or persistence of high-risk NMIBC with CIS are at high risk of progression to muscle-invasive or metastatic bladder cancer.	Patients with NMIBC are at high risk for recurrence and progression to advanced and metastatic disease despite treatment with currently available treatment modalities.
Current Treatment Options	<ul style="list-style-type: none"> • Valrubicin; 18% CR rate, 13.5 month median duration of response. • Radical cystectomy; 1-15% 90-day post-operative mortality rate. Rate of cure poorly defined in the BCG-unresponsive patient population due to heterogeneity of population and prior BCG exposure. • Pembrolizumab; 41% CR rate, 16.2 month median duration of response, however associated with systemic immune-related toxicities. 	<ul style="list-style-type: none"> • Cystectomy is a procedure that can offer potential for cure, however is associated with significant morbidity and mortality that can impact on physical and psychosocial well-being. • FDA-approved treatment options include valrubicin and pembrolizumab.
Benefit	<ul style="list-style-type: none"> • In the CIS cohort with or with/out associated high-grade papillary disease the demonstrated CR rate at 3 months post treatment was 53.4% with the median durability of CR of 9.69 months. • 23% of all treated patients remained in complete response at least one year following response. 	The observed complete response rate and duration of complete response are clinically meaningful in that nearly 1 in 4 patients treated did not need radical cystectomy for at least one year.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	<ul style="list-style-type: none"> • The most common (incidence >10%) adverse events in rAd-IFN-CS-003 included instillation site discharge, fatigue, micturition urgency, bladder spasm, chills, pyrexia, and dysuria. • 19% of patients experienced a Grade 3-4 AE, of which hypertension (2.5%) was the most common. • Two (1.9%) with CIS experienced disease progression on study prior to cystectomy. In the subset of patients with CIS who underwent subsequent cystectomy, the incidence of pathologic upstaging to muscle-invasive disease was not higher than expected (3/32; 9%). 	<ul style="list-style-type: none"> • Serious toxicity associated with nadofarogene firadenovec was infrequent. Adverse events were typically local in nature and low-grade given the intravesical therapy. • Although interpretation of a single-arm trial is limited, there did not appear to be an increased risk of progression during nadofarogene firadenovec therapy compared to undergoing immediate radical cystectomy. However, the duration of follow-up is insufficient to fully characterize this risk.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

<input type="checkbox"/>	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
<input type="checkbox"/>	Clinical outcome assessment (COA) data, such as	[e.g., Section 6.1 Study endpoints]
<input type="checkbox"/>	Patient reported outcome (PRO)	
<input type="checkbox"/>	Observer reported outcome (ObsRO)	
<input type="checkbox"/>	Clinician reported outcome (ClinRO)	
<input type="checkbox"/>	Performance outcome (PerfO)	

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<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Section 2.1 Analysis of Condition]
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Natural history studies	
<input type="checkbox"/>	Patient preference studies (e.g., submitted studies or scientific publications)	
<input type="checkbox"/>	Other: (Please specify)	
<input checked="" type="checkbox"/>	Patient experience data that was not submitted in the application, but was considered in this review.	

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

The proposed indication for ADSTILADRIN is for the treatment of high-grade, Bacillus Calmette-Guérin (BCG)-unresponsive, non-muscle invasive bladder cancer (NMIBC). Bladder cancer is the fifth most common malignancy in the USA ([Siegel et al, 2019](#)) where, every year, the condition is responsible for 80,000 diagnosed cases and over 17,000 deaths. It is the most costly cancer among the elderly (the average age at the time of diagnosis is 73 years), estimated at nearly \$4 billion per year, and has the highest cost of any cancer when categorized on a per patient basis ([Mossanen and Gore, 2014](#)).

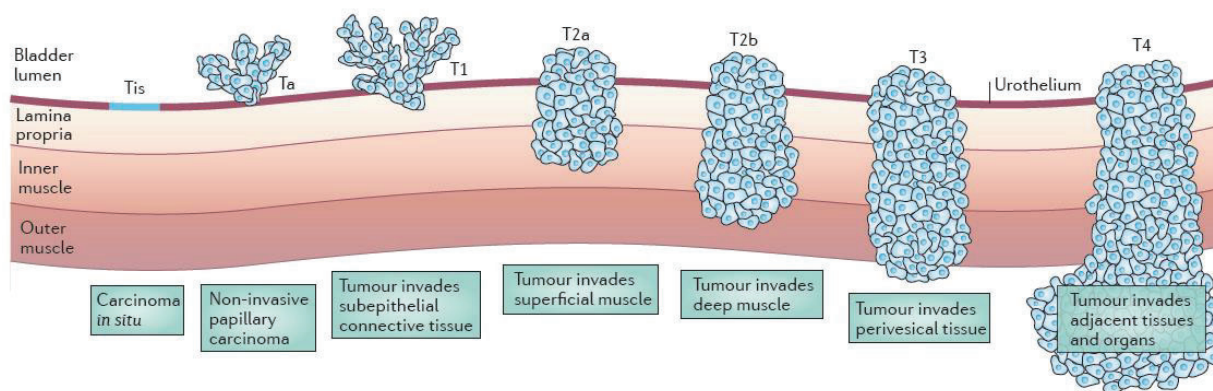
Bladder cancer can be divided into metastatic, locally advanced and non-muscle invasive disease. Amongst the last group there is low- and high- risk NMIBC. The issue with low risk NMIBC is recurrence since it rarely progresses. This development plan deals with the worst of the high risk (disease that persists or rapidly recurs following standard therapy, BCG). This group of patients was formerly known as BCG recurrent and/or refractory but a more rigid and standardized definition for this group of high-risk patients was identified as BCG unresponsive in the most recent FDA guidance. The standard of care management for this patient population is radical cystectomy, a procedure with significant morbidity and mortality. The only FDA-approved therapy for these patients is Valstar® (valrubicin) which is limited to those patients who are not candidates for cystectomy and the reported complete response rate is only 18% at 6 months and 10% at one year.

Approximately 75-85% of patients with bladder cancer present with NMIBC ([Anastasiadis and de Reijke, 2012](#)), which comprises papillary disease (Ta and T1 tumors) and carcinoma *in situ* (CIS) ([Edge et al, 2010](#)). The majority of cases of NMIBC are low-grade; however, 7% of NMIBC are highly aggressive, high-grade papillary disease or CIS ([Grignon, 2009](#); [Berdik, 2017](#)).

Bladder cancer staging is illustrated in Figure 1. The staging and grading of Ta vs. T1 vs. CIS is made histologically by the pathologist based on bladder biopsies. Patients with low-grade Ta disease fall into the low-intermediate risk group. Patients with high grade Ta tumors, CIS (also known as Tis), or T1 tumors which invade into the lamina propria are considered to be at high risk for tumor recurrence and progression, with an increased risk of invasive disease that requires careful life-long surveillance ([Pashos et al, 2002](#)). The goals of treatment for NMIBC are to prevent recurrence and, more importantly, to prevent progression to muscle invasion and metastatic disease.

Up to 40% of patients with high-grade NMIBC eventually fail standard of care therapeutic treatment (BCG; [Zlotta et al, 2009](#)) and, for these patients, radical cystectomy is currently the next treatment option. Indeed, it is known that the risk of radical cystectomy is 3-fold higher in patients who have failed BCG induction and maintenance therapy, compared to patients who have failed BCG induction therapy alone ([Li et al, 2019](#)). These patients, presently known as high-grade BCG-unresponsive NMIBC patients, remain a group with high clinical need, where new effective therapeutic treatments are required as alternatives to cystectomy. In 2012, the Society of Urologic Oncology, the American Urologic Association, and the FDA launched a collaborative effort to address this deficiency, with an initial focus on defining a pathway for drug registration for BCG-unresponsive NMIBC, in order to stimulate drug development in this space. This work led to the publication of the FDA guidelines in February 2018 and the acceptance of a single-arm trial design for testing of novel therapies in patients with BCG-unresponsive tumors including CIS, as well as high-grade Ta/T1 papillary tumors alone or with an element of CIS. Further, an understanding was reached that the primary endpoint for these trials would be the rate and durability of a complete response for CIS, with the anticipation of an incremental but meaningful improvement in the outcomes compared to that achieved by Valstar® (valrubicin).

Figure 1: Bladder Cancer Classification ([Knowles and Hurst, 2015](#))



The FDA's Assessment:

High-risk 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. Based on the FDA Guidance to Industry titled "BCG-Unresponsive Non-muscle Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment," BCG-unresponsive CIS was defined as persistent or recurrent CIS alone or with recurrent Ta/T1 disease within 12 months of adequate BCG therapy. Adequate BCG therapy

was defined as at least five of six doses of an initial induction course plus at least two of three doses of maintenance BCG or at least five of six doses of an initial induction course plus at least two of six doses of a second induction course.

2.2. Analysis of Current Treatment Options

Table 1: Summary of Treatment Armamentarium Relevant to Proposed Indication

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments						
Thiotepa	Treatment of superficial papillary carcinoma of the urinary bladder	1959 (full)	60 mg once weekly for 4 weeks	None stated	Warnings for death resulting from bone marrow depression, septicemia and hemorrhage; hematopoietic toxicity; teratogenicity; mutagenicity; carcinogenicity	None
TICE BCG	Treatment and prophylaxis of CIS of the urinary bladder; prophylaxis of primary or recurrent stage Ta and/or T1 papillary tumors following transurethral resection	1989 (full)	1 to 8 x 10 ⁸ colony forming units once weekly for at least 6 weeks and then once monthly for up to 12 months	CIS: 50% complete response (median duration, 4 years) Ta/T1: 53-57% disease-free survival at 2 years	Warnings for death (systemic BCG infection and sepsis); tuberculin sensitivity	None
Valrubicin	Intravesical	1998	800 mg	CIS: 18%	Warnings	None

	therapy of BCG-refractory CIS of the urinary bladder in patients for whom immediate cystectomy would be associated with unacceptable morbidity or mortality	(full)	intravesically once weekly for 6 weeks	complete response at 6 months	include fetal harm; use in patients with perforated bladder or compromised integrity or severe irritable bladder symptoms	
Other Treatments						

*Accelerated approval or full approval

The Applicant's Position:

The treatment of NMIBC is directed at eliminating recurrences and preventing progression to muscle-invasive bladder cancer (MIBC) and subsequent metastases.

High-grade papillary tumors (Ta and T1) and CIS are associated with a high risk of progression (50% at 3 years) and the greatest risk for cancer-related death ([Hussain et al, 2009](#)). For high-risk tumors, irrespective of whether they are Ta, T1, or CIS all guidelines recommend transurethral resection of bladder tumor (TURBT) with or without mitomycin C treatment within 24 hours followed by intravesical treatment with BCG induction immunotherapy with BCG maintenance treatments. Cytolytic agents such as mitomycin C or gemcitabine are reserved for those with low or intermediate-risk disease ([NCCN Clinical Practice Guidelines in Bladder Cancer, 2019](#)).

BCG has been the most effective therapy for the treatment of patients with high-grade NMIBC since the 1970s ([Kamat et al, 2015](#)). Typically, this agent is instilled into the bladder through a urethral catheter (i.e. intravesically) and patients retain the BCG solution for up to one hour. BCG is given weekly for 6 weeks. Maintenance treatment regimens of up to 3 years have been shown to be more effective than induction therapy alone ([Lamm, 2009](#)) with complete response rates approximating 70% reported at 24 months. Patients who respond to BCG undergo a rigorous surveillance with cystoscopy and urinary cytology every 3 months for 2 years and every 6 months thereafter until 5 years and then yearly. Despite optimal maintenance therapy, bladder cancer eventually recurs in most patients and in some as advanced disease ([Zlotta et al, 2009](#)). Subsequent therapy is based on the timing and grade of the recurrence. Several agents have been tested as second line therapy but none have provided durable outcomes ([Steinberg et al, 2000](#); [Dinney et al, 2013](#)). Cystectomy remains the most effective treatment option to prevent disease progression and subsequent metastasis. In men, radical cystectomy comprises the

removal of the bladder, prostate and seminal vesicles; in women, it comprises the removal of the bladder, urethra, uterus and sometimes the anterior wall of the vagina. Many physicians and patients choose to delay cystectomy in favor of preserving bladder function in order to avoid the morbidity and mortality associated with radical cystectomy, despite the possibility of disease progression ([Elmussareh et al, 2019](#)).

The term, “BCG unresponsive” is now widely used to capture those patients with high-grade NMIBC who have been treated with adequate BCG (≥2 courses of intravesical BCG – defined as at least 5 of 6 induction instillations of BCG and at least 2 of 3 instillations of maintenance BCG) and are unlikely to benefit from, and should not receive, further intravesical BCG ([Lerner et al, 2015](#), [Catalona et al, 1987](#)). This is recognized in the FDA’s February 2018 final “Guidance for Industry on BCG-Unresponsive Non-Muscle Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment”. Patients meeting the definition of BCG-unresponsive NMIBC should not receive additional BCG; cystectomy is considered the standard of care in these patients ([Lerner et al, 2015](#)), and is recommended in current NCCN guidelines ([NCCN Clinical Practice Guidelines in Bladder Cancer, 2019](#)).

Therapeutic agents currently FDA-approved for the treatment of NMIBC are shown in Table 1. Specifically with reference to those patients who are not good candidates for cystectomy because of unacceptable morbidity or mortality, Valstar® (valrubicin) was approved by the FDA in 1998 for the treatment of BCG-refractory carcinoma *in situ* of the urinary bladder. In the registration trial (which formed the basis for FDA approval of the product) intravesical administration of Valstar® to 230 patients with transitional cell carcinoma of the bladder resulted in only 18% of the treated patients with BCG-refractory CIS achieving a complete response (free of disease recurrence or progression) at 6 months ([Valstar® US Prescribing Information](#), revised 4/2016). The probability of disease-free status following Valstar treatment was 10% at 1 year, and 4% at 2 years ([Dinney et al, 2013](#)).

As no meaningful advances in therapy for the treatment of bladder cancer have been made since BCG was approved in 1989, and up to 40% of patients with NMIBC will fail BCG therapy and there is no gold-standard for second line intravesical therapy ([Zlotta et al, 2009](#)), it is clearly recognized that more effective drugs, associated with fewer complications and better patient compliance, and drugs that are active in unresponsive patients, are needed for NMIBC ([Jarow et al, 2015](#)). Thus, the identification of effective second-line therapy for patients with NMIBC who are facing radical cystectomy remains an unmet need ([Jarow et al, 2015](#)).

In summary, BCG immunotherapy is usually the standard first line therapy for the treatment of high-grade NMIBC and has been used since the 1970s ([Kamat et al, 2015](#)). Currently, there are no effective second-line drugs available for patients with BCG unresponsive NMIBC, and radical cystectomy, which is associated with significant morbidity and mortality, is the standard of care for these patients ([von Rundstedt and Lerner, 2015](#); [Elmussareh et al, 2019](#)). It is clear that effective second-line therapy for patients with BCG-unresponsive NMIBC remains a critical unmet

need for patients facing radical cystectomy (Jarow et al, 2015). ADSTILADRIN has been developed to address this high unmet medical need.

The FDA's Assessment:

FDA agrees that BCG is the standard first-line therapy for high-grade NMIBC and that there are limited treatment options available aside from radical cystectomy for the treatment of BCG-unresponsive NMIBC. Intravesical valrubicin was approved in 2011 for the treatment of patients with BCG-refractory NMIBC based on a CR rate of 18% and median duration of response of 13.5 months in a single-arm trial of 90 patients. However, valrubicin is not widely used and is not favored in clinical guidelines for the management of BCG-unresponsive NMIBC due to the perceived lack of efficacy. There are limited data from small single-arm trials available for several alternative intravesical chemotherapies, including gemcitabine and docetaxel, however none of these agents are approved for BCG-unresponsive NMIBC. Additionally, the response rates and duration for these agents have been generally comparable to valrubicin, although interpretation is limited due to heterogeneity of the patient population, adequacy of prior BCG therapy, and the stringency of assessment.

Pembrolizumab received full approval in the US for patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) on January 8, 2020 based on results of KEYNOTE 057 (NCT02625961). This study was a multicenter, single-arm trial that enrolled 148 patients with high-risk NMIBC, 96 of whom had BCG-unresponsive CIS with or without papillary tumors. The major efficacy outcome measures were complete response (as defined by negative results for cystoscopy [with TURBT/biopsies as applicable], urine cytology, and computed tomography urography [CTU] imaging) and duration of response. The complete response rate in the 96 patients with high-risk BCG-unresponsive NMIBC with CIS was 41% (95% CI: 31, 51) and median response duration was 16.2 months (0.0+, 30.4+). Forty-six percent (46%) of responding patients experienced a complete response lasting at least 12 months.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

This section is not applicable, as ADSTILADRIN® is not marketed in any territory.

The FDA's Assessment:

The FDA concurs with the applicant's assessment.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Schering Plough Corporation's Investigational New Drug (IND) application (12547) was allowed to proceed by the FDA in August 2005 (adenovirus vector containing interferon alfa-2b gene [SCH 721015] with the excipient Syn3®, a polyamide surfactant that facilitates transduction of cells in the urothelium by the adenoviral vector [Connor et al, 2001]). 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 (Meeting ID#: 8327, SN0037). Following the successful completion of this study, an End of Phase 2 meeting was held with FDA in July 2015 (Meeting ID:9851, SN0071) to discuss the design of the 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 Biologics License Application (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 the product for the treatment of transitional cell carcinoma of the bladder was granted on December 13, 2016.

An Initial Comprehensive Multidisciplinary Breakthrough Therapy teleconference was held on June 29, 2017 (Ref: CRMTS 10712), subsequent to which the Sponsor further engaged with the FDA (at teleconferences held on September 14, 2017 and December 5, 2017) to align the primary endpoint for the Phase 3 study with FDA's recommendations and its February 2018 final "Guidance for Industry on BCG-Unresponsive Non-Muscle Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment" (hereafter referred to as the "FDA's February 2018 guidance"). As a consequence of those meetings, the primary endpoint for the Phase 3 study was amended from the incidence of Event-Free Survival at 12 months in all patients to complete response at any time after the first administration of ADSTILADRIN in patients with CIS with or without concomitant high-grade Ta/T1 disease, with durability of complete response defined as the key secondary endpoint. Efficacy in patients with Ta/T1 disease without concomitant CIS was evaluated as a secondary endpoint (specifically, incidence and durability of high-grade recurrence-free survival).

The clinical program for ADSTILADRIN was designed in the context of the available guidances, namely, relevant International Conference on Harmonization (ICH) guidelines, the FDA's Guidance for Industry: Guidance for Industry Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events (November 2006) and, latterly, the Guidance for Industry on BCG-

Unresponsive Non-Muscle Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment (February 2018). The studies were performed in the US in accordance with ICH (E6 [R]2) Good Clinical Practice (GCP). Further, the design of each study was discussed with FDA at milestone meetings (pre-IND, End of Phase 1, and End of Phase 2) and during additional interactions.

The Phase 3 study was designed to evaluate the incidence of event-free survival at 12 months in high-grade BCG unresponsive patients with NMIBC (i.e. patients with CIS, and patients with papillary disease). The primary endpoint of the study was most recently discussed with FDA at two key teleconferences held on September 14, 2017 and December 5, 2017, respectively. Subsequent to these discussions, the primary endpoint was amended from “the incidence of Event-Free Survival at 12 months in all patients” to “complete response at any time after the first administration of ADSTILADRIN in patients with CIS with or without concomitant high-grade Ta/T1 disease”. Complete response was deemed to have occurred at an efficacy assessment when urine cytology is negative and there are no lesions on cystoscopy. Patients with positive cytology or with findings on cystoscopy that were suspicious for recurrent cancer underwent biopsy(ies). In addition, all patients underwent mandatory biopsies of the bladder at the Month 12 efficacy assessment.

Once a complete response is achieved, recurrence of low-grade disease only at any subsequent time point is not considered a treatment failure. The use of complete response as the primary efficacy endpoint is consistent with FDA’s February 2018 guidance. At the time this change was made, duration of complete response in patients with CIS was classified as a key secondary endpoint. Other secondary endpoints of note include the incidence and duration of high-grade recurrence-free survival in patients with papillary disease.

Finally, during development, the excipient Syn3 was presented as a lyophilized powder, which was provided with separate vials of rAd-IFN and diluent (the final formulation buffer) for clinical use, and an (b) (4) for intravesical instillation was prepared using these components at clinical sites. As discussed with the FDA at a teleconference on October 15, 2018 (Ref: CRMTS #11400), ADSTILADRIN is proposed for commercial use as a constituted Ready to Use (RTU) presentation for administration to the patient. This presentation was developed to eliminate the handling of multiple components in the pharmacy (particularly the need for BioSafety Level 2 [BSL-2] conditions to prepare the instillation), to remove the requirement for different storage conditions (below (b) (4) for vector, and (b) (4) for Syn3 and diluent) required for the components in the Phase 3 clinical presentation, and to accommodate the lack of expert pharmacy and (b) (4) facilities in the commercial environment, which could materially limit patient access to the treatment. The formulation, volume, concentration of vector and concentration of excipients in the RTU is identical to the instillation used in clinical trials. Comparability between the admixture used in the clinical trials and the RTU presentation has been established.

The FDA’s Assessment:

The FDA concurs with the applicant's summary of pre-submission and submission regulatory activities.

The Phase 3 study, rAd-IFN-CS-003, was initiated in September 2016. The protocol was amended five times during the course of the clinical trial. Most significantly, as stated by the applicant, after communications between the applicant and the FDA the protocol was amended to change the primary endpoint from "the incidence of Event-Free Survival at 12 months in all patients" to "complete response at any time after the first administration of ADSTILADRIN in patients with CIS with or without concomitant high grade Ta/T1 disease in order to more consistently align with the 2018 FDA guidance on BCG-unresponsive nonmuscle invasive bladder cancer. The FDA considered evaluation of complete response rate and duration of response in a single-arm study in CIS patients with BCG-unresponsive NMIBC to be an allowed study endpoint. For patients with papillary-only disease, a randomized trial would be required to evaluate efficacy as complete response rate cannot be easily assessed in this population of patients who would ordinarily have surgical resection of these papillary disease, thus have no evidence of disease at baseline prior to ADSTILADRIN treatment. In addition, a time-to-event endpoint, such as event-free survival, cannot be interpreted in a single-arm trial. Therefore, this clinical review and assessment focuses on patients with CIS (with or without papillary disease).

4 Sources of Clinical Data

4.1. Table of Clinical Studies

The Applicant's Position:

ADSTILADRIN has been studied in 221 patients enrolled in 4 clinical trials conducted in the US (Table 2). These studies include a Phase 1 rising single-dose study (P03816), a Phase 1b study (2009-0938) conducted under an Investigator-initiated IND, a Phase 2 multi-center, randomized, parallel arm, open label, repeat dose study (rAd-IFN-CS-002) and a Phase 3 multi-center, open label, repeat dose study (rAd-IFN-CS-003). The Phase 2 and Phase 3 studies were designed following consultation with the FDA. The protocol, administrative oversight, and accrual timelines for the Phase 2 and 3 studies were designed and conducted in association with the Society for Urologic Oncology Clinical Trials Consortium (SUO CTC).

Included in this application are Phase 3 data as reported, pending full database lock, up to a data cutoff date of 08-March-2019 (after all patients completed their Month 9 Efficacy Assessment Visit or had withdrawn prior). Efficacy data collected and available at time points later than the Month 9 Efficacy Assessment Visit are not included in the analyses, as agreed with FDA and documented in its Written Response of 15 March 2019. This study forms the basis for the efficacy claims in the BLA; data from the 12-month efficacy and safety assessment visits will be provided within three months of submission of the complete BLA (as agreed in FDA's Written Response of March 15, 2019 [[CRMTS#11664](#)]).

Table 2. Listing of Clinical Trials Relevant to this BLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
<i>Controlled Studies to Support Efficacy and Safety</i>								
rAd-IFN-CS-003	NCT02773849	Multi-center, open label, repeat dose Phase 3 safety and efficacy study	ADSTILADRIN 2.25 x 10 ¹³ vp every 3 months (intravesical)	Complete response ^a	Maximum of 4 administrations in 12 months; if CR or absence of high-grade recurrence at Month 12, treatment every 3 months at discretion of treating physician	157	High-grade BCG unresponsive NMIBC, defined as: • CIS only, • Ta/T1 high-grade disease with concomitant CIS, or • Ta/T1 high-grade disease without concomitant CIS	34 Centers (USA)
rAd-IFN-CS-002	NCT01687244	Multi-center, randomized, parallel arm, open-label, repeat dose Phase 2 safety and efficacy	ADSTILADRIN 7.5 x 10 ¹² vp or 2.25 x 10 ¹³ vp every 3 months (intravesical)	Tumor recurrence	Maximum of 4 administrations in 12 months	40	High-grade BCG-refractory or relapsed NMIBC	14 Centers (USA)
2009-0938	NCT01162785	Single-center, single-arm Phase 1b	ADSTILADRIN 2.25 x 10 ¹³ vp (intravesical)	Complete response ^b	Two administrations on Days 1 and 4	7	BCG-refractory NMIBC who refused radical cystectomy	1 Center (USA)
P03816	NCT00536588	Phase 1, non-randomized, open-label, dose escalation	ADSTILADRIN (intravesical) 2.25 x 10 ¹¹ vp 7.5 x 10 ¹¹ vp 2.25 x 10 ¹² vp 7.5 x 10 ¹² vp 2.25 x 10 ¹³ vp	Safety and tolerability	ADSTILADRIN Single administration (Part 1) If CR, patient able to receive 2 nd administration (Part 2)	17	BCG-refractory superficial transitional cell carcinoma (TCC) of the bladder	2 Centers (USA)

^a Defined as negative urine cytology and no lesions on cystoscopy; if random biopsies of the bladder are performed these should be negative

^b Defined as lack of tumor recurrence 3 months after treatment

The FDA's Assessment:

The FDA concurs with the Applicant's description of clinical studies. The Applicant's clinical development plan for ADSTILADRIN included two Phase 1 trials and a Phase 2 trial which were sufficient to confirm proof of principle and provide initial efficacy and safety data supportive of the Phase 3 trial. In the multicenter Phase 3 open-label trial 107 subjects were enrolled with CIS disease. The primary objective of this study was to evaluate the complete response (CR) rate in patients with CIS (with or without concomitant high-grade Ta or T1 papillary disease.) At the time of the Month 15 efficacy report (Data cutoff: NOV-15-2019) all study subjects had completed Month 15 assessments. Efficacy results presented in this review are based on the NOV-15-2019 cutoff (BLA Amendment #25).

5 Statistical and Clinical Evaluation

5.1. Review of Relevant Individual Trials Used to Support Efficacy

5.1.1. rAd-IFN-CS-003

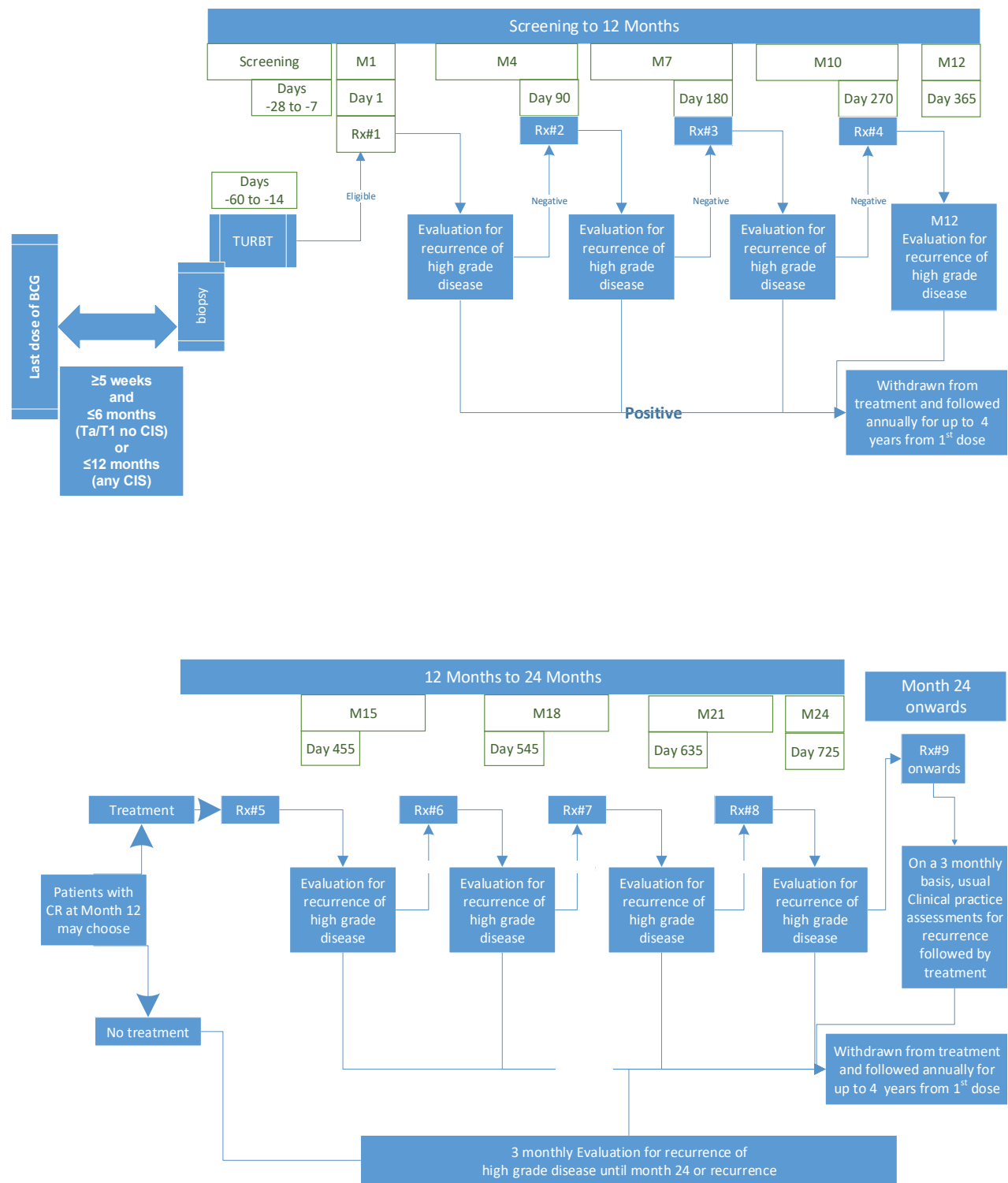
Trial Design

The Applicant's Description:

rAd-IFN-CS-003 is an open label study to evaluate the safety and efficacy of ADSTILADRIN administered intravesically to patients with high-grade, BCG unresponsive NMIBC. The primary objective of the study is to evaluate the complete response rate in patients with CIS, with secondary objectives including duration of complete response and incidence of high-grade recurrence-free survival in patients with CIS (with or without concomitant high-grade Ta/T1 disease and in patients with papillary disease without concomitant CIS).

This study was conducted at 34 centers in the US. A study flow chart is provided in Figure 2.

Figure 2 Study Flow Chart



Diagnostic criteria

The Phase 3 study entry criteria took into account the experience and feedback gained during study feasibility assessment and following consultation with members of the SUO CTC, and the FDA's guidance. The proposed indication wording reflects not only the patient population that has been, and continues to be, studied in the Phase 3 trial, but also the real-world patient population as currently diagnosed and managed by urologists (by whom use of the commercial product is intended). Hence, no extrapolation from the Phase 3 patient population to the proposed commercial population is required.

Key inclusion/exclusion criteria

The Phase 3 study recruited patients with BCG-unresponsive NMIBC; the definition of "BCG unresponsive" employed in the study is based on the proposal of Lerner et al (2013) and also reflects the FDA's February 2018 guidance. Variations in clinical practice regarding administration of BCG therapy and, particularly, the number of courses and timing of administration are also reflected in the definition and in other related entry requirements.

The inclusion and exclusion criteria are listed below.

Inclusion criteria

1. Aged 18 years or older at the time of consent
2. Able to give written informed consent
3. Have at entry, confirmed by a pathology report:
 - Carcinoma *in situ* (CIS) only
 - Ta/T1 high-grade disease with concomitant CIS or
 - Ta/T1 high-grade disease without concomitant CIS (Montrioni and Lopez-Beltran, 2005)
4. Are "BCG Unresponsive" which refers to patients with high-grade NMIBC who are unlikely to benefit from and who will not be receiving further intravesical BCG. The term "BCG Unresponsive" includes patients who did not respond to BCG treatment and have a persistent high-grade recurrence within 12 months after BCG was initiated, and those who despite an initial CR to BCG, relapse with CIS within 12 months of their last intravesical treatment with BCG or relapse with high-grade Ta/T1 NMIBC within 6 months of their last intravesical treatment with BCG. The following criteria define the patients who may be included in the study:
 - a. Have received at least two previous courses of BCG within a 12 month period – defined as at least 5 of 6 induction BCG instillations and at least two out of three instillations of maintenance BCG, or at least two of six instillations of a second induction course, where maintenance BCG is not given.
 - i. Exception: those who have T1 high-grade disease at 1st evaluation after induction BCG alone (at least 5 of 6 doses) may qualify in the absence of disease progression

- b. At the time of tumor recurrence, patients with CIS alone or high-grade Ta/T1 with CIS should be within 12 months of last exposure to BCG and patients with high-grade Ta/T1 without CIS should be within 6 months of last exposure to BCG
 - c. No maximum limit to the amount of BCG administered
 - d. All visible papillary tumors must be resected and those with persistent T1 disease on transurethral resection of bladder tumor (TURBT) should undergo an additional re-TURBT within 14 to 60 days prior to beginning study treatment. Obvious areas of CIS should also be fulgurated
- 5. Available for the whole duration of the study
 - 6. Life expectancy >2 years, in the opinion of the investigator
 - 7. Eastern Cooperative Oncology Group (ECOG) status 2 or less ([Oken et al 2002](#))
 - 8. 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, evidence of upper tract tumor by either intravenous pyelogram, retrograde pyelogram, computed tomography (CT) scan with or without urogram, or magnetic resonance imaging (MRI) with or without urogram performed within 6 months of enrollment
 - 9. Patients with prostate cancer on active surveillance at low risk for progression, defined as prostate-specific antigen (PSA) <10 ng/dL, Gleason score 6 and cT1 are permitted to be included into the study at the discretion of the Investigator (see exclusion criterion 10)
 - 10. Female patients of childbearing potential must use maximally effective birth control during the period of therapy, must be willing to use contraception for 1 month following the last study drug infusion and must have a negative urine or serum pregnancy test upon entry into this study. Otherwise, female patients must be postmenopausal (no menstrual period for a minimum of 12 months) or surgically sterile. Maximally effective birth control means that the patient, if sexually active, should be using a combination of two methods of birth control that are approved and recognized to be effective by regulatory agencies
 - 11. Male patients must 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
 - 12. Adequate laboratory values.
 - Hemoglobin ≥ 10 g/dL
 - White blood cells (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)* below institutional upper limit of normal (ULN)

- Activated partial thromboplastin time (aPTT)* below institutional ULN
- Aspartate aminotransferase (AST) $\leq 1.5 \times$ ULN
- Alanine aminotransferase (ALT) $\leq 1.5 \times$ ULN
- Total bilirubin $\leq 1.5 \times$ ULN
- Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m²

* It is accepted that patients receiving anticoagulation therapy would not have INR and aPTT results that fall within 'normal limits'. It is not intended to exclude these patients and therefore medical discretion is permitted for patients who have clinically acceptable results in regards to their current concomitant anticoagulant therapy

Exclusion criteria

1. Current or previous evidence of muscle invasive (muscularis propria) or metastatic disease presented at the screening visit. Examples of increased risk of metastatic disease include but are 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
2. Current systemic therapy for bladder cancer
3. Current or prior pelvic external beam radiotherapy within 5 years of entry
4. Prior treatment with adenovirus-based drugs
5. Suspected hypersensitivity to IFN α 2b
6. Symptomatic urinary tract infection or bacterial cystitis (once satisfactorily treated, patients can enter the study)
7. Clinically significant and unexplained elevated liver or renal function tests
8. Women who are pregnant or lactating or refuse to commit to use contraception throughout during the study
9. Any other significant disease or other clinical findings which in the opinion of the investigator would prevent study entry
10. History of malignancy of other organ system within past 5 years, except treated basal cell carcinoma or squamous cell carcinoma of the skin and \leq pT2 upper tract urothelial carcinoma at least 24 months after nephroureterectomy. Also patients with genitourinary cancers other than urothelial cancer or prostate cancer that are under active surveillance are excluded (see inclusion criterion 9)
11. Patients who cannot hold instillation for 1 hour
12. Patients who cannot tolerate intravesical dosing or intravesical surgical manipulation
13. 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 is permitted between 14 to 60 days prior to beginning study treatment

- Previous intravesical BCG therapy, which can be given at least 5 weeks before the diagnostic biopsy required for entry into the study

Dose selection and study treatments

ADSTILADRIN is administered via intravesical instillation. This route of administration is standard and is widely used in the hospital setting for the administration of existing bladder cancer therapies.

The dosage regimen for the Phase 3 study, and that intended for commercialization, is based on data from the nonclinical and clinical development program for ADSTILADRIN. Repeat dosing of rAd-IFN with Syn3 was initially evaluated in rats, where optimal IFN α 2b expression was observed at dosing intervals of 90 days (b) (4). This dosing interval was also used in a toxicology study in the cynomolgus monkey (SN03245), which demonstrated expression of IFN α 2b protein and an acceptable safety profile. Subsequently, in the Phase 1 trial (P03816), single doses of 2.25×10^{11} to 2.25×10^{13} viral particles (vp) were well tolerated; dose dependent increases in urinary IFN α concentrations confirmed efficient gene transfer and expression. In the Phase 2 trial (rAd-IFN-CS-002), a dose of 2.25×10^{13} vp every three months was well tolerated and demonstrated promising efficacy; the median time to disease progression at this dose was numerically superior to a dose of 7.5×10^{12} vp (11.7 months vs. 3.5 months) and, since no safety issues were identified at either dose level, it was decided to use the higher of the two doses in the Phase 3 study to maximize the potential benefit for patients. No further dose-response evaluations have been performed or are considered necessary.

Therefore, in the Phase 3 trial (rAd-IFN-CS-003), patients receive ADSTILADRIN at a dose of 2.25×10^{13} vp on each treatment day. After the first administration of ADSTILADRIN, patients with no evidence of high-grade disease continue to receive further treatment with ADSTILADRIN every three months up to Month 12. Thereafter, patients continue to receive ADSTILADRIN every 3 months, at the discretion of the investigator, provided there is no evidence of high grade disease.

During the dwell time, it is recommended that the patient is repositioned from left to right, back and abdomen to maximize bladder surface exposure, with repositioning occurring approximately every 15 minutes. If, during the dwell time, the patient exhibits bladder cramping and/or premature voiding, turning of the patient can be adjusted.

Assignment of patients to treatment

The Phase 3 study is an open-label, single-arm study of one dose level of ADSTILADRIN. As such, randomization and stratification were not included in the protocol. However, data from patients with CIS (with or without concomitant high-grade Ta/T1 papillary disease) and patients with high-grade Ta/T1 disease (without concomitant carcinoma *in situ*) were analyzed separately and together (see Section 5.1.2).

Blinding

The Phase 3 study is an open-label, single-arm study of one dose level of ADSTILADRIN. No blinding was employed. This does not impact on the robustness of the primary endpoint analysis due to the nature of the assessments and subsequent determination of whether or not a patient has achieved a complete response.

Dose modifications and discontinuations

The protocol allows for a delay to treatment (maximum 14 days) if any toxicity experienced is not recovered to less than Grade 2 in severity. No dose reductions are permitted. Adjustments to the instillation dwell time (defined in the protocol as 60 minutes) or splitting of the dose (e.g., 37.5 mL × 2) are made based upon assessments of local tolerability, as permitted in the protocol.

Administrative structure

The Safety Management Committee, comprising the Sponsor's Medical Monitor and an independent reviewer selected by the Sponsor, and other Sponsor representatives as a minimum, meets at regular intervals, and as events dictated, to review emerging safety data. The Committee has reviewed, as a minimum, safety data from the first 20, 40 and 60 patients treated in the study.

Procedures and schedule

The trial schedule of events is shown in Table 3.

NDA/BLA OCE MORE Team Clinical Review and Evaluation (BLA 125700)
ADSTILADRIN® (nadofaragene firadenovec)

Table 3: Schedule of Study Assessments

Visit Number	1	2	3		4	5	6		7	8			9	10			11
Month (4 weeks) and Day of Month	Screening	M1 D1	M1 D3 ^t	Phone Calls ^j	Efficacy Assessments ^f	M4 D1	M4 D3 ^t	Phone Calls ^j	Efficacy Assessments ^f	M7 D1	M7 D3 ^t	Phone Calls ^j	Efficacy Assessments ^f	M10 D1	M10 D3 ^t	Phone Calls ^j	M12
Day relative to initial dosing (days) ^s	D-28 to D-7	Day 1	+2 days	Mthly ^u	M4D1 -14days	M1D 1+90 ±5 days	M4D 1 +2 days	Mthly ^u	M7D1 -14days	M1D 1+18 0 ±5 days	M7D 1 +2 days	Mthly ^u	M10D1 -14 days	M1D 1 +270 ±5 days	M10D1 +2 days	Mthly ^u	M1D 1 +365 ±5 days
Informed consent	X																
Medical history (inc. demographics)	X																
Inclusion/exclusion	X																
Pregnancy test ^c	X	X				X				X				X			X
Physical examination ^d	X	X				X				X				X			X
ECG ^o	X	X	X			X	X			X				X			X
Vital signs ^e	X	X	X			X	X			X				X			X
ECOG performance status ^l	X	X				X				X				X			X
Urinary Symptoms	X	X	X			X	X			X				X			X
TURBT ^r and endoscopic resection	X																
Cystoscopy					X				X				X				X
Biopsy ^{n,q}					(X) ^g				(X) ^g				(X) ^g				(X) ^g

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Visit Number	1	2	3		4	5	6		7	8			9	10			11
Month (4 weeks) and Day of Month	Screening	M1 D1	M1 D3 ^t	Phone Calls ^j	Efficacy Assessments ^f	M4 D1	M4 D3 ^t	Phone Calls ^j	Efficacy Assessment ^{s f}	M7 D1	M7 D3 ^t	Phone Calls ^j	Efficacy Assessments ^f	M10 D1	M10 D3 ^t	Phone Calls ^j	M12
Day relative to initial dosing (days) ^s	D-28 to D-7	Day 1	+2 days	Mthly ^u	M4D1 -14days	M1D 1+90 ±5 days	M4D 1 +2 days	Mthly ^u	M7D1 -14days	M1D 1+180 ±5 days	M7D 1 +2 days	Mthly ^u	M10D1 -14 days	M1D 1 +270 ±5 days	M10D1 +2 days	Mthly ^u	M1D 1 +365 ±5 days
Urine Cytology	X				X				X				X				X
Blood sample for antibody level ^h assessments	X					X				X				X			X
Exploratory Urine samples ^m	X		X			X	X			X				X			X
Clinical chemistry ⁱ	X	X	X			X	X			X				X			X
Hematology ⁱ	X	X	X			X	X			X				X			X
Blood Sample exploratory analysis	X																X
Urinalysis ^k	X	X	X			X	X			X				X			X
Concomitant medications ^j	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events ^j	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bladder Capacity ^p	X																
Study Drug administration	X					X				X				X			X ^v
Annual updates on patient response and survival																	

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Visit Number		12	13
Month (4 weeks) and Day of Month	Withdrawal from Study\ End of treatment ^a	Follow up every 3 months ^q	Long-term follow-up following treatment. Annual data collection ^b
Day relative to initial dosing (days) ^e		M1D1 +M15, +M18, +M21,+M24 etc	
Informed consent			
Medical history (inc. demographics)			
Inclusion/exclusion			
Pregnancy test ^c	X	X	
Physical examination ^d	X	X	
ECG ^o	X	X	
Vital signs ^e	X	X	
ECOG performance status ^l	X	X	
Urinary Symptoms	X	X	
TURBT ^r and endoscopic resection			
Cystoscopy	X	X	
Biopsy ^{n,q}	X	(X) ^g	
Urine Cytology	X	X	
Blood sample for antibody level ^h assessments	X		
Exploratory Urine samples ^m	X		
Clinical chemistry ^j	X	X	
Hematology ⁱ	X	X	
Blood Sample exploratory analysis	X		
Urinalysis ^k	X	X	
Concomitant medications ^j	X	X	
Adverse events ^j	X	X	X (Related SAEs Only)

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Visit Number		12	13
Bladder Capacity ^P			
Study Drug administration		X	
Annual updates on patient response and survival			X

Footnotes to Table 3 Schedule of Study Assessments

- a. The assessments detailed in the Withdrawal Visit will only be performed for patients who are withdrawn from treatment
- b. After withdrawal from the study, patients will be followed as per clinical practice to determine duration of response, progression to invasive disease, date of cystectomy and survival for up to 4 years from first dose,
- c. Pregnancy test to be performed in women of child bearing potential during screening, prior to commencing treatment, prior to repeat administration, end of month 12 and at Withdrawal visit
- d. Physical examination to be performed prior to treatment and should include neurological examination and body weight
- e. Vital signs are to be assessed pre- and post-dose. Blood pressure measurements will be made after the patient has been resting supine or semi supine for a minimum of 5 minutes
- f. Efficacy assessments (urine cytology and cystoscopy only) must be performed up to 2 weeks (14 days) before re-treatment. Only patients who do not have recurrence of High-Grade disease will receive the next dose
- g. Biopsies will be performed if evident or suspicious lesions are seen during cystoscopy at efficacy visits. No instillations are permitted until at least 2 weeks after a biopsy. Biopsies must be done at withdrawal and at the end of month 12 (day 365) for all patients
- h. Anti-adenoviral antibodies samples will be taken at M1D1, M4D1, M7D1, M10D1, M12 or at a withdrawal from treatment \study visit
- i. Hematology and clinical chemistry samples may be taken the previous day to ensure results are available before dosing. See Appendix A for full panel listing
- j. Patients will be contacted monthly by phone following each dose to provide information regarding AEs and concomitant medications. Annual follow up will collect Serious Adverse Events only
- k. Urinalysis on dosing days to be taken pre-dose
- l. Eastern Cooperative Oncology Group (ECOG) assessments to be performed pre-dose
- m. Urine samples for exploratory work should be taken pre-dose at M1D1, M4D1, M7D1, M10D1, M12 and also post dose at M1D3 and M4D3. Samples should also be collected at a withdrawal visit
- n. Biopsy slides will be stored centrally for possible correlation to local pathology. Biopsy tissue and/ blocks (if permissible) will also be collected for central storage

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- o. All ECGs should be performed pre-dose. Clinically significant ECG abnormalities are to be reviewed by the investigator prior to dosing. QTcF measurement will be recorded in the eCRF
- p. May be performed at screening if investigator feels it is necessary to determine whether or not a patient can hold an instillation of INSTILADRIN
- q. During the first 12 months of the Long Term Follow Up period for patients having a complete response at month 12, assessments at months 15, 18, 21, and 24 will be performed by cytology, cystoscopy and a biopsy if clinically indicated. Continued dosing at least 14 days from biopsy may take place for patients with no evidence of high grade disease recurrence at month 12, After M24, treatment may continue for patients who are responding to INSTILADRIN and assessments performed in accordance with usual clinical practice to demonstrate the patient suitability.
- r. TURBT/fulguration procedure is permitted up 14 to 60 days prior to beginning study treatment
- s. Dosing should occur within ± 5 days of the target timepoint e.g., M4D1 has a target timepoint of 90 days, therefore the dosing should be scheduled for between day 85 and 95 and the other assessments scheduled to this date.
- t. Where day 3 falls on a non working day, the visit can be delayed by up to 2 days.
- u. Mthly: Approximately every 30 days, telephone calls after each dose for concomitant medication and adverse event collection

Concurrent medications

The Phase 3 protocol included a recommendation to use anticholinergic agents on each dosing day (unless contraindicated) to reduce potential bladder irritation and to prevent premature voiding of the bladder.

No non-specified systemic anti-cancer therapy or radiotherapy is to be used during the study. Prohibited medications prior to screening, and during the study, include immunosuppressive therapies (3 months prior to screening), investigational drugs (30 days prior to screening), and intravesical therapy within 8 weeks prior to beginning study treatment, with the exception of a) cytotoxic agents when administered as a single instillation immediately following a TURBT procedure (which is permitted between 14 to 60 days prior to beginning study treatment) and b) previous intravesical BCG therapy, which can be given at least 5 weeks before the diagnostic biopsy required for entry into the study).

Dietary restrictions/instructions

Owing to the nature of ADSTILADRIN, dietary restrictions are not required.

Treatment compliance

The Phase 3 protocol required ADSTILADRIN to be administered by a urologist in the hospital setting. Treatment compliance is assessed by the percentage of protocol defined instilled dose and the percentage of protocol defined dwell time.

The allowable time windows for the following study assessments are listed below:

Study Assessment	Allowable timeframe window
Pregnancy testing	Prior to dosing on dosing days
Physical examination	Prior to dosing on dosing days
Vital signs	Pre-dose: Up to 2 hours prior to dosing Post-dose: after dosing, during that specific visit
ECG	Pre-dose: performed at any time between 24 hours and 1 hour pre-dose
ECOG performance status	Prior to dosing on dosing days
Urine cytology and cystoscopy	Up to 2 weeks prior to re-treatment to ensure results available prior to planned dosing
TURBT/ fulguration and endoscopic resection	Between 14 and 60 days prior to the beginning of study treatment (first dose)
Blood sample for antibody levels	Performed at any time between 24 hours and 1 hour pre-dose
Blood and urine sample for exploratory assays	Performed at any time between 24 hours and 1 hour pre-dose
Safety labs (clinical chemistry, and hematology)	Pre-dose: May be taken on day -1 prior to dosing to ensure results are available pre-dose

Safety labs (urinalysis only)	Performed at any time between 24 hours and 1 hour pre-dose
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Rescue medication

Owing to the nature of ADSTILADRIN, the use of rescue medication was not planned in the study.

Subject completion, discontinuation, or withdrawal

In accordance with the protocol, the primary analysis of the study will be performed when the required number of evaluable CIS (with or without concomitant high-grade Ta/T1 papillary disease) patients have either completed the month 12 assessment or have been withdrawn from the study and undergone a withdrawal from treatment/study assessment. The current analysis was performed when all patients remaining on treatment in the study had completed the Month 9 safety and efficacy assessment visit.

Patients with evidence of high-grade disease after receiving at least one dose of ADSTILADRIN are withdrawn from treatment, but are followed for survival and time to cystectomy on an annual basis. In addition, long term follow-up safety and survival data are being collected for up to 4 years from the first dose for all patients, including information regarding progression to invasive disease and cystectomy.

Patients withdrawn from the study undergo a series of tests at the withdrawal/end of treatment visit, including urine pregnancy test (if applicable), physical examination and weight, vital signs, resting 12 lead ECG, ECOG performance status, collection of urinary symptom information, urine cytology, cystoscopy and biopsy(ies) (if clinically indicated), collection of a) blood sample for clinical chemistry and hematology profile, b) serum for anti-adenoviral antibody assessment and c) urine sample for biomarker assessment, urinalysis, concomitant medications, and adverse events. Patients who entered the study (signed the informed consent) but were not enrolled (dosed) could be replaced.

The FDA's Assessment:

The FDA concurs with the Applicant's description of the design of trial rAd -IFN-CS-003. The final design of this study including the patient population, disease assessment and efficacy endpoints was consistent with the 2018 FDA Guidance to Industry on BCG-unresponsive NMIBC. The inclusion criteria included subjects who had either CIS with or without concomitant high-grade Ta or T1 disease or high-grade papillary disease alone.

Of note, mandatory biopsies at five locations in the bladder were performed at the Month 12 assessment. This was recommended but was not required by the FDA guidance. Mandatory biopsies may capture occult CIS which was not detected either by cystoscopic visualization or by cytology, although it is not currently generally considered a standard of care. The protocol for study rAd-IFN-CS-003 did not require a specific imaging technology to be used by investigators participating in the clinical trial. Information on the imaging modality/(ies)

used for the assessment of individual patients was not recorded in the eCRF. The applicant did not consider it appropriate or feasible to mandate advanced cystoscopy imaging technologies as a requirement for participation in the study, given that not all sites had the capacity for these enhanced techniques. Investigators were advised to use the same modality consistently screening and each efficacy assessment for an individual patient. The data provided by the applicant regarding use of blue light, narrow band and white light was not sufficient to infer any bias in determining the true response rate in study participants.

In the protocol, the applicant specified only that the investigational agent be administered via a urinary catheter. The BLA submission did not provide any efficacy data related to differences in the type of urinary catheter used at each investigator site. It is possible that the differences in catheter construction, length, coatings, colorants, gauge size and connector style may impact the stability of the product. The applicant may need to address these concerns in package labeling and provide guidance to the end user regarding urinary catheter selection for optimal product delivery.

Study Endpoints

The Applicant's Description:

The following efficacy endpoints are stipulated in the Phase 3 study protocol and the Statistical Analysis Plan (SAP):

- Whether or not a patient with CIS (with or without concomitant high-grade Ta/T1 disease) responds to treatment, defined as complete response at any time after first administration of ADSTILADRIN (*primary endpoint*)
- Durability of complete response in patients with CIS (with or without concomitant high-grade Ta/T1 disease) who show a complete response at any time after first administration of ADSTILADRIN (*key secondary endpoint*)
- Whether or not a patient with high-grade Ta or T1 papillary disease (without concomitant CIS) responds to treatment, defined as absence of recurrence of high-grade disease (*secondary endpoint*)
- Event-free survival in patients with high-grade Ta or T1 papillary (without concomitant CIS) disease and in patients with CIS (with or without papillary disease) (*secondary endpoint*)
- Incidence of and time to cystectomy (*secondary endpoint*)
- Overall survival (*secondary endpoint*)

Any patient with positive cytology or with findings on cystoscopy that are suspicious for recurrent cancer undergoes biopsy of the lesion(s) to confirm disease recurrence at each efficacy assessment (every three months). Therefore, the diagnosis of high-grade or low-grade recurrence is based on bladder biopsy. The timing of efficacy assessments aligns with the FDA's February 2018 guidance. No adjudication was used for any of the current pathological analyses.

Patients in the Phase 3 study are being followed for duration of complete response, commencing from time of first documented response until recurrence of high-grade disease, at which point they are discontinued from study treatment but continue to be followed for survival and time to cystectomy on an annual basis.

No measures of pharmacodynamic effect are included in the protocol.

The FDA's Assessment:

As stated by the applicant, efficacy was assessed separately for the CIS disease cohort and the papillary disease cohort. The FDA considered patients with BCG-unresponsive NMIBC with CIS with or without concomitant papillary disease to constitute the primary efficacy population. The efficacy endpoint for the papillary disease cohort with resected disease at study entry is considered exploratory in rAD-IFN-CS-003, a single-arm study. As stated in the 2018 FDA guidance for BCG-unresponsive NMIBC, the FDA recommends a randomized controlled trial design for patients with resected papillary-only disease given that complete response cannot be assessed in the absence of active disease at study entry.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The draft SAP was submitted to the FDA on May 25, 2016. The SAP was updated to align with the current protocol and finalized on November 7, 2018 (prior to database lock for the current analysis), and was submitted to FDA on November 12, 2018.

The Efficacy Analysis Set (EAS) comprises all members of the Safety Analysis Set (all patients who have received at least one dose of ADSTILADRIN) with a diagnosis of high-grade, BCG unresponsive NMIBC. The EAS is the primary analysis set for the analyses of efficacy data.

The Per Protocol Analysis Set comprises all patients in the EAS who had no major protocol violation and either:

- Completed their 12 month assessment at earliest Day +357 and at latest Day +396; or
- Withdrew before their 12 month assessment because of disease recurrence or progression, death, adverse event related to the disease or treatment, or lack of tolerability.

In terms of missing data, patients were deemed not to have achieved a complete response or high-grade recurrence-free survival if there were insufficient data to determine whether or not a complete response or high-grade-recurrence-free survival had occurred. It was considered sufficient evidence for high-grade-recurrence-free-survival if a subsequent assessment showed high-grade-recurrence-free survival and there was no intermediate treatment for bladder cancer

other than ADSTILADRIN. The FDA's February 2018 guidance does not provide any indication of the magnitude of a clinically meaningful response.

A conservative approach was taken to the handling of missing or partial dates for classification of prior and concomitant medications and for calculation of time from initial diagnosis. No imputations were made for any other endpoints; the data were treated as missing.

In accordance with the FDA's February 2018 guidance, a plan for the evaluation of patients with suspicious urine cytology was implemented. Specifically, in determining whether a patient with CIS had achieved a complete response, the following conservative approach was taken in accordance with a pre-defined rule in the Statistical Analysis Plan (SAP), where it is specified that a patient will be judged to have *not* achieved a complete response where:

- Urine cytology is reported as suspicious, malignant cells or not done, *and*
- Bladder biopsy/ies have not been performed, *and*
- There is high-grade recurrence, confirmed by bladder biopsy/ies, observed at the next scheduled visit.

In accordance with the SAP, 100 patients with CIS provide 90% power to reject the hypothesis that the true response rate is 27% at a one-sided alpha of 2.5%. Thirty-seven responding patients (response rate of 37%, two-sided 95% Clopper-Pearson CI = [27.5%, 47.3%]) are sufficient to reject the hypothesis if 100 evaluable patients are enrolled. A total of 103 evaluable CIS patients were enrolled and, therefore, 38 responding patients (response rate of 36.9%, two-sided 95% Clopper-Pearson CI = [27.5%, 47.0%]) are sufficient to reject the hypothesis.

The FDA's Assessment:

The FDA concurs with the applicant's definition of study populations and the stated plan for handling of missing data. The enrolled sample size of the CIS cohort was adequate to achieve the stated study power. The lower bound of the 95% CI for the null hypothesis excluded the CR rate seen in previous studies in this patient population.

The FDA considered the CR rate and duration of response to provide additional evidence of efficacy. FDA agrees that recurrence of high-grade disease is more clinically meaningful compared to recurrence of low-grade disease, which may not significantly impact oncologic outcome.

Protocol Amendments

The Applicant's Description:

The protocol has been amended five times since initiation of the study. The changes largely consisted of minor amendments to provide further clarity on the protocol content, including additional detail on continued dosing and management of patients beyond Month 12, and on the number of biopsies to be taken, along with minor changes to the study entry criteria.

There has been one significant change to the design of the study during its conduct which was implemented on FDA recommendation during a teleconference on December 5, 2017: a change to the primary endpoint, as discussed previously, along with a resulting change to the patient population on which the primary endpoint analysis is based, and the final sample size for the study (increased from 135 patients to approximately 150 patients), with enrolment to end when approximately 100 evaluable CIS (with or without concomitant high-grade Ta/T1 disease) has been dosed. These changes are not considered to have adversely affected the robustness or validity of the study as the conduct of the study itself was not affected, and the changes were made prior to analysis of the data.

The FDA's Assessment:

The FDA concurs with the applicant's description of protocol amendments.

5.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant's Position:

The Phase 3 study was conducted in accordance with 21 CFR part 50, the relevant Institutional Review Board requirements (21 CFR part 56), the obligations of clinical investigators (21 CFR 312.50 to 312.70), the principles of the Declaration of Helsinki, and in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice (GCP)(ICH E6[R2]). All of the studies included in the BLA were conducted in the US and therefore the requirements of 21 CFR 312.120 and GCP as it applies to foreign clinical studies not conducted under an IND are not applicable.

Written informed consent was obtained from each participant prior to enrolment in the study, and the initial study protocol and all subsequent protocol amendments were submitted to the IND and approved by local IRBs prior to implementation. Finally, until the changes to arrangements for protocol review came into effect in 2018, the initial protocol and all protocol amendments were submitted to the National Institute of Health Recombinant DNA Advisory Committee (NIH RAC).

The FDA's Assessment:

The FDA concurs with the applicant's description of compliance with good clinical practices (GCP)(ICH E6[R2]) in the conduct of trial rAd-IFN -CS-003.

Financial Disclosure

The Applicant's Position:

Financial disclosures for all investigators participating in the Phase 3 study are available (and were provided in Module 1). None of the investigators are full- or part-time employees of the Sponsor, and none have disclosable financial interests in, or arrangements with, the Sponsor.

The FDA's Assessment:

The FDA concurs with the applicant's assessment of financial disclosures of study investigators.

Patient Disposition

Table 4: Patient Disposition – All Enrolled Patients

	CIS n (%)	Papillary Disease n (%)	Total n (%)
Patients enrolled (received first dose) [1]	107 (100.0)	50 (100.0)	157 (100.0)
Patients treated			
At Month 4 Day 1 [2]	63 (58.9)	35 (70.0)	98 (62.4)
At Month 7 Day 1 [3]	43 (40.2)	31 (62.0)	74 (47.1)
At Month 10 Day 1 [4]	36 (33.6)	26 (52.0)	62 (39.5)
Patients who are ongoing with study treatment	31 (29.0)	27 (54.0)	58 (36.9)
Patients who discontinued study treatment	76 (71.0)	23 (46.0)	99 (63.1)
Disease recurrence	73 (68.2)	22 (44.0)	95 (60.5)
Adverse event	2 (1.9)	1 (2.0)	3 (1.9)
Patient request	1 (0.9)	0 (0.0)	1 (0.6)
Patients who discontinued early from study follow-up	4 (3.7)	1 (2.0)	5 (3.2)
Death	2 (1.9)	1 (2.0)	3 (1.9)
Withdrawal of consent	1 (0.9)	0 (0.0)	1 (0.6)
Other	1 (0.9)	0 (0.0)	1 (0.6)

[1] Patients enrolled included all patients who signed the ICF, were enrolled in a cohort, and received the first dose.

[2] Patient (b) (6) achieved HGRF survival at Month 3, but received no study drug at Month 4 Day 1.

[3] Patient (b) (6) achieved HGRF survival at Month 6, but received no study drug at Month 7 Day 1.

[4] Patients (b) (6) achieved HGRF survival at Month 9, but received no study drug at Month 10 Day 1.

Abbreviations: CIS = carcinoma *in situ*; HGRF = high-grade recurrence-free; ICF = informed consent form; n = number

Note: CIS = CIS only; Ta + CIS, and T1 + CIS; papillary disease = high grade Ta and T1.

Percentage was calculated using the total number of treated patients as the denominator.

Source: Study Report rAd-IFN-CS-003, Post text [Table 14.1.1.1](#) and [14.1.4.1](#)

The Applicant's Position:

A total of 157 patients were enrolled and treated, including 107 patients in the CIS cohort and 50 patients in the papillary disease cohort. The patient disposition for all enrolled patients is presented in Table 4. A greater proportion of patients in the papillary disease cohort were treated at each respective Efficacy Assessment Visit. In both cohorts, disease recurrence was the most common reason for discontinuing study treatment: 73 (68.2%) patients in the CIS cohort and 22 (44.0%) patients in the papillary disease cohort. The three patients who discontinued due to adverse events are described in Section 5.2.

The FDA's Assessment:

The applicant submitted updated patient disposition information in the Month 15 efficacy analysis. These data were used to compile the following table:

Table 5: Patient Disposition - All Enrolled Patients (DCO: NOV-15-2019)

	CIS n (%)	Papillary Disease n (%)	Total n (%)
Patients enrolled (received first dose)	107 (100.0)	50 (100.0)	157 (100.0)
Patients treated			
At Month 4 Day 1	63 (58.9)	35 (70.0)	98 (62.4)
At Month 7 Day 1	43 (40.2)	31 (62.0)	74 (47.1)
At Month 10 Day 1	36 (33.6)	26 (52.0)	62 (39.5)
At Month 12 Day 1	23 (21.5)	17 (34.0)	40 (25.5)
At Month 15 Day 1	23 (21.5)	15 (30.0)	38 (24.2)
Patients who completed the Month 12 Efficacy Assessment	36 (33.6)	27 (54.0)	63 (40.1)
Patients who did not complete the Month 12 Efficacy Assessment	71 (66.4)	23 (46.0)	94 (59.9)
Patients who completed the 12-month treatment period	33 (30.8)	25 (50.0)	58 (36.9)
Patients who did not complete the 12-month treatment period	74 (69.2)	25 (50.0)	99 (63.1)
Patients who continued treatment post 12-months	24 (22.4)	18 (36.0)	42 (26.8)
Patients who discontinued study treatment	85 (79.4)	37 (74.0)	122 (77.7)
Disease recurrence	80 (74.8)	30 (60.0)	110 (70.1)

	CIS n (%)	Papillary Disease n (%)	Total n (%)
Adverse event	2 (1.9)	1 (2.0)	3 (1.9)
Patient request	1 (0.9)	1 (2.0)	2 (1.3)
Patients who discontinued early from study follow-up	11 (10.3)	5 (10.0)	16 (10.2)
Death	5 (4.7)	2 (4.0)	7 (4.5)
Withdrawal of consent	4 (3.7)	3 (6.0)	7 (4.5)
Lost to Follow-up	2 (1.9)	0 (0.0)	2 (1.3)

Source: Month 15 efficacy report-January 2020

These data are consistent with the efficacy analysis. The majority of CIS study subjects discontinued treatment due to disease recurrence. Study subjects with papillary-only disease were observed to have a lower recurrence rate than patients with CIS which may reflect differences in biology/prognosis, difference in response to the study drug, or may be a chance finding in a single-arm trial. Comparison between the CIS and papillary-only cohorts was not a pre-specified analysis and, as previously stated, the efficacy endpoint of disease-free survival in papillary-only disease requires a randomized study for interpretation.

Protocol Violations/Deviations

Data:

Table 6: Tabulated Summary of Patients Excluded from the Efficacy Analysis

Patient ID	Tumor Type	Rationale	Outcome
(b) (6)	Ta + CIS	Did not receive 2 courses of BCG within a 12-month period	CR at M3 HG recurrence at M6 (CIS + papillary)
(b) (6)	Ta + CIS	Was not within 12 months of last exposure to BCG at time of diagnosis of recurrence	HG recurrence at M3 (papillary)
(b) (6)	CIS	Was not within 12 months of last exposure to BCG at time of diagnosis of recurrence	HG recurrence at M3 (CIS)
(b) (6)	CIS	Did not receive 2 courses of BCG within a 12-month period Was not within 12 months of last exposure to BCG at time of diagnosis of recurrence	HG recurrence at M3 (CIS)

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(b) (6)	Ta	Did not receive 2 courses of BCG within a 12-month period Diagnostic biopsy performed <5 weeks after last dose of BCG	HG recurrence free at M3 and M6
(b) (6)	Ta	Was not within 6 months of last exposure to BCG at time of diagnosis of recurrence	HG recurrence at M3 (CIS + papillary)

Abbreviations: BCG = Bacillus Calmette-Guérin; CIS = carcinoma *in situ*; CR = complete response; HG = high-grade; ID = identification; M3 = month 3; M6 = month 6

Source: Study Report rAd-IFN-CS-003 [Section 10.3](#), [Post text Data Listing 16.2.3](#)

The Applicant's Position:

The Efficacy Analysis Set was defined as all patients in the Safety Analysis Set who met the protocol definition of high-grade, BCG unresponsive NMIBC. The efficacy analysis set (N=151; 103 patients with CIS, 48 patients with papillary disease) excludes 6 patients (4 patients with CIS with or without concomitant high-grade Ta/T1 disease, and 2 patients with papillary disease) who, on data review (and in accordance with the intention to treat principles described in ICH E9), did not meet the protocol definition of high-grade, BCG unresponsive NMIBC at the time of enrolment into the study (see Table 6).

Protocol deviations were categorized by the Sponsor as major or minor during data review and prior to database lock. All major protocol deviations were CSR reportable and are presented below.

- Seventeen patients had their Month 1 Day 1 Visit conducted outside of the protocol defined window.
- Sixteen patients did not meet the entry criteria. Of these, 6 patients were not included in the Efficacy Analysis Set because they did not meet the protocol definition of high-grade, BCG unresponsive NMIBC. The unmet entry criteria for the remaining 10 patients were determined by the Sponsor to have no impact on the key patient requirements as defined for BCG unresponsive NMIBC.
- Twelve patients had deviations relating to the dosing of ADSTILADRIN. Nine patients did not receive the correct dose of ADSTILADRIN, 2 patients received ADSTILADRIN within 14 days of a biopsy, and 1 patient received treatment with ADSTILADRIN following temperature excursions during storage that had not been reported by the site.
- Four patients received an excluded medication.
- Two patients were in major violation of the informed consent process. One patient signed the ICF or reconsent form improperly and had their Month 1 Day 1 Visit conducted 29 days

after the ICF was signed due to a prolonged screening period. The second patient was not reconsented with the updated ICF.

- One patient did not have biopsies performed at Month 12 in accordance with protocol requirements because the patient withdrew consent for biopsy collection. This patient was not withdrawn from the study.
- One patient had biopsies collected from locations not specified in the protocol.

With the exception of the patients excluded from the efficacy analysis set, these deviations do not impact upon the efficacy analysis.

The FDA's Assessment:

FDA concurs with the applicant's assessment of protocol deviations/violations and agrees that the identified primary efficacy population of 103 patients with BCG-unresponsive NMIBC with CIS with or without papillary disease is concordant with the criteria recommended by the FDA guidance. FDA reviewed case report forms for patients enrolled in the CIS cohort and did not identify additional cases of ineligible study subjects beyond those identified by the applicant. The applicant did not identify any new protocol deviations in the Month 15 efficacy report submitted in amendment 25 and received on January 10, 2020. Therefore, the protocol deviations reported by the applicant do not appear to represent a pattern of bias or adversely impact the efficacy analysis.

Table of Demographic Characteristics

Data:

Table 7: Demographic and Baseline Characteristics (Efficacy Analysis Set)

Demographic/Baseline Characteristics Statistic/Category	CIS (n=103) n (%)	Papillary Disease (n=48) n (%)	Total (n=151) n (%)
Age at informed consent (years)			
N	103	48	151
Mean (SD)	71.0 (8.88)	69.9 (9.92)	70.7 (9.15)
Age group at informed consent (n, %)			
<65 years	24 (23.3)	13 (27.1)	37 (24.5)
≥65 years	79 (76.7)	35 (72.9)	114 (75.5)
Sex (n, %)			
Male	91 (88.3)	34 (70.8)	125 (82.8)
Female	12 (11.7)	14 (29.2)	26 (17.2)

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Demographic/Baseline Characteristics Statistic/Category	CIS (n=103) n (%)	Papillary Disease (n=48) n (%)	Total (n=151) n (%)
Race (n, %)			
White	95 (92.2)	45 (93.8)	140 (92.7)
Black or African American	6 (5.8)	2 (4.2)	8 (5.3)
Asian	2 (1.9)	1 (2.1)	3 (2.0)
Ethnicity (n, %)			
Hispanic or Latino	3 (2.9)	1 (2.1)	4 (2.6)
Not Hispanic or Latino	95 (92.2)	47 (97.9)	142 (94.0)
Not reported	1 (1.0)	0 (0.0)	1 (0.8)
Unknown	4 (3.9)	0 (0.0)	4 (2.6)
Height (cm)			
N	103	47	150
Mean (SD)	175.0 (9.91)	171.2 (10.38)	173.8 (10.18)
Baseline weight (kg)			
N	103	48	151
Mean (SD)	90.33 (21.132)	86.80 (18.133)	89.21 (20.234)
Baseline BMI (kg/m ²)			
N	103	47	150
Mean (SD)	29.35 (5.741)	29.31 (4.831)	29.34 (5.456)
Baseline ECOG status (n, %)			
0	93 (90.3)	41 (85.4)	134 (88.7)
1	7 (6.8)	6 (12.5)	13 (8.6)
2	3 (2.9)	1 (2.1)	4 (2.6)

Abbreviations: BMI = body mass index; CIS = carcinoma *in situ*; ECOG = Eastern Cooperative Oncology Group; N= number; SD = standard deviation

Note: CIS = CIS only, Ta + CIS, and T1 + CIS; papillary disease = high grade Ta and T1

Percentage was calculated using the number of patients in the column heading as the denominator

Baseline was defined as the last observation before the first dose of the study drug

Source: Study Report rAd-IFN-CS-003, Post text [Table 14.1.2.5](#)

The Applicant's Position:

In the Efficacy Analysis Set ([Table 7](#)), the majority of patients were male (82.8%) and were ≥65 years old (75.5%), White (92.7%), and not Hispanic or Latino (94.0%). In total, 134 (88.7%) patients had a baseline ECOG status of 0, 13 (8.6%) patients had a baseline ECOG status of 1, and 4 (2.6%) patients had a baseline ECOG status of 2. The mean height, baseline weight, and baseline body mass index for the Efficacy Analysis Set were 173.8 cm, 89.21 kg, and 29.34 kg/m²,

respectively. This patient population is representative of the patient population proposed for commercialization.

The FDA's Assessment:

The study population enrolled in rAd-IFN-CS-003 was predominately male and older than 65. Approximately 11% of the study population was female, 5.8% were Black or African-American and 2.9% were Hispanic or Latino. Due to the low percentage of non-white study participants differences in outcome based on ethnicity were not analyzed.

According to the American Cancer Society in the U.S. the average age at the time of diagnosis of bladder cancer is 73. SEER registry data suggest similar demographics between the US population and that enrolled in rAd-IFN-CIS-003 with the majority of patients with NMIBC being male (74%) and non-Latino white (87%). While survivorship was worse among racial and ethnic subgroups other than non-Latino whites in the SEER NMIBC population (Seo et al; J Prev Med Public Health 2018), it is not clear whether this is due to biological differences in the disease and prognosis versus other factors. The results of rAd-IFN-CS-003 are considered to be generalizable to the entire U.S. population.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Disease history characteristics are presented in Table 8 for the Efficacy Analysis Set. Table 9 presents the BCG history (number of prior courses of BCG administered) for the Efficacy Analysis Set.

Table 8: Disease History Characteristics (Efficacy Analysis Set)

Disease History Characteristic Statistic/Category	CIS (n=103)	Papillary Disease (n=48)	Total (n=151)
Time from initial diagnosis of bladder cancer (months) [1]			
N	103	48	151
Mean (SD)	28.56 (24.961)	20.26 (18.433)	25.92 (23.349)
Disease classification at initial diagnosis (n, %)			
CIS only	23 (22.3)	1 (2.1)	24 (15.9)
Ta	33 (32.0)	18 (37.5)	51 (33.8)
Ta + CIS	11 (10.7)	4 (8.3)	15 (9.9)
T1	22 (21.4)	23 (47.9)	45 (29.8)
T1 + CIS	9 (8.7)	1 (2.1)	10 (6.6)
Unknown	5 (4.9)	1 (2.1)	6 (4.0)
Grade at initial diagnosis (n, %)			
High	92 (89.3)	43 (89.6)	135 (89.4)
Low	8 (7.8)	4 (8.3)	12 (7.9)
Unknown	3 (2.9)	1 (2.1)	4 (2.6)

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Disease History Characteristic Statistic/Category	CIS (n=103)	Papillary Disease (n=48)	Total (n=151)
Time from the last TURBT/endoscopic resection or fulguration (months) [1]			
N	103	48	151
Mean (SD)	1.60 (0.755)	1.33 (0.438)	1.52 (0.681)
Current status at entry (n, %)			
Refractory	55 (53.4)	34 (70.8)	89 (58.9)
Relapsed	48 (46.6)	14 (29.2)	62 (41.1)
Current stage at entry (n, %)			
CIS only	79 (76.7)	0 (0.0)	79 (52.3)
Ta	0 (0.0)	33 (68.8)	33 (21.9)
Ta + CIS	19 (18.4)	0 (0.0)	19 (12.6)
T1	0 (0.0)	15 (31.3)	15 (9.9)
T1 + CIS	5 (4.9)	0 (0.0)	5 (3.3)
Urine cytology result at Screening (n, %)			
No evidence of malignant urothelial cells	37 (35.9)	33 (68.8)	70 (46.4)
Atypical/suspicious cells	46 (44.7)	12 (25.0)	58 (38.4)
Positive for malignant urothelial cells	14 (13.6)	1 (2.1)	15 (9.9)
Missing	6 (5.8)	2 (4.2)	8 (5.3)
Prior surgery resection (non-TURBT resection) (n, %)			
Yes	4 (3.9)	0 (0.0)	4 (2.6)
No	99 (96.1)	48 (100.0)	147 (97.4)
Prior radiotherapy (n, %)			
Yes	4 (3.9)	1 (2.1)	5 (3.3)
No	99 (96.1)	47 (97.9)	146 (96.7)
Prior cancer therapy/medication regimen (n, %) [2]			
Yes	31 (30.1)	7 (14.6)	38 (25.2)
No	72 (69.9)	41 (85.4)	113 (74.8)
Type of most recent prior cancer therapy/medications (n, %) [2]			
Chemotherapy	26 (25.2)	7 (14.6)	33 (21.9)
Small molecule targeted therapy	2 (1.9)	0 (0.0)	2 (1.3)
Monoclonal antibody	1 (1.0)	0 (0.0)	1 (0.7)
Vaccine	1 (1.0)	0 (0.0)	1 (0.7)
Hormone	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (1.0)	0 (0.0)	1 (0.7)
Number of prior regimens (n, %) [2]			
0	72 (69.9)	41 (85.4)	113 (74.8)

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Disease History Characteristic Statistic/Category	CIS (n=103)	Papillary Disease (n=48)	Total (n=151)
1	18 (17.5)	6 (12.5)	24 (15.9)
2	5 (4.9)	1 (2.1)	6 (4.0)
3	7 (6.8)	0 (0.0)	7 (4.6)
4	0 (0.0)	0 (0.0)	0 (0.0)
≥5	1 (1.0)	0 (0.0)	1 (0.7)
Line of the most recent prior cancer therapy (n, %) [2]			
First line	7 (6.8)	1 (2.1)	8 (5.3)
Second line	5 (4.9)	3 (6.3)	8 (5.3)
Third line	3 (2.9)	0 (0.0)	3 (2.0)
Fourth line	3 (2.9)	0 (0.0)	3 (2.0)
Sixth line	1 (1.0)	0 (0.0)	1 (0.7)
Adjuvant	9 (8.7)	1 (2.1)	10 (6.6)
Neoadjuvant	3 (2.9)	2 (4.2)	5 (3.3)
Best overall response to the most recent line of prior cancer therapy (n, %) [2]			
Complete response	4 (3.9)	2 (4.2)	6 (4.0)
Partial response/low-grade regrowth	1 (1.0)	0 (0.0)	1 (0.7)
Progressive disease	18 (17.5)	2 (4.2)	20 (13.2)
Not evaluable	4 (3.9)	2 (4.2)	6 (4.0)
Unknown	4 (3.9)	1 (2.1)	5 (3.3)

[1]Time from diagnosis/resection (months) was calculated as (date of first dose – date of diagnosis/resection + 1)/30.4375.

[2]Prior non-BCG cancer therapy/regimen was summarized. BCG history was summarized in: rAd-IFN-CS-003_CSR_ Post text Tables 14.1.2.4 and 14.1.2.8.

Abbreviations: BCG = Bacillus Calmette-Guérin; CIS = carcinoma *in situ*; n = number; SD = standard deviation; TURBT = transurethral resection of bladder tumor

Note: CIS = CIS only, Ta + CIS, and T1 + CIS; papillary disease = Ta and T1

Percentage was calculated using the number of patients in the column heading as the denominator

Source: Study Report rAd-IFN-CS-003, Post text [Table 14.1.2.6](#)

Table 9: Bacillus Calmette-Guérin History (Efficacy Analysis Set)

BCG History Statistic/category	CIS (n=103) n (%)	Papillary Disease (n=48) n (%)	Total (n=151) n (%)
Number of prior courses of BCG administered (n, %)			
1	0 (0.0)	4 (8.3)	4 (2.6)
2	43 (41.7)	27 (56.3)	70 (46.4)
3	28 (27.2)	12 (25.0)	40 (26.5)

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4	12 (11.7)	2 (4.2)	14 (9.3)
5	6 (5.8)	2 (4.2)	8 (5.3)
6	7 (6.8)	0 (0.0)	7 (4.6)
7	0 (0.0)	0 (0.0)	0 (0.0)
8	2 (2.9)	0 (0.0)	3 (2.0)
≥9	4 (3.9)	1 (2.1)	5 (3.3)
Time from last exposure to BCG (months) [1]			
Mean (SD)	5.70 (2.523)	5.34 (1.913)	5.59 (2.345)

[1] Time from last exposure (months) was calculated as (date of first dose – date of last exposure + 1)/30.4375.

Abbreviations: BCG = Bacillus Calmette-Guerin; CIS = carcinoma *in situ*; N = number; SD = standard deviation

Note: CIS = CIS only, Ta + CIS, and T1 + CIS; papillary disease = Ta and T1

Percentage was calculated using the number of patients in the column heading as the denominator

Source: Study Report rAd-IFN-CS-003, Post text [Table 14.1.2.8](#)

The Applicant's Position:

There were no meaningful differences across the treatment groups (CIS with or without concomitant high-grade Ta/T1 disease, and Ta/T1 disease without concomitant CIS) that could potentially impact on the interpretation of efficacy or safety in the studied (and commercial target) population. The studied population is considered to be the same as the proposed commercial population.

The FDA's Assessment:

The majority of subjects enrolled in the CIS cohort had CIS only disease (79%). Slightly more patients had BCG-refractory disease than BCG-relapsed disease. Patients with refractory disease are considered at higher risk for recurrence and progression compared to those with relapsed disease. There were only five patients (4.9%) with CIS with concomitant T1 disease, a population that may be at particularly high risk of recurrence and progression. The median number of prior BCG doses administered to subjects in this cohort was twelve, ranging from 8-18. FDA reviewed the case report forms of enrolled subjects and verified the diagnosis recorded as well as Bacillus Calmette-Guérin history. FDA review confirmed that enrolled subjects met the entry criteria of "BCG-unresponsive" disease with the exception of those subjects identified by the Applicant as not meeting the protocol definition and who were excluded from the Efficacy Analysis.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Treatment compliance was assessed by the percentage of protocol defined instilled dose and the percentage of protocol defined dwell time; in the CIS cohort and papillary disease cohort, the average percentage of protocol defined instilled dose was 99.7% and 100.0%, respectively, and the average percentage of protocol defined dwell time was 96.1% and 99.3%, respectively. No rescue medication was included. Generally, the proportion of patients receiving concomitant medications was similar in both cohorts (CIS with or without concomitant high-grade Ta/T1 disease, and Ta/T1 disease without concomitant CIS). The most common concomitant medications were lidocaine (90 [57.3%] patients), acetylsalicylic acid (62 [39.5%] patients), paracetamol (50 [31.8%] patients), plain multivitamin (47 [29.9%] patients), oxybutynin (46 [29.3%] patients), propofol (41 [26.1%] patients), colecalciferol (40 [25.5%] patients), ondansetron (39 [24.8%] patients), fentanyl (38 [24.2%] patients), ciprofloxacin (34 [21.7%] patients), and atorvastatin (32 [20.4%] patients).

The FDA's Assessment:

The FDA concurs with the applicant's assessment of treatment compliance, concomitant medications and rescue medication use.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Table 10: Incidence of Complete Response at Any Time in Patients with Carcinoma *in situ* (Efficacy Analysis Set)

Patients Who Have Achieved CR [1]	CIS (n=103) n, %
By Month 3 95% CI (%) [2]	55 (53.4) (43.3, 63.3)
During Months 4 to 6 95% CI (%) [2]	0 (0.0) (0.0, 3.5)
During Months 7 to 9 95% CI (%) [2]	0 (0.0) (0.0, 3.5)
Total 95% CI (%) [2]	55 (53.4) (43.3, 63.3)

[1] Patients who achieved CR included CIS patients (with or without papillary disease) who had CR reported by the Investigator at any time after the administration of ADSTILADRIN, but excluded patients who had CR reported by the Investigator but were judged to have not achieved CR per the definition in the SAP (ie, urine cytology was reported as suspicious, malignant cells or not done, and bladder biopsy were not performed at the CR, and there was a high-grade recurrence, confirmed by bladder biopsy, observed at the next visit for response assessment OR no biopsy was performed at the next response assessment but the urine cytology result at the next response assessment was reported as "suspicious" or "malignant").

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[2] A 95% exact binomial CI for rate of CR was calculated using the Clopper-Pearson method.

Abbreviations: CI = confidence interval; CIS = carcinoma *in situ*; CR = complete response; N = number; SAP = statistical analysis plan

Note: Percentage was calculated using the number of patients in the column heading as the denominator

Source: Study Report rAd-IFN-CS-003, Post text [Table 14.2.1.1](#)

Table 11: Incidence of Complete Response at Any Time in Patients with Carcinoma *in situ* by Subgroup (Efficacy Analysis Set)

Subgroup	CIS (n=103)	
	n/N (%)	95% CI [1]
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)

[1] A 95% exact binomial CI for rate of CR was calculated using the Clopper-Pearson method.

Abbreviations: CI = confidence interval; CIS = carcinoma *in situ*; N = number

Note: CIS = CIS only, Ta + CIS, and T1 + CIS.

Percentage was calculated using the number of patients in the column heading as the denominator.

Patients who achieved CR included CIS patients (with or without papillary disease) who had CR reported by the Investigator at any time after the administration of ADSTILADRIN, but excluded patients who had CR reported by the Investigator but were judged to have not achieved CR per the definition in the SAP (ie, urine cytology was reported as suspicious, malignant cells or not done, and bladder biopsy were not performed at the CR, and there was a high-grade recurrence, confirmed by bladder biopsy, observed at the next visit for response assessment OR no biopsy was performed at the next response assessment but the urine cytology result at the next response assessment was reported as “suspicious” or “malignant”).

Source: Study Report rAd-IFN-CS-003, Post text [Table 14.2.1.3](#)

The Applicant's Position:

A total of 62 patients with CIS were judged by the investigator to have achieved a complete response at 3 months. Of these 62 patients, 7 patients had: urine cytology reported as suspicious, malignant cells or not done; **and** bladder biopsy/ies were not performed; **and** high grade recurrence confirmed by bladder biopsy/ies, was observed at the next scheduled visit. These 7 patients were therefore excluded based on this pre-defined rule in the SAP and thus 55 patients (53.4%) achieved a complete response at 3 months. Therefore, the incidence of complete response in patients with CIS based on analysis of complete datasets at the 3, 6 and 9 month time points is 53.4% (Table 11).

Further analysis of the data through the Month 9 Efficacy Assessment Visit by subgroup (e.g. age [<65 years and ≥65 years], gender, race, time from initial diagnosis of bladder cancer, and tumor type at study entry) did not reveal any clinically meaningful differences (the small difference between white and non-white patients [54.7% vs. 37.5%] is likely due to the very small sample size [n=95 vs. n=8, respectively]) (Table 11).

The FDA's Assessment:

FDA's evaluation of the efficacy endpoint of rAd-IFN-CS-003 is based on the 103 patients in the CIS cohort that met the FDA definition of BCG-unresponsive NMIBC. Four patients (of the 107 enrolled in the study) were excluded from the efficacy analysis set as they did not meet the definition of "BCG-unresponsive" disease. The median duration of follow-up in the 107 patients in the CIS safety analysis set was 23.3 months, ranging from 2.7 to 36.9 months.

Fifty-five (53.4% of 103 patients with CIS, CI: 43,63%) patients experienced a CR at the 3-month evaluation. There were no additional responders on subsequent evaluations. Twenty-four of the 55 patients who achieved a complete response (43.6%) had an ongoing response at the 15-month efficacy follow-up evaluation and were censored at the time of data cut-off (November 15, 2019). This is equivalent to 23.3% (24/103) of all treated patients. While evaluation of complete response across subgroups is considered exploratory, there was no clear indication of any subgroups who had outlying results.

Eleven patients experienced recurrence of high-grade disease at the Month 12 assessment. Of these, eight recurrences were identified via abnormal cytology and/or cystoscopy visualization results that prompted a directed biopsy. The remaining three patients had atypical/normal cytology and normal cystoscopy, however recurrence was identified via mandatory biopsy. In these three patients, two patients had recurrence in 1 out of 5 sites and the other patient had recurrence at 2 out of 5 sites. This highlights the importance of random biopsies at specific time points during a clinical trial as recommended in the 2018 FDA guidance for industry: BCG-unresponsive, non-muscle invasive bladder cancer.

The efficacy reviewer considers the demonstrated CR rate of 53.4% at 3 months with a lower bound of 43% to be clinically meaningful when considered alongside the demonstrated duration of response in this patient population. and durability of response 23.3% HGRF at month 15 follow-up (12 months after a demonstrated CR) to be clinically meaningful in this patient population. The median duration of response (secondary endpoint) by Kaplan-Meier estimate is 9.69 months (95% CI 9.9, 13.9).

Table 13 below indicates the reasons for censoring among the patients with complete response. Twenty-four patients were censored at time of data cut-off on November 15, 2019 due to ongoing response.

Table 12: rAD-IFN-CS-003 Summary of Response Duration Among 103 Patients with BCG-Unresponsive CIS-Containing NMIBC per FDA Guidance: DCO 15-November 2019 (FDA Table)

Endpoint	CIS Cohort
Complete Response, n (%) [95% CI]	55 (53.4%; 95% CI 43, 63%)
Duration of Response	
Median in months (range)	9.69 (3.0+, 31.1+)
Duration ≥ 6 months	38 (36.9%)
Duration ≥ 12 months	24 (23.3%)
Duration ≥ 18 months	13 (12.6%)
Duration ≥ 24 months	4 (3.9%)

Table 13: rAD-IFN-CS-003 Summary of Reasons Patients with Complete Response Among 103 Patients are Censored from the DOR Analysis of High-risk NMIBC per FDA Analysis (FDA Table)

Number of Patients, n (%)	CIS Cohort
Complete Response	55 (53.4%)
Non-complete Response or Died	31
Recurrent Disease	30
Progression to T2	1
Extravesical Disease	1
Died	3
Censored Patients	24
Non-Complete Response or Died Immediately After 2 or More NE	0

Data Quality and Integrity

The Applicant's Position:

Data for the Phase 2 and Phase 3 studies presented here were collected using an electronic case report form (eCRF). All data collected were entered into a validated computerized clinical data management system. The data collected were monitored on a regular basis by the study monitor who reviewed the patient case notes for consistency with the data entered into the eCRF.

Auditing of both investigative sites and the contract research organization (CRO) was conducted by the Sponsor in accordance with the Sponsor's audit plan. Analysis of the data was performed after all queries within the system were resolved and the database considered clean. The activities outlined above were adequate to maintain the data quality and integrity for analysis.

The FDA's Assessment:

The FDA concurs with the applicant's stated procedures which preserved data quality.

Efficacy Results – Secondary and other relevant endpoints

Data:

Table 14: Summary of Incidence of High-Grade-Recurrence-Free Survival in Patients with CIS who Achieved Complete Response (Efficacy Analysis Set)

Patients who achieved HGRF survival at [1]	CIS (n=55) n, %
Month 3 95% CI [%] [2]	55 (100.0) [93.5, 100.0]
Month 6 95% CI [%] [2]	42 (76.4) [63.0, 86.8]
Month 9 95% CI [%] [2]	37 (67.3) [53.3, 79.3]

[1] A patient achieved HGRF survival at a time point if the patient was alive and without documented recurrence of high-grade disease or muscle-invasive disease progression as assessed by the Investigator at that time point. Note: a patient was judged to have not achieved HGRF survival at the initial Month 3 Efficacy Assessment Visit if urine cytology was reported as suspicious, malignant cells, or not done, and no bladder biopsy was performed at the Month 3 Efficacy Assessment Visit, and there was high-grade recurrence, confirmed by bladder biopsy, observed at the next scheduled visit OR biopsy was not performed at the next visit but urine cytology result at the next scheduled visit was reported as "suspicious" or "malignant."

[2] A 95% exact binomial CI for HGRF survival rate was calculated using the Clopper-Pearson method.

Abbreviations: CI = confidence interval; CIS = carcinoma *in situ*; HGRF = high-grade-recurrence-free; N = number
Note: CIS = CIS only, Ta + CIS, and T1 + CIS.

Percentage was calculated using the number of patients in the column heading as the denominator.

Source: Study Report rAd-IFN-CS-003, Post text [Table 14.2.3.1.1](#)

Table 15: Summary of Incidence of High-Grade-Recurrence-Free Survival (Efficacy Analysis Set)

Patients Achieving HGRF Survival at [1]	CIS (n=103) n, %	Papillary Disease (n=48) n, %	Total (n=151) n, %
Month 3 95% CI (%) [2]	55 (53.4) (43.3, 63.3)	35 (72.9) (58.2, 84.7)	90 (59.6) (51.3, 67.5)
Month 6 95% CI (%) [2]	42 (40.8) (31.2, 50.9)	30 (62.5) (47.4, 76.0)	72 (47.7) (39.5, 56.0)
Month 9 95% CI (%) [2]	37 (35.9) (26.7, 46.0)	28 (58.3) (43.2, 72.4)	65 (43.0) (35.0, 51.3)

[1] A patient achieved HGRF survival at a time point if the patient was alive and without documented recurrence of high-grade disease or muscle-invasive disease progression as assessed by the Investigator at that time point. Note: a patient was judged to have not achieved HGRF survival at the initial Month 3 Efficacy Assessment Visit if urine cytology was reported as suspicious, malignant cells or not done, and no bladder biopsy was performed at the Month 3 Efficacy Assessment Visit, and there was high-grade recurrence, confirmed by bladder biopsy, observed at the next scheduled visit OR biopsy was not performed at the next visit but urine cytology result at the next scheduled visit was reported as “suspicious” or “malignant.”

[2] A 95% binomial CI for HGRF survival rate was calculated using the Clopper Pearson method.

Abbreviations: CI = confidence interval; CIS = carcinoma *in situ*; HGRF = high-grade-recurrence-free; N = number

Note: CIS = CIS only, Ta + CIS, and T1 + CIS; papillary disease = Ta and T1

Percentage was calculated using the number of patients in the column heading as the denominator.

Source: Study Report rAd-IFN-CS-003, Post text [Table 14.2.3.1](#).

The Applicant’s Position:

Table 14 presents HGRF survival in the patients with CIS who achieved a CR. Of the 55 patients with CIS who achieved CR by the Month 3 Efficacy Assessment Visit, 42 (76.4%) patients remained HGRF at the Month 6 Efficacy Assessment Visit and 37 (67.3%) patients remained HGRF at the Month 9 Efficacy Assessment Visit.

Over 50% of CIS patients who achieved CR remained HGRF at the Month 9 Efficacy Assessment Visit, and consequently, the median durability of complete response could not be estimated.

It is recognized that FDA has previously noted (at the End of Phase 1 meeting; Meeting ID#: [8327](#)) that patients with papillary disease essentially achieve complete response by TURBT at initiation of therapy, and thus a recurrence-free endpoint such as time to recurrence or disease-free survival would be appropriate.

The incidence of high-grade recurrence-free survival in patients with papillary disease was 72.9% at 3 months, 62.5% at 6 months, and 58.3% at 9 months. The median durability of high-grade

recurrence-free survival could not be accurately estimated based on an analysis of data up to and including the Month 9 Efficacy Assessment Visit, since >50% of patients remained HGRF at the Month 9 Efficacy Assessment Visit.

The FDA's Assessment:

The FDA considers CR rate and duration of CR in the CIS population to be endpoints evaluable for clinical meaningfulness in a single-arm trial. High-grade recurrence free survival is difficult to interpret in this setting.

Dose/Dose Response

Data:

No data are available.

The Applicant's Position:

A single dose level was included in the Phase 3 study. Therefore, no dose-response analyses were performed.

The FDA's Assessment:

The FDA concurs with the applicant's assessment.

Durability of Response

Data:

Of the 55 patients with CIS who achieved a complete response at Month 3, 42 (76.4%) and 37 (67.3%) remained high-grade recurrence free at 3 months and 6 months after the complete response was achieved (Table 14). Median durability cannot be calculated since >50% of patients with CIS remained high-grade recurrence free at the 9 month efficacy assessment..

The Applicant's Position:

Results for durability are not presented for either cohort of patients. In patients with CIS, the median durability of complete response could not be accurately estimated based on an analysis of data up to and including the Month 9 Efficacy Assessment Visit since >50% of patients who achieved complete response remained HGRF at the Month 9 Efficacy Assessment Visit. Similarly, in patients with papillary disease, the median durability of high-grade recurrence-free survival could not be accurately estimated based on an analysis of data up to and including the Month 9 Efficacy Assessment Visit since >50% of patients remained HGRF at the Month 9 Efficacy Assessment Visit. Data continue to be collected in the study, and median durability will be calculated (if possible) once all patients have completed the 12 month efficacy assessment, alongside the remaining secondary efficacy endpoints. However, of the 55 patients with CIS who

achieved a complete response at Month 3, 42 (76.4%) and 37 (67.3%) remained high-grade recurrence free at 3 months and 6 months after the complete response was achieved, indicating that the median durability of complete response in these patients is >6 months.

The FDA's Assessment:

The estimate of median duration of CR in patients with CIS, using the Kaplan-Meier method was provided by the applicant in the Month 15 efficacy analysis and found to be 9.72 months (95% CI: [9.17, not estimable (NE)]). The probability of durability of CR for at least 12 months in patients with CIS was 46.5%. FDA analysis showed the median duration of response (secondary endpoint) by Kaplan-Meier estimate is 9.69 months (95% CI 9.9, 13.9).

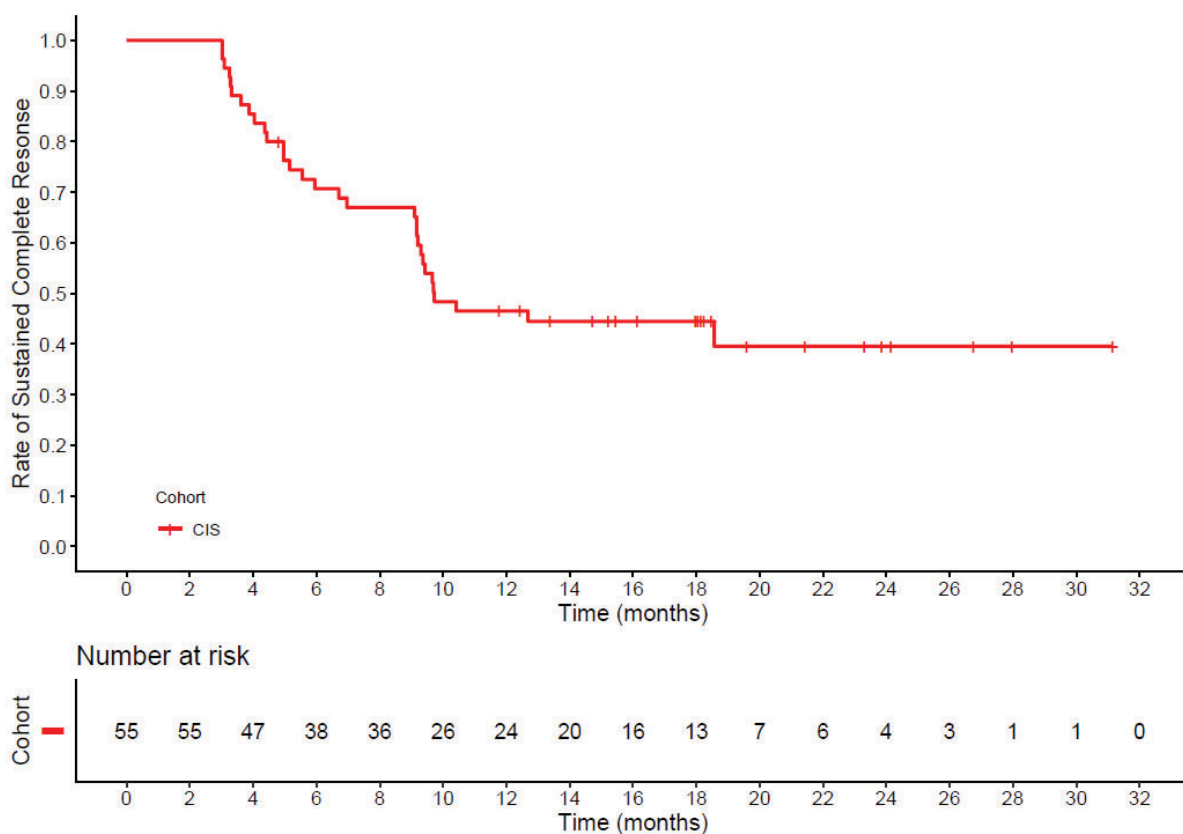


Figure 3: FDA Kaplan-Meier Plot-CIS patients who achieved CR, N =55

The durability of response supports the clinical meaningfulness of the complete response rate of the CIS cohort.

Persistence of Effect

Data:

No data are available.

The Applicant's Position:

As the Phase 3 study remains ongoing, no data are available on persistence of effect after treatment is stopped or withheld.

The FDA's Assessment:

The FDA concurs with this assessment.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

Not applicable.

The Applicant's Position:

Patient-reported outcomes were not included in the Phase 3 study.

The FDA's Assessment:

The FDA concurs with this assessment.

Additional Analyses Conducted on the Individual Trial

Data:

Not applicable.

The Applicant's Position:

No additional analyses were conducted for the Phase 3 study.

The FDA's Assessment:

The FDA concurs with this assessment.

5.1.3. rAd-IFN-CS-002

Trial Design

The Applicant's Description:

The Phase 2 multicenter, randomized, parallel arm, open label study was conducted to investigate the safety and efficacy of ADSTILADRIN administered intravesically in 40 patients with high-grade BCG refractory or relapsed NMIBC (definition in Table 16)(rAd-IFN-CS-002; Figure 4). The purpose of the study was to evaluate the incidence of high-grade recurrence-free survival at 12 months. Patients were randomized to receive ADSTILADRIN by intravesical administration at a dose of either 7.5×10^{12} vp or 2.25×10^{13} vp on Day 1 of the study. Treatment was repeated at 3 monthly intervals, for a maximum of 4 doses, provided there was no high-grade recurrence in the interim. Patients that completed the study entered the long term follow up period for 3 years per protocol.

Following the initial treatment on Day 1 of the study, patients were re-treated with the same dose at the Month 4, 7, and 10 time points. The decision to repeat treatment administration after each 3-month interval was determined by the clinical response observed following the previous treatment(s). Therefore, patients could receive up to four intravesical administrations of ADSTILADRIN over the 12-month treatment phase of the study. Patients who had recurrence of high-grade disease were withdrawn from treatment but were followed for survival and time to cystectomy.

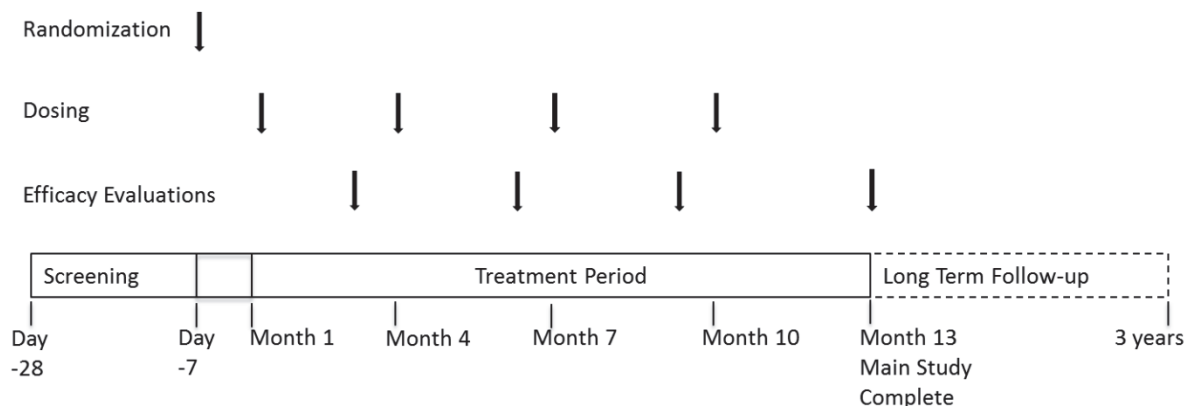
The final efficacy evaluation was performed at 12 months (Month 13 assessment). This included cystoscopy, cytology, and protocol-mandated biopsies. Follow-up long term survival data and information regarding invasive disease and cystectomy were collected from all patients for three years after completion of the study.

This study was conducted at 14 centers in the US.

The design of the Phase 2 study was similar to that of the Phase 3 study, albeit with the following exceptions:

- Terminology used to describe response to prior BCG treatment (see Table 16);
- Randomization of patients to one of two dose levels (rather than single dose level);
- Administration of a total of four doses (rather than continued dosing from Months 12 to 24, and then beyond Month 24 for patients who achieve and maintain a complete response).

Figure 4: rAd-IFN-CS-002 Flow Chart



Source: Study Report rAd-IFN-CS-002, [Figure 9.5.1](#)

Diagnostic criteria

In the studies included in this BLA, there were no major differences in the populations enrolled with respect to definition of BCG failure, although there has been an evolution in terminology during the development program (Table 16, where differences in definitions in this regard are noted in bold underline). Specifically, there has been a transition from the use of terms “BCG relapsed” and “BCG refractory” (used in Phase 1 and Phase 2) to “BCG unresponsive” (used in Phase 3). This definition of “BCG unresponsive” employed in the Phase 3 study is based on the proposal of Lerner et al (2013) and also reflects the FDA’s February 2018 guidance. Variations in clinical practice regarding administration of BCG therapy and, particularly, the number of courses and timing of administration are also reflected in the definition and in other related entry requirements.

Table 16 NMIBC Patient Populations in ADSTILADRIN Studies

Study	Disease	Prior BCG Treatment
P03816 Phase 1	<ul style="list-style-type: none"> Transitional cell carcinoma of the bladder, Stage Tis, Ta Transitional cell carcinoma of the bladder Stage T1 in subjects who did not wish to have a cystectomy 	<ul style="list-style-type: none"> Failed at least two prior courses of BCG with or without recombinant interferon α administration
2009-0938 Phase 1b	<ul style="list-style-type: none"> NMIBC who refused radical cystectomy 	<ul style="list-style-type: none"> Refractory to BCG therapy <ul style="list-style-type: none"> BCG-refractory NMIBC was defined as recurrence or persistence of \leqT1 bladder cancer after treatment with a 6 week induction course and at least one additional course of BCG (either a 3 week maintenance course or a repeat 6 week induction course).

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Study	Disease	Prior BCG Treatment
rAd-IFN-CS-002 Phase 2	<ul style="list-style-type: none"> 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. 	<ul style="list-style-type: none"> BCG-refractory or relapsed <ul style="list-style-type: none"> Refractory was defined as failure to achieve a disease-free state at 6 months after adequate induction of BCG therapy with either maintenance or re-induction at 3 months. Adequate induction was defined as a minimum of 5 out of 6 induction doses and adequate maintenance is defined as a minimum of 2 out of 3 doses of treatment. Relapse was defined as recurrence within 1 year after CR to BCG treatment.
rAd-IFN-CS-003 Phase 3	<ul style="list-style-type: none"> CIS only Ta/T1 high-grade disease with concomitant CIS or without concomitant CIS 	<ul style="list-style-type: none"> “BCG Unresponsive” - includes patients <ul style="list-style-type: none"> unlikely to benefit from and who will not be receiving further intravesical BCG did not respond to BCG treatment and have a persistent high-grade recurrence within 12 months after BCG was initiated who despite an initial CR to BCG, relapse with CIS within 12 months of their last intravesical treatment with BCG or relapse with high-grade Ta/T1 within 6 months of their last intravesical treatment with BCG. Prior BCG treatment requirements: <ul style="list-style-type: none"> Receipt of at least 2 previous courses of BCG within a 12 month period – defined as at least 5 of 6 induction BCG instillations and at least 2 out of 3 instillations of maintenance BCG, or at least 2 of 6 instillations of a second induction course, where maintenance BCG is not given <ul style="list-style-type: none"> ❖ <u>Exception</u>: those who have T1 high-grade disease at 1st evaluation after induction BCG alone (at least 5 of 6 doses) may qualify in the absence of disease progression At the time of tumor recurrence, patients with CIS alone or high-grade Ta/T1 with CIS should be within 12 months of last exposure to BCG and patients with high-grade Ta/T1 without CIS should be within 6 months of last exposure to BCG No maximum limit to the amount of BCG administered

Abbreviations: BCG = Bacillus Calmette-Guerin; CIS = carcinoma in situ; CR = complete response; NMIBC = non muscle invasive bladder cancer; Tis = TURBT = transurethral resection of bladder tumor

Source: [Study Report P03816](#); [Navai et al, 2016](#); [Study Report rAd-IFN-CS-002](#); [Study Report rAd-IFN-CS-003](#)

Key inclusion/exclusion criteria

The inclusion and exclusion criteria were similar to those for the Phase 3 study (see Table 16).

Dose selection and study treatments

The 2 doses of ADSTILADRIN selected for this study were the two highest doses administered in the single-dose escalation Phase 1 study, P03816. The safety profile in the Phase 1 study was acceptable for both doses selected.

Assignment of patients to treatment

Patients were assigned a screening number by the site. The Investigator or designated staff was responsible for allocating and recording patient numbers at the time of screening. Treatment allocation was performed centrally for all patients who had successfully completed screening. Patients were randomized and assigned a unique randomization/patient number. No stratification was employed.

Blinding

As with the Phase 3 study, blinding was not employed in this study. Again, this does not impact on the robustness of the analysis owing to the nature of the assessments and subsequent determination of Phase 3 dose and efficacy.

Dose modifications and discontinuations

Delays between treatments and allowed adjustments to the dwell time or splitting of the dose were as previously described for the Phase 3 study. Again, no dose reductions were permitted.

Administrative structure

The Safety Review Committee for the study comprised the Co-ordinating Study Investigator and the Sponsor's Medical Monitor or representative and independent clinical professionals. The committee met at regular intervals, and as events dictated, to review emerging safety data. The Committee reviewed safety data from the first 10, 20 and 30 subjects treated in the study at a minimum.

Procedures and schedule

The trial schedule of events is shown in Table 17.

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Table 17: Schedule of Study Assessments

Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Month (4 weeks) and Day of Month	Screenin g	M1 D1	M1 D2	M1 D4	M1 D12	M4 D1	M4 D2	M4 D4	M4 D12	M7 D1	M7 D2	M10 D1	M10 D2	M13	Withdrawal from treatment safety assessment	Long-term follow-up ^b
Day relative to initial dosing (days)	D-28 to D-7	0	+1	+3	+11	+90	+91	+93	+101	+180	+181	+270	+271	+360	NA	NA
Allowable window (days) -not applicable to efficacy assessment – see 'g'	0	0	0	0	± 1	± 5	0	0	0	±5	0 relati ve to M7D1	±5	0 relativ e to M10D 1	±5	NA	NA
							Relative to M4D1									
Informed consent	X															
Medical history (incl. demographics)	X															
Inclusion/exclusion	X															
Pregnancy test ^c	X	X				X				X		X		X	X	
Physical examination ^d	X	X				X				X		X		X	X	
Vital signs	X	X ^e				X ^e				X ^e		X ^e		X	X	
ECOG performance status ^q	X	X				X				X		X		X	X	
Urinary Symptoms	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
TURBT and endoscopic resection	X															
ECG ^f	X	X				X				X		X		X	X	
Urine Cytology ^g	X					X				X		X		X	X	
Cystoscopy ^g	X					X				X		X		X	X	
Biopsy ^h	X													X	X	
Blood sample for rAd-IFN DNA ⁱ measurements		X	X	X	X	X	X	X	X							
Blood sample for IFNalpha2b measurements		j	X	X	X	X ^j	X	X	X							
Blood sample for antibody levels ^k assessments	X	X			X										X	

Disclaimer: In this document, the sections labeled as “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Urine sample for rAd-IFN DNA ^l measurements		X	X	X	X	X	X	X	X							
Urine sample for IFNalpha2b measurements ^l		X	X	X	X	X	X	X	X							
Urine sample for exploratory assays		X ^q	X	X												
Clinical chemistry ^m	X	X	X	X		X	X	X		X	X	X	X	X	X	
Hematology ^m	X	X	X	X		X	X	X		X	X	X	X	X	X	
Urinalysis ^o	X	X	X	X		X	X	X		X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events ⁿ		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Randomization	X															
Study Drug administration		X				X				X		X				
Annual updates on patient response and survival																X

a. The assessments at visit 15 was only performed for patients who are withdrawn from treatment before the Month 13 visit.

b. After completion of the study, patients were followed as per clinical practice to determine duration of response, date of cystectomy and survival for up to 3 years. These data were to be transmitted by separate communication with the sponsor on a yearly basis

c. Pregnancy test to be performed in fertile women during screening, prior to commencing treatment and prior to repeat administration of ADSTILADRIN .

d. Physical examination to be performed prior to treatment and should include neurological examination and body weight.

e. Vital signs were to be assessed pre- and post-dose.

f. All ECGs had to be performed pre-and post-dose in triplicate with a mean of the 3 values used for decision making purposes. Patients should not have been discharged with a QTcF >460 msec or an increase from baseline >60 msec. Assessment were done against baseline electrocardiogram (ECG) performed up to 1 hour prior to treatment.

g. Efficacy assessments (urine cytology and cystoscopy only) were performed up to 2 weeks before re-treatment. Only patients who did not have recurrence of high-grade disease received re-treatment. Bladder capacity was also determined.

h. Biopsies on months 4,7 and 10 were only performed if evident or suspicious lesions had been seen during cystoscopy

i. Blood samples for rAd-IFN DNA were collected prior to dosing, end of instillation (1 h), 2 h, 24 h (Day 2), , and 72 h post-dose (Day 4) and Day 12 during Month 1 from patients who received ADSTILADRIN. During Month 4, samples were collected prior to dosing, end of instillation (1 hour), 2 h, 24 h (Day 2), and 72 h post-dose (Day 4) and Day 12.

j. Blood samples for IFNalpha2b were collected pre-dose on Day1 of Months 1 and 4 from patients who had received ADSTILADRIN.

k. Antibody levels (anti-adenoviral and anti-IFNalpha2b) were determined. Assessments on Day 1 at Month 1, 7 and 10 were conducted pre-dose for patients who received ADSTILADRIN.

l. Urine samples for rAd-IFN DNA and IFNalpha2b were collected pre-dose Months 1 and 4.

m. Hematology and clinical chemistry samples were to be taken the previous working day to ensure results were available before dosing (samples may be taken on the Friday before a Monday/Tuesday scheduled dosing). Samples had also to be collected 2 h after dosing.

n. Patients were contacted weekly by phone for the first month after each treatment and then monthly to provide information regarding AEs and concomitant medications up to Month 13 or the safety visit assessment

o. Urinalysis on dosing days to be taken pre-dose.

p. ECOG assessments to be performed pre-dose.

q. Urine samples for exploratory RNA and other immunological assays were taken at pre-dose on Day 1.

Concurrent medications

Permitted and non-permitted concomitant medications were the same as in the Phase 3 study (rAd-IFN-CS-003), with the exception of prior intravesical BCG. In this study, intravesical BCG was not permitted for 3 months prior to beginning study treatment, whereas in the Phase 3 study, intravesical BCG could be given no less than 5 weeks before the diagnostic biopsy required for entry into the study. However, this minor change to the intravesical BCG requirements does not result in critical differences between the patient populations across the studies.

Dietary restrictions/instructions, treatment compliance and rescue medication

Please refer to Section 5.1.1.

Subject completion, discontinuation, or withdrawal

In accordance with the final SAP, the study was considered complete when all subjects had either completed the Month 13 assessment or had been withdrawn from treatment and had undergone a safety assessment.

Subjects who had recurrence of high grade disease were withdrawn from treatment but were followed for survival and time to cystectomy. Following withdrawal from treatment, all patients underwent a safety assessment a minimum of 30 days after the last treatment. Follow-up long term survival data and information regarding invasive disease and cystectomy were collected from all subjects for three years after completion of the study.

Patients withdrawn from the study underwent the same assessments as in the Phase 3 protocol.

The FDA's Assessment:

The FDA concurs with applicant's description of the Phase 2 randomized parallel arm study. In this study 19 subjects received ADSTILADRIN at the same dose as was used in the Phase 3 trial. The rate of high-grade recurrence free survival rate in these subjects was considered supportive of the efficacy results reported in rAd-IFN-CS-003.

Study Endpoints

The Applicant's Description:

The study endpoints were as follows:

Primary endpoint

1. Whether or not a subject responds to treatment; defined as no evidence of recurrence of high grade disease at 12 months.

Secondary endpoints

1. Whether or not a subject responds to treatment; defined as no evidence of recurrence of high grade disease at 3, 6 and 9 months.
2. Time to progression to muscle-invasive disease assessed by cystoscopy
3. Incidence of and time to cystectomy
4. Overall survival
5. Number of copies of the viral genome in the urine and plasma
6. Quantification of the levels of anti-IFNalpha2b
7. Measurement of anti-adenoviral antibodies and anti-IFNalpha2b antibodies
8. Concentration of IFNalpha2b in the urine
9. Type, incidence, relatedness and severity of treatment emergent adverse events as assessed by NCI-CTCAE V4.03.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The SAP was finalised prior to database lock for the study.

The Efficacy Analysis Set included all randomized patients who received study drug, and was used in the analysis of primary and secondary efficacy endpoints. All patients in the analysis set were analyzed according to the dose they received.

A patient was deemed not to have achieved high-grade recurrence-free survival if there were insufficient data to determine whether or not high-grade recurrence-free survival had occurred. It was considered sufficient evidence for high-grade recurrence-free survival if a subsequent assessment showed high-grade recurrence-free survival and there had been no intermediate treatment for bladder cancer other than ADSTILADRIN.

A conservative approach was taken to the handling of missing or partial dates for classification of prior and concomitant medications and for calculation of time from initial diagnosis. No imputations were made for any other endpoints; the data were treated as missing.

The FDA's Assessment:

The FDA concurs with the applicant's description of study endpoints and statistical analysis plan in the Phase 2 study.

Protocol Amendments

The Applicant's Description:

The protocol was amended three times during the conduct of the study, largely to ensure consistency within the document, to add additional information to assist in the conduct of the study, and to remove research-related assessments that were considered unnecessary. Protocol amendment 3 permitted the use of intravesical cytotoxic agents when administered as a single instillation immediately following a TURBT procedure (permitted up to 14-60 days prior to beginning study treatment; the protocol previously excluded all intravesical therapies within 3 months of the beginning of study treatment). This change is not considered to have adversely affected the conduct of the study or the robustness of the data.

The FDA's Assessment:

The FDA concurs with the applicant's description of protocol amendments in the Phase 2 study.

5.1.4. Study Results

Compliance with Good Clinical Practices

The Applicant's Position:

This study was performed following GCP as per Phase 3 study rAd-IFN-CS-003. Please see Section 5.1.2.

The FDA's Assessment:

The FDA concurs with the applicant's assessment that the Phase 2 study was performed following GCP.

Financial Disclosure

The Applicant's Position:

Financial disclosures for all investigators participating in the Phase 2 study are available (and were provided in Module 1). None of the investigators are full- or part-time employees of the Sponsor, and none have disclosable financial interests in, or arrangements with, the Sponsor.

The FDA's Assessment:

The FDA concurs with the applicant's assessment.

Patient Disposition

The Applicant's Position:

Table 18 displays the disposition of patients during this study.

Overall, 43 patients were randomized into the study; 22 patients in the 1×10^{11} vp/mL dose group and 21 patients in the 3×10^{11} vp/mL dose group. Three patients (7.0%) were not dosed:

- One patient was withdrawn prior to dosing due to events of pulmonary edema.
- One patient 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.
- One patient did not meet the inclusion criterion regarding the definition of high grade BCG refractory or relapsed NMIBC; the patient did not have high grade bladder cancer.

Forty (40) patients (93.0%) received the study drug. A total of 17 patients (42.5%) completed the primary endpoint assessment at 12 months.

Overall 23 patients (57.5%) did not complete the primary endpoint assessment at 12 months. 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, non-compliance, protocol violations, or losses to follow-up.

Table 18: Patient disposition (All Enrolled)

	1x10¹¹ vp/mL N=22 (n [%])	3x10¹¹ vp/mL N=21 (n [%])	Overall N=43 (n [%])
Randomized patients	22	21	43
Dosed [1]	21 (95.5)	19 (90.5)	40 (93.0)
Not dosed [1]	1 (4.5)	2 (9.5)	3 (7.0)
Dosed patients	21	19	40
Completed study [2]	8 (38.1)	9 (47.4)	17 (42.5)
Patients ongoing [2]	0	0	0
Did not complete study [2]	13 (61.9)	10 (52.6)	23 (57.5)
Disease recurrence	13 (61.9)	8 (42.1)	21 (52.5)
Patient request	0	1 (5.3)	1 (2.5)
Safety reasons	0	1 (5.3)	1 (2.5)
Other	0	0	0

Source: Table 14.1.1, [Section 14.1](#)

[1] Percentages based on the number of randomized patients within each dose group.

[2] Percentages based on the number of patients dosed.

The FDA's Assessment:

The FDA concurs with the applicant's assessment of patient disposition in the Phase 2 trial.

Protocol Violations/Deviations

The Applicant's Position:

There were 7 patients with protocol violations. However, no patient discontinued the study due to a protocol violation. Further, there were 14 patients who entered the Phase 2 study even though they had deviations from the entry criteria. The deviations were discussed by the responsible study team members and a documented decision was made to include these patients into the study. Details on the protocol violations and deviations are provided in [Appendix 16.2.2](#) of the Phase 2 study CSR.

The FDA's Assessment:

The FDA concurs with the applicant's assessment of protocol deviations in the Phase 2 study.

Table of Demographic Characteristics

Data:

Table 19 Patient demographics and baseline characteristics (Safety Analysis Set)

	1x10 ¹¹ vp/mL N=21	3x10 ¹¹ vp/mL N=19	Overall N=40
Age (years) [1]			
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
Race (n [%])			
American Indian/Alaska Native	0	0	0
Asian	0	1 (5.3)	1 (2.5)
Black or African American	1 (4.8)	0	1 (2.5)
Native Hawaiian or Pacific Islander	0	0	0
White	20 (95.2)	18 (94.7)	38 (95.0)
Other	0	0	0
Ethnicity (n [%])			
Hispanic/Latino	0	1 (5.3)	1 (2.5)
Not Hispanic/Latino	17 (81.0)	15 (78.9)	32 (80.0)

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	1x10¹¹ vp/mL N=21	3x10¹¹ vp/mL N=19	Overall N=40
Not reported	0	2 (10.5)	2 (5.0)
Unknown	4 (19.0)	1 (5.3)	5 (12.5)
Gender (n [%])			
Male	19 (90.5)	14 (73.7)	33 (82.5)
Female	2 (9.5)	5 (26.3)	7 (17.5)
ECOG PS (n [%])			
0	16 (76.2)	18 (94.7)	34 (85.0)
1	5 (23.8)	1 (5.3)	6 (15.0)
Urinary symptoms			
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: Table 14.1.2, [Section 14.1](#)

Min=minimum, Max=maximum, n=number of observations, SD=standard deviation

[1] Age=(informed consent date - birthdate)/365.25

The Applicant's Position:

Demographics and baseline characteristics of the Safety Analysis Set (the same as the EAS) are shown in Table 19.

The overall 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%]). 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 overall 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).

Dose groups were comparable regarding their baseline characteristics.

The FDA's Assessment:

The FDA concurs with the applicant's assessment of patient demographics in the Phase 2 study.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The Applicant's Position:

Overall, the mean total duration of disease was 3.57 years (SD: 4.696). The current status was 'relapsed' for 19 patients (47.5%) and 'refractory' for 21 patients (52.5%).

At screening, most patients had either Stage 0is (N=21 [52.5%]) or Stage I (N=14 [35.0%]), while the Grade was 3 for all patients (N=40 [100%]).

The majority of patients had CIS as primary tumor classification (N=21 [52.5%]). Overall 5 patients (12.5%) had a combined classification of T1 and CIS and 4 patients (10.0%) had a combination of Ta and CIS. All patients had a metastasis category of either M0 or MX at screening, in line with the inclusion criterion.

All patients had prior cancer therapies while 34 patients (85.0%) had prior cancer-related surgeries. Only 3 patients (7.5%) underwent previous radiotherapy:

- One patient had a prior pelvic external beam radiotherapy; however, the medical monitor reviewed this case and approved the enrollment of the patient.
- One patient had an external beam radiation therapy 14 years ago (1999), so the medical monitor approved the enrollment of the patient.

- One patient had prior pelvic external beam radiotherapy in 2003; the medical monitor reviewed this case and approved the enrollment of the patient.

Dose groups were comparable regarding their disease history.

The FDA's Assessment:

The FDA concurs with the applicant's assessment of baseline characteristics of subjects enrolled in the Phase 2 study.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

As noted in Section 5.1.3, no measures of treatment compliance were included in the Phase 2 study. Similarly, no rescue medication was included.

The most frequently taken concomitant medications by Anatomical, Therapeutic, Chemical (ATC) classification were for alimentary tract and metabolism, used by 38 patients (95.0%), and for the cardiovascular system, used by 37 patients (92.5%).

On PT level, the most frequent concomitant medications overall were acetylsalicylic acid (N=20 [50.0%]), simvastatin (N=15 [37.5%]) and paracetamol (N=10 [25.0%]).

The FDA's Assessment:

The FDA concurs with the applicant's assessment.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Table 20: Incidence of High-Grade Recurrence-Free Survival at 12 Months (Efficacy Analysis Set)

High-grade recurrence-free at	7.5 x 10 ¹² vp (n=21) n (%)	2.25 x 10 ¹³ vp (n=19) n (%)	Overall (n=40) n (%)
12 months 90% CI [1]	7 (33.3%) (16.8%, 53.6%)	7 (36.8%) (18.8%, 58.2%)	14 (35.0%) (22.6%, 49.2%)

[1] 90% CIs are based on the exact binomial method.

Abbreviations: CI = confidence interval; N = number

Source: Study Report rAd-IFN-CS-002, Table 14.2.1, [Section 14.2](#)

The Applicant's Position:

14/40 patients (35.0%) were high-grade recurrence-free at 12 months (Table 20). The incidence was comparable between dose groups with 7/21 patients (33.3%) in the 7.5×10^{12} vp dose group and 7/19 patients (36.8%) in the 2.25×10^{13} vp dose group. The confidence intervals indicate that both the hypothesis that the high-grade recurrence-free incidence rate in the 7.5×10^{12} vp dose group is as low as 16% and the hypothesis that the high-grade recurrence-free incidence rate in the 2.25×10^{13} vp dose group is as low as 18% can be rejected at a one-sided significance level of less than 5%.

Data Quality and Integrity

The Applicant's Position:

Data for the Phase 2 and Phase 3 studies presented here were collected using an electronic case report form (eCRF). All data collected were entered into a validated computerized clinical data management system. The data collected were monitored on a regular basis by the study monitor who reviewed the the patient case notes for consistency with the data entered into the eCRF.

Auditing of both investigative sites and the contract research organization (CRO) was conducted by the Sponsor in accordance with the Sponsor's audit plan. Analysis of the data was performed after all queries within the system were resolved and the database considered clean. Overall, the activities outlined above were adequate to maintain the data quality and integrity for analysis.

The FDA's Assessment:

The FDA concurs that the data obtained from the Phase 2 and Phase 3 studies was of adequate quality and integrity to facilitate sufficient review of the application.

Efficacy Results – Secondary and other relevant endpoints

Data:

Table 21: Incidence of High-Grade Recurrence-Free Survival at 3, 6 and 9 Months (Efficacy Analysis Set)

High-grade recurrence-free at	7.5 x 10 ¹² vp (n=21) n (%)	2.25 x 10 ¹³ vp (n=19) n (%)	Overall (n=40) n (%)
3 months 90% CI [1]	10 (47.6%) (28.6%, 67.2%)	13 (68.4%) (47.0%, 85.3%)	23 (57.5%) (43.3%, 70.8%)
6 months 90% CI [1]	8 (38.1%) (20.6%, 58.3%)	9 (47.4%) (27.4%, 68.0%)	17 (42.5%) (29.2%, 56.7%)
9 months 90% CI [1]	8 (38.1%) (20.6%, 58.3%)	9 (47.4%) (27.4%, 68.0%)	17 (42.5%) (29.2%, 56.7%)
Incidence of cystectomy 90% CI [1]	0 (0.0%, 13.3%)	0 (0.0%, 14.6%)	0 (0.0%, 7.2%)

[1] 90% CIs are based on the exact binomial method.

Abbreviations: CI = confidence interval; N = number

Source: Study Report rAd-IFN-CS-002, Table 14.2.2, [Section 14.2](#)

Table 22: Kaplan Meier Estimates and Analysis of Duration of High-Grade Recurrence-Free Survival (Efficacy Analysis Set)

Parameter	7.5 x 10 ¹² vp (n=21)	2.25 x 10 ¹³ vp (n=19)	Overall (n=40)
Number of patients with high-grade recurrence	14	11	25
Number of patients censored [n (%)]	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

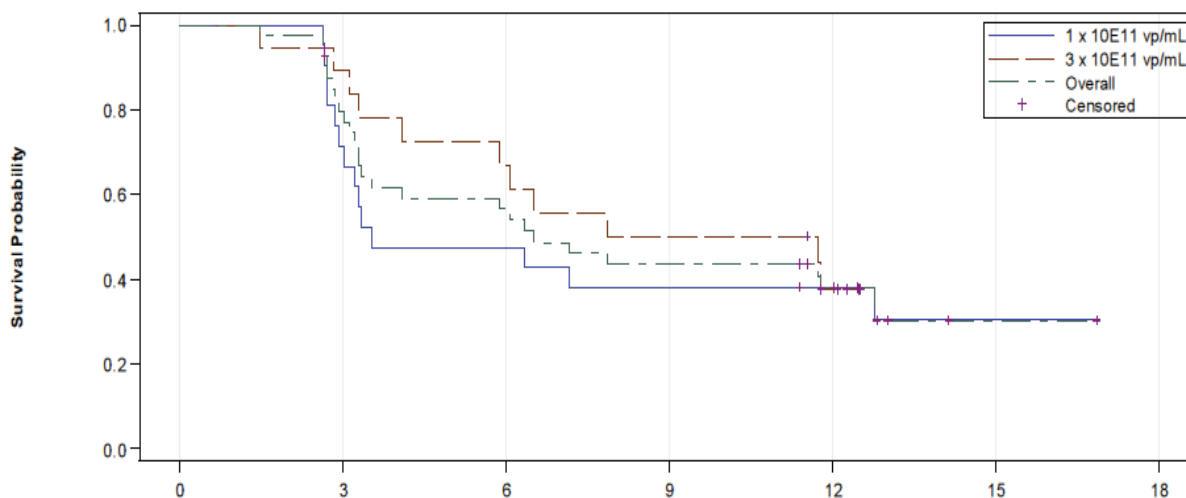
Abbreviations: CI = confidence interval; Max = maximum; Min = minimum; N = number; NE = not evaluable; Q1 = lower quartile; Q3 = upper quartile

Note: High-grade recurrence-free survival (months)=(event date (date of first drug administration))/30.4375

Patients were censored at the last time known to be free of high-grade lesions before the end of follow-up if high-grade recurrence-free survival event did not occur.

Source: Study Report rAd-IFN-CS-002, Table 14.2.3, [Section 14.2](#)

Figure 5: Kaplan-Meier Curves for Duration of High-Grade Recurrence-Free Survival (Efficacy Analysis Set)



Source: Study Report rAd-IFN-CS-002, Figure 14.2.3, [Section 14.2](#)

The Applicant's Position:

Twenty-five patients had high-grade recurrence of disease during the study, with 15 patients (37.5%) censored (Table 22 and Figure 5). Fifteen patients received 4 doses of drug and were assessed for disease recurrence at Month 13, of which 14 patients were free of disease and 1 patient had high-grade disease recurrence. The overall median time to high-grade recurrence was 6.51 months. The individual maximum time to high-grade recurrence was 12.78 months. The median time to recurrence was longer in the 2.25×10^{13} vp dose group with a median of 11.73 months compared to the 7.5×10^{12} vp dose group with a median of 3.52 months.

In this study, the majority of patients had CIS as the primary tumor classification (N=21 [52.5%]). Overall 5 patients (12.5%) had a combined classification of T1 and CIS and 4 patients (10.0%) had a combination of Ta and CIS. Long-term follow-up of patients in this study indicated that, of the 30 CIS patients who were treated with at least 1 dose of ADSTILADRIN, 9 had a complete response at 12 months and 6 were recurrence free at 3 years ([rAd-IFN-CS-002 \[long-term follow-up\]](#)).

Time to muscle-invasive progression was not analyzed as no biopsies were performed for this specific purpose.

No cystectomies were performed on-study on patients up to the 12-month time point, thus time to cystectomy was not evaluated.

No deaths occurred before end of follow up for any patient, therefore overall survival was censored for all patients.

The FDA's Assessment:

As the applicant has stated, 19 subjects in the Phase 2 trial received ADSTILADRIN at the dose administered in the Phase 3 trial and the planned marketing dose. These subjects demonstrated high-grade recurrence free survival at 3 months of 68.4%. The enrollment criteria for the Phase 2 differed from the enrollment criteria of the Phase 3 trial which was based on the 2018 FDA Guidance on BCG-Unresponsive Nonmuscle Invasive Bladder Cancer. Therefore, the results of the Phase 2 trial are considered supportive of the data submitted from the Phase 3 trial, however may not be fully applicable to the population of patients with BCG-unresponsive NMIBC.

Dose/Dose Response

The Applicant's Position:

At all time points, the incidence of high-grade recurrence-free survival was numerically higher in the 2.25×10^{13} vp dose group compared to the 7.5×10^{12} vp dose group. As no difference in the effects at 12 months in terms of complete response was seen between the 2.25×10^{13} vp dose group and the 7.5×10^{12} vp dose group, but a difference was observed in the time to disease progression in the 2.25×10^{13} vp dose group (11.7 months) compared to the 7.5×10^{12} vp dose group (3.5 months), and no safety issues were identified between the two dose levels (see Table 30), it was decided to use the higher of the two doses in the Phase 3 study to maximise the potential benefit for patients.

The FDA's Assessment:

The FDA concurs with the applicant's assessment of the dose and dose response in the Phase 2 trial.

Durability of Response

The Applicant's Position:

Twenty of the 40 patients completed the 3-year follow up period. Fourteen patients completed the main study with a disease assessment of complete or partial response, with all except one of these receiving 4 doses of ADSTILADRIN. Of the patients that completed the main study with complete or partial response, 8 patients were reported as progression-free at their last visit in the long-term follow up phase. Of the 30 CIS patients who were treated with at least 1 dose of ADSTILADRIN, 9 had a complete response at 12 months and 6 were recurrence free at 3 years ([Study Report rAd-IFN-CS-002 \[long-term follow-up\]](#)).

The FDA's Assessment:

The FDA concurs with the applicant's assessment of durability of response. The applicant reports a 3-year recurrence free rate of 20% among the 30 CIS study subjects.

Persistence of Effect

The Applicant's Position:

See Applicant's Position on Durability of Response.

The FDA's Assessment:

The FDA concurs with the applicant's assessment.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

No data are available.

The Applicant's Position:

Patient-reported outcomes were not included in the Phase 2 study.

The FDA's Assessment:

The FDA concurs with the applicant's assessment.

Additional Analyses Conducted on the Individual Trial

Data:

No data are available.

The Applicant's Position:

No additional analyses were conducted for the Phase 2 study.

The FDA's Assessment:

The FDA concurs with the applicant's assessment.

5.1.5. Integrated Review of Effectiveness

The FDA's Assessment:

Integrated efficacy analyses was not conducted by the applicant for ADSTILADRIN across studies due to the small number of studies conducted.

5.1.6. Assessment of Efficacy Across Trials

Primary Endpoints

Data:

Table 23 Comparison of Phase 2 and Phase 3 Study Data (Incidence of High-Grade Recurrence-Free Survival)

Patient group	Phase 2**	Phase 3
Month 3		
CIS ± Ta/T1 disease	50.0% (15/30)	53.4% (55/103)
Ta/T1 disease	80.0% (8/10)	72.9% (35/48)
All patients*	57.5% (23/40)	59.6% (90/151)
Month 6		
CIS ± Ta/T1 disease	36.7% (11/30)	42.7% (44/103)
Ta/T1 disease	60.0% (6/10)	62.5% (30/48)
All patients*	42.5% (17/40)	49.0% (74/151)
Month 9		
CIS ± Ta/T1 disease	36.7% (11/30)	35.9% (37/103)
Ta/T1 disease	60.0% (6/10)	58.3% (28/41)
All patients*	42.5% (17/40)	43.0% (65/151)

* All patients refers to all recruited patients (patients with CIS [with or without concomitant high-grade Ta/T1 papillary disease] and patients with high-grade Ta/T1 disease (without concomitant carcinoma *in situ*)

** Based on retrospective manual calculations

The Applicant's Position:

As discussed with FDA at the Initial Comprehensive Multidisciplinary Breakthrough Therapy teleconference held on June 29, 2017 (Ref: CRMTS 10712), the clinical efficacy data are not pooled. This strategy is based on the small number of patients (17 patients) and multiple dose levels in Phase 1 study P03816 and differences between the Phase 2 (rAd-IFN-CS-002) and Phase 3 (rAd-IFN-CS-003) studies with regard to the number of dose levels of ADSTILADRIN under evaluation.

ADSTILADRIN has demonstrated robust efficacy in the Phase 3 study, in which 55 patients (53.4%) with CIS have demonstrated a complete response to ADSTILADRIN. The primary endpoint of the study has thus been met. Of the 55 patients who achieved a complete response at Month 3, 42 (76.4%) and 37 (67.3%) remained high-grade recurrence free at 3 months and 6 months after the complete response was achieved; the median durability of complete response cannot therefore be calculated based on an analysis at the 9 month time point, since >50% of patients who achieved a complete response remained high-grade recurrence-free at Month 9. These data are clinically meaningful for patients with BCG unresponsive disease who lack an effective medical therapy. Furthermore, the clinical benefit of ADSTILADRIN in patients with papillary disease has been clearly demonstrated (see Table 23).

The Phase 3 efficacy data are consistent with those reported in the Phase 2 study (rAd-IFN-CS-002; Table 23). Collectively, these studies provide robust efficacy data to support the proposed indication of ADSTILADRIN for the treatment of BCG unresponsive NMIBC, defined as CIS or papillary disease, at the proposed commercial dose of 2.25×10^{13} vp.

The proposed labeling includes a summary of the available data on complete response in patients with CIS (with or without concomitant high-grade Ta/T1 disease) and on the incidence of high-grade recurrence-free survival in both patients with CIS (with or without concomitant high-grade Ta/T1 disease) and patients with high-grade Ta or T1 papillary (without concomitant CIS); the latter also clearly demonstrate the clinically meaningful benefit afforded by ADSTILADRIN treatment in patients with papillary disease. In this patient population of high unmet medical need, radical cystectomy is currently the next treatment option, a complex and life-altering surgical procedure associated with surgical complications and risk of mortality (Elmussareh et al, 2019). This remains the only option to prevent disease invasion into muscle and prevent metastasis. Given the lack of effective therapies, ADSTILADRIN is an effective therapeutic alternative to repeated surgery and its use is thus proposed in the submitted labeling.

The FDA's Assessment:

FDA agrees that the demonstrated CR rate of 53.4% with 23% of patients remaining in CR for at least 12 months in the Phase 3 trial using a dose of 2.25×10^{13} vp is clinically meaningful in the setting of patients with BCG-unresponsive high-risk NMIBC with CIS with or without papillary disease. These results are consistent with those seen in earlier phase trials, which are considered supportive. The FDA does not consider efficacy to have been demonstrated in

patients with papillary-only disease, for whom a randomized trial using a time-to-event endpoint is necessary.

Secondary and Other Endpoints

The Applicant's Position:

Durability of CR in the Phase 3 study has been discussed in the preceding section. Durability of CR was not specifically assessed in the Phase 2 study.

The FDA's Assessment:

The FDA concurs with the applicant's assessment. The durability of complete response in the Phase 2 trial is considered supportive data in the evaluation of the Phase 3 trial for licensing purposes.

Subpopulations

The Applicant's Position:

As described above, the efficacy data are not pooled. However, analysis of the Phase 3 data by subgroup (e.g. age [<65 years and ≥ 65 years], gender, race, time from initial diagnosis of bladder cancer, and tumor type at study entry) did not reveal any clinically meaningful differences.

The FDA's Assessment:

The FDA concurs with the applicant's assessment.

Additional Efficacy Considerations

The FDA's Assessment:

There were no additional efficacy considerations.

5.1.7. Integrated Assessment of Effectiveness

The Applicant's Position:

Results from the Phase 2 and Phase 3 trials demonstrate the clear benefit of ADSTILADRIN in the proposed indication, as clinically meaningful evidence of effectiveness has been demonstrated in the Phase 3 study (see Section 5.1.2) in which 55 patients (53.4%) with CIS have demonstrated a complete response to ADSTILADRIN.

The FDA's February 2018 guidance places emphasis on the importance of median durability of complete response (in that a high complete response rate is not clinically meaningful if the response duration is short). It is therefore particularly noteworthy that, of the 55 patients who achieved a complete response at Month 3, 42 (76.4%) and 37 (67.3%) remained high-grade

recurrence free at 3 months and 6 months after the complete response was achieved (i.e., at Month 6 and Month 9 respectively) indicating that the median durability of complete response in these patients is >6 months. The incidence of high-grade recurrence-free survival was also clinically meaningful in patients with papillary disease (72.9%, 62.5% and 43.0% at Months 3, 6 and 9, respectively). The maintenance of high-grade recurrence-free survival in the ongoing Phase 3 study is indicative of the continued benefit (avoidance of cystectomy) offered to patients as a result of treatment with ADSTILADRIN. Median durability of complete response will be calculated (if possible) once all patients have completed the 12 month efficacy assessment.

Complete responses to ADSTILADRIN treatment are rapidly apparent following initiation of dosing; as evidenced in the Phase 3 study, those patients who responded to treatment did so within 3 months of administration of the first dose. This offers an opportunity for early cessation of dosing in those patients who will not gain clinical benefit from further treatment, i.e., patients with high-grade disease observed at the first post-treatment clinical assessment, 3 months after the start of therapy.

The patient population recruited to the Phase 3 study is representative of that proposed for commercial use of ADSTILADRIN. In addition, the reliance on a single, uncontrolled registration study is reasonable, given that the study itself is of an acceptable design for registration (per the FDA's February 2018 guidance) and the available data indicate a robust treatment effect that is consistent with the similarly-designed Phase 2 study. Therefore, the design of the clinical program supports the approval of ADSTILADRIN for the treatment of patients with high-grade BCG unresponsive NMIBC, and furthermore that the overall efficacy database is acceptable.

The ADSTILADRIN treatment regimen (dosing once every three months) adds only a minimal treatment burden for patients, as it aligns with the recommended standard follow-up and management of these patients per the NCCN guidelines. For commercial use, it is proposed that treatment may continue indefinitely at the physician's discretion, provided that the patient remains free from recurrence of high-grade disease. This proposal reflects the treatment of patients in the Phase 3 study.

In order to place into context the clinical significance of the complete response data, the available response data in the public domain has been collated for similar patient populations (patients with CIS, which may include patients with CIS with papillary disease in some cases) for Valstar® (valrubicin) and the most recent FDA-reviewed product, MCNA, in Table 24. On the basis of these data, ADSTILADRIN compares favorably for high-grade BCG-unresponsive NMIBC.

Table 24 Comparison of ADSTILADRIN Complete Response Rate in Patients with CIS with Valstar® and MCNA

Product	Development stage	Timepoint (months)		
		3	6	9
ADSTILADRIN®	Phase 3	53.4%	40.8%	35.9%
Valstar (valrubicin) ^{1*}	Approved	Not reported	18%	Not reported
MCNA ^{2*}	Phase 3	Not reported	27%	Not reported

*All data rounded to nearest whole number and expressed as a percentage

1. [Steinberg et al, 2000](#); [Dinney et al, 2013](#)
2. MCNA briefing document, FDA Advisory Committee (FDA analysis)

In conclusion, the available Phase 3 data provide substantial evidence of effectiveness and support a clinically meaningful treatment effect for patients with high-grade BCG unresponsive disease who lack an effective medical therapy and for whom the only treatment option is radical cystectomy (see Section 5.1.1). ADSTILADRIN presents a much-needed opportunity for patients to achieve complete response and maintain high-grade recurrence-free survival with no additional treatment burden above and beyond that associated with current management of their disease.

The FDA's Assessment:

The Phase 3 trial was not designed to be a comparative study. The cross-trial comparison of response rates with study results of valrubicin and MCNA may not be informative as these studies may have enrolled different patient populations, used different primary endpoint, and various assessment methods and schedule. However, comparison of the response rate of ADSTILADRIN to that of pembrolizumab may be informative in determining the clinical significance of the efficacy data from rAD-IFN-CS-003 with above caveats of cross-trial comparison noted above.

The FDA approved pembrolizumab for the treatment of patients with BCG-unresponsive high-risk NMIBC with CIS on January 8, 2020 based on the results of KEYNOTE-057. This trial was a multicenter, open-label, single-arm trial that enrolled 96 patients with BCG-unresponsive high-risk NMIBC with CIS with or without papillary tumors who were ineligible for or had elected not to undergo cystectomy. This study showed a complete response rate of 41% with a median duration of response of 16.2 months. Forty-six percent of responding patients had a duration of response of at least 12 months. The efficacy results of ADSTILADRIN demonstrated in rAD-IFN-CS-003 compare favorably with the results of pembrolizumab in KEYNOTE-57 in this patient population.

5.2. Review of Safety

The Applicant's Position:

The adverse events reported across the ADSTILADRIN clinical program confirm that the safety of the product is acceptable and manageable in the hospital setting.

No safety review issues were identified during the non-clinical or clinical development of ADSTILADRIN that required specific evaluation in clinical trials. As such, the standard safety assessments included in the clinical studies are considered adequate to enable characterization of the clinical safety profile.

The safety database for ADSTILADRIN comprises 221 patients across the four clinical studies, of whom 197 participated in the Phase 2 and 3 studies, which used similar designs. There were no substantive differences between these two trials in the patient populations studied or the initial treatment duration (12 months); however, the Phase 2 study evaluated two dose levels whereas the Phase 3 study evaluated a single dose level (the higher of the two dose levels evaluated in the Phase 2 study)(see Table 2 and Section 5.1.7). The Phase 3 study permitted continued dosing after the Month 12 efficacy assessment, at 3 monthly intervals, in patients who remained free from high grade recurrence. This patient population is representative of that proposed for commercial use of ADSTILADRIN. The IND was never placed on clinical hold during the conduct of the clinical program.

The adverse events in the clinical program (involving a total of 221 patients) were generally short-lived in duration and reversible. In the Phase 3 clinical study, [rAd-IFN-CS-003](#), the most frequent treatment-emergent adverse events (TEAEs) were instillation site discharge, fatigue, bladder spasm, micturition urgency, chills, pyrexia, and dysuria. Treatment-emergent serious adverse events (SAEs) comprised coronary artery disease, and acute coronary syndrome, atrial fibrillation, cardiac failure, pericarditis, brain edema, syncope, transient ischemic attack, dehydration, hypoglycemia, bile duct stone, anaphylactic reaction, sepsis, corneal abrasion, and hematuria, each occurring in 0.6% of patients and only one of which (syncope) was considered related to treatment by the investigator. This side effect profile is consistent with that observed in the Phase 2 study [rAd-IFN-CS-002](#), and is manageable in the hospital setting and supportive of a positive benefit-risk assessment for ADSTILADRIN.

The FDA's Assessment:

The primary safety analysis of ADSTILADRIN was conducted on data submitted for the 157 patients enrolled in the open-label efficacy and safety Phase 3 registration study ([rAd-IFN-CS-003](#)) in patients with BCG-unresponsive NMIBC conducted in the US. The safety population consisted of patients in Cohort A with BCG-unresponsive, NMIBC with CIS with or without papillary tumors and patients in Cohort B with BCG-unresponsive NMIBC with papillary tumors

only.

The safety analysis dataset consisted of 157 patients enrolled to rAd-IFN-CS-003 who received at least one dose of ADSTILADRIN administered at a dose of 2.25×10^{13} vp by intravesical instillation every 3 months prior to the data cut-off of 15 November 2019. Adverse events (AE) were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 21.0.

The AE dataset review was focused primarily on the Phase 3 registration trial. It consisted of 157 patients who were enrolled and treated with ADSTILADRIN at least Month 1 Day 1 (107 in CIS cohort and 50 in Papillary Disease cohort).

There were no significant discrepancies identified between the dataset and the information provided in the clinical study report.

5.2.1. Safety Review Approach

The Applicant's Position:

Although all subjects who received ADSTILADRIN for the treatment of NMIBC in any of the four clinical studies were included in the safety review in [Module 2.7.4](#), the safety profile of ADSTILADRIN is primarily supported by data resulting from administration of either 2.25×10^{13} vp (the proposed commercial dose studied in the Phase 2 and Phase 3 studies) or 7.5×10^{12} vp (evaluated in the Phase 2 study), in which a total of 197 patients received at least a single dose. The demographic characteristics of patients across the Phase 2 and Phase 3 studies were similar, as summarized in [Module 2.7.4, Section 1.3](#). In both studies, the Safety Analysis Set was defined as all patients who received at least one dose of ADSTILADRIN.

As the Phase 2 and Phase 3 studies were not prospectively designed to be pooled, and the inclusion criteria are different, as discussed with FDA at the Initial Comprehensive Multidisciplinary Breakthrough Therapy teleconference held on June 29, 2017 (Ref: CRMTS [10712](#)), the data are not pooled.

The FDA's Assessment:

As the Phase 2 and Phase 3 studies were not prospectively designed to be pooled, and the inclusion criteria are different, as discussed with FDA at the Initial Comprehensive Multidisciplinary Breakthrough Therapy teleconference held on June 29, 2017 (Ref: CRMTS [10712](#)), the data from the Phase 2 and the Phase 3 studies were not pooled.

5.2.2. Review of the Safety Database

Overall Exposure

Data:

Table 25: Safety Population, Size, and Denominators

Safety Database for the Study Drug ¹ Individuals exposed to the study drug in this development program for the indication under review N=221 (N is the sum of all available numbers from the columns below)			
Clinical Trial Groups	New Drug (n=221)	Active Control (n= 0)	Placebo (n= 0)
Controlled trials conducted for this indication ²	0	0	0
All other than controlled trials conducted for this indication ³	Phase 3 (rAd-IFN-CS-003): n=157 Phase 2 (rAd-IFN-CS-002): n=40 Phase 1 (P03816): n=17 Phase 1 2009-0938 n=7	0	0
Controlled trials conducted for other indications ⁴	0	0	0

¹ *study drug* means the drug being considered for approval.

² to be used in product's labeling

³ if placebo arm patients switch to study drug in open label extension, the n should include their number; do not count twice patients who go into extension from randomized study drug arm

⁴ include n in this column only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review. Consider n=0 in this column if no patients treated for other indication(s) were included in this safety database.

The Applicant's Position:

In the Safety Analysis Set of the Phase 3 study (rAd-IFN-CS-003) at the data cutoff date of 08-March-2019, 98 (62.4%) patients were treated at Month 4 Day 1, 74 (47.1%) patients were treated at Month 7 Day 1, and 62 (39.5%) patients were treated at Month 10 Day 1; 58 (36.9%) patients were receiving ongoing treatment with ADSTILADRIN: 31 (29.0%) patients in the CIS cohort and 27 (54.0%) patients in the papillary disease cohort. In total, 99 (63.1%) patients have discontinued ADSTILADRIN: 76 (71.0%) patients in the CIS cohort and 23 (46.0%) patients in the papillary disease cohort.

In the Phase 2 study, overall, the majority of patients received either 1 or 4 doses of ADSTILADRIN (17 patients each; 42.5%).

The FDA's Assessment:

An updated safety data cut-off of 15 November 2019 was used for safety analyses. As of the updated data cut-off, 35 (22.3%) patients were receiving ongoing treatment with ADSTILADRIN: 22 (20.6%) patients in the carcinoma in situ (CIS) cohort and 13 (26.0%) patients in the papillary disease cohort. In total, 122 (77.7%) patients have discontinued ADSTILADRIN: 85 (79.4%) patients in the CIS cohort and 37 (74.0%) patients in the papillary disease cohort. In total, 57 (36.3%) patients experienced a dose interruption: 41 (38.3%) patients in the CIS cohort and 16 (32.0%) patients in the papillary disease cohort. The dose interruptions were primarily due to adverse events.

The safety reviewer did not identify significant discrepancies between the results based on the FDA analyses of the datasets and the information the applicant provided in the clinical study report at each of the data cutoff dates of 08-March-2019 and 15-November-2019. Additionally, no new clinically significant safety findings were observed between the two data cut-offs.

Relevant characteristics of the safety population:

The Applicant's Position:

There were no substantive differences between the Phase 2 and Phase 3 trials in the patient populations studied or the initial treatment duration (12 months); however, the number of dose levels of ADSTILADRIN evaluated in the 2 studies differed (see Table 2 and Section 5.1.7). This patient population is representative of that proposed for commercial use of ADSTILADRIN.

No subgroup analyses were performed for the Phase 1 and 2 studies owing to the small number of patients recruited to the trials. The final subgroups for analysis in the Phase 3 study were selected based on the mechanism of action of ADSTILADRIN and/or the lack of systemic exposure to the vector. In summary, using the recommendations within ICH E5 as a guide, effect of liver, kidney, and cardiovascular function, and smoking, food habits, diseases and traditional absorption, metabolism, distribution and elimination and receptor binding characteristics were not considered to be relevant for ADSTILADRIN. The analysis of the Phase 3 data is, therefore, limited to gender, weight, age, height, and race. With the exception of age, all other subgroup analyses will be performed as exploratory analyses and the data will be available in the full clinical study report based on the 12 month data.

Owing to the nature and mode of action of ADSTILADRIN, no formal studies have been conducted to assess safety in patients with hepatic or renal impairment. Similarly, as NMIBC primarily occurs

in the elderly, no studies in the pediatric population have been conducted and a Pediatric Waiver was agreed with FDA in March 2016. In summary, the absence of formal studies and extensive data on safety in special populations is considered to be acceptable.

The FDA's Assessment:

The size, extent of exposure to ADSTILADRIN and the patient composition of the safety population was adequately large to provide a sufficient characterization of the adverse event profile associated with ADSTILADRIN in the target population. However, the majority of trial patients (approximately 90%) were ECOG 0 at baseline, indicating the enrollment of a potentially healthier NMIBC patient population than the general population of patients with NMIBC and may limit the generalizability of the safety results to a NMIBC population with comorbid medical conditions. In addition, due to the predominance of Caucasian patients (over 90%) on trial, the safety results may not reflect potential treatment toxicity in non-Caucasian populations.

Adequacy of the safety database:

The Applicant's Position:

The safety database for ADSTILADRIN comprises 221 patients across the four clinical studies, of whom 197 participated in the Phase 2 and 3 studies, which used similar designs. In these two studies, a total of 176 patients have been exposed to the proposed commercial dose level (19 patients in the Phase 2 study and 157 patients in the Phase 3 study). However, the Phase 2 and Phase 3 studies were not prospectively designed to be pooled, and there were minor differences in the inclusion criteria between studies (see Table 16), and thus the data are presented as side-by-side tabular presentations where relevant.

Patients in the Phase 2 study received up to 4 doses of ADSTILADRIN; in comparison, dosing in the Phase 3 study may continue beyond Month 12, permitting patients with no evidence of high-grade disease recurrence to receive more than 4 doses, therefore mirroring the proposals for continued dosing in the USPI.

The demographics and disease characteristics of patients recruited to the Phase 2 and 3 studies are sufficiently similar to provide adequate support for the BLA. Therefore, in conclusion, the safety database is adequate to characterize the safety of ADSTILADRIN in the treatment of NMIBC.

The FDA's Assessment:

The size of the safety database and the extent of ADSTILADRIN exposure were sufficient to provide a preliminary characterization of the safety profile of ADSTILADRIN for the treatment of BCG-Unresponsive NMIBC CIS with or without papillary tumors, a serious and life-threatening

disease.

Cases of serious and life-threatening toxicity were not observed in patients who enrolled in the four clinical ADSTILADRIN trials (N = 221). Although ADSTILADRIN appeared to be well-tolerated in the Phase 3 study of BCG-unresponsive NMIBC, the study consisted of a relatively small number of patients (N = 157) that received therapy. Administration of ADSTILADRIN in larger numbers of patients with the target indication may identify a toxicity profile that was not observed in this study.

5.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

No data quality issues were identified during the course of the study or the current analyses that had the potential to impact upon an assessment of the safety of ADSTILADRIN. In addition, there were no patterns in terms of adverse events (AEs) across sites that warranted further investigation.

The FDA's Assessment:

There were no significant discrepancies identified between the results based on the FDA analyses of datasets and the information the applicant provided in the clinical study report at the data cutoff date of 15-November-2019.

Categorization of Adverse Events

The Applicant's Position:

Adverse events and SAEs observed by the Investigator, or reported by the patient spontaneously or in response to a direct question were defined in accordance with ICH E2A, coded using the version of MedDRA current at the time of analysis (version 15.0 for the Phase 2 study, and version 19.0 for the Phase 3 study), and graded according to NCI CTCAE V4.03 for severity in both the Phase 2 and 3 studies.

New AEs were recorded from patient consent until 30 days after last treatment administration in the Phase 2 study, and until month 24 or withdrawal from study/end of treatment in the Phase 3 study. In the Phase 2 study, TEAEs were captured from the time of first dose until Month 13, and any SAEs were followed up until resolution or until stable. In the Phase 3 study, a TEAE was defined as any AE that occurred or worsened at or after the first dose of study drug. Causality was assessed by the Investigator and Sponsor.

All AEs and TEAEs were presented by incidence.

Special attention was paid to the monitoring of selected urinary signs and symptoms (micturition urgency, dysuria and nocturia) in Phase 1 study [P03816](#). No events of special interest were prospectively identified prior to the conduct of the Phase 2 and Phase 3 studies.

The FDA's Assessment:

FDA concurs with the applicant that no events of special interest were prospectively identified prior to the conduct of the Phase 2 and Phase 3 studies.

Routine Clinical Tests

The Applicant's Position:

Routine assessments of safety (resting 12-lead electrocardiograms [ECGs], physical examinations, vital signs, subjective symptomatology, and anti-adenoviral antibody levels) and laboratory tests (haematology, clinical chemistry, and urinalysis) were included in both the Phase 2 and 3 studies; in addition, the Phase 2 study also included assessment of anti-IFN α 2b antibodies, autopsy and concomitant medications. Clinically significant laboratory abnormalities are reported as AEs and are followed until resolution. With the exception of the antibody level analyses, all assessments were performed locally. The scheduling of these assessments, as summarized in Table 3 and Table 17, is adequate.

The FDA's Assessment:

The schedule of routine laboratory testing, clinical testing and clinical evaluations for patients enrolled in the trial, including assessment of adverse events and vital signs, was sufficient to adequately characterize the incidence of adverse events as well as the risk of progression to muscle-invasive or metastatic disease.

5.2.4. Safety Results

Deaths

The Applicant's Position:

There were no adverse events leading to patient deaths during treatment reported during any of the clinical studies performed as part of the ADSTILADRIN development program.

The FDA's Assessment:

Death due to an adverse event was reported in a total of 6 patients in ADSTILADRIN studies at the time of the Month 12 clinical study report. As of November 15, 2019, two more deaths have been reported. All these 8 patients were in the long-term follow-up period and had been withdrawn from study treatment prior to death. All deaths occurred at least 4 months after the last administration of the study drug.

The applicant did not attribute the cause of any of these deaths to ADSTILADRIN. There were no adverse events leading to patient deaths during treatment reported during any of the clinical studies performed as part of the ADSTILADRIN development program.

Upon review of the death information, FDA did not consider any of the reported deaths to be related to ADSTILADRIN.

Adverse Events

Data:

Table 26: Overview of Adverse Events - Safety Analysis Set

Adverse Event Category	CIS (N=107) n (%)	Papillary Disease (N=50) n (%)	Total (N=157) n (%)
TEAE			
Any TEAE	101 (94.4)	45 (90.0)	146 (93.0)
Serious TEAE	9 (8.4)	8 (16.0)	17 (10.8)
NCI-CTCAE Grade 3/4/5 TEAE	20 (18.7)	11 (22.0)	31 (19.7)
Study drug-related			
Any TEAE	77 (72.0)	33 (66.0)	110 (70.1)
Serious TEAE	0 (0.0)	1 (2.0)	1 (0.6)
NCI-CTCAE Grade 3/4/5 TEAE	3 (2.8)	3 (6.0)	6 (3.8)
Deaths due to TEAE	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuation of study drug due to			
Any TEAE	3 (2.8)	1 (2.0)	4 (2.5)
Study drug-related TEAE	3 (2.8)	1 (2.0)	4 (2.5)
<p>Note: CIS = CIS only, Ta + CIS, and T1 + CIS; papillary disease = Ta and T1. Percentage was calculated using the number of patients in the column heading as the denominator. Treatment- emergent adverse events were defined as adverse events that occurred or worsened in severity at or after the first dose of the study drug. CIS = carcinoma in situ; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; TEAE = treatment-emergent adverse event. Source: Post-text Table 14.3.1.1</p>			

Table 27: Study rAd-IFN-CS-003: Overview of Serious Adverse Events (Safety Analysis Set)

System Organ Class Preferred Term	CIS (N = 107) n (%)	Papillary Disease (N = 50) n (%)	Total (N = 157) n (%)
Patients with Any Treatment-Emergent Serious AEs	7 (6.5)	6 (12.0)	13 (8.3)
Cardiac disorders	4 (3.7)	2 (4.0)	6 (3.8)

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System Organ Class Preferred Term	CIS (N = 107) n (%)	Papillary Disease (N = 50) n (%)	Total (N = 157) n (%)
Coronary artery disease	1 (0.9)	1 (2.0)	2 (1.3)
Acute coronary syndrome	1 (0.9)	0 (0.0)	1 (0.6)
Arrhythmia	1 (0.9)	0 (0.0)	1 (0.6)
Atrial fibrillation	1 (0.9)	0 (0.0)	1 (0.6)
Cardiac failure	0 (0.0)	1 (2.0)	1 (0.6)
Myocardial infarction	0 (0.0)	1 (2.0)	1 (0.6)
Pericarditis	0 (0.0)	1 (2.0)	1 (0.6)
Nervous system disorders	1 (0.9)	2 (4.0)	3 (1.9)
Brain edema	1 (0.9)	0 (0.0)	1 (0.6)
Syncope	0 (0.0)	1 (2.0)	1 (0.6)
Transient global amnesia	0 (0.0)	1 (2.0)	1 (0.6)
Metabolism and nutrition disorders	1 (0.9)	1 (2.0)	2 (1.3)
Dehydration	1 (0.9)	0 (0.0)	1 (0.6)
Hypoglycemia	0 (0.0)	1 (2.0)	1 (0.6)
Hepatobiliary disorders	0 (0.0)	1 (2.0)	1 (0.6)
Bile duct stone	0 (0.0)	1 (2.0)	1 (0.6)
Immune system disorders	0 (0.0)	1 (2.0)	1 (0.6)
Anaphylactic reaction	0 (0.0)	1 (2.0)	1 (0.6)
Infections and infestations	1 (0.9)	0 (0.0)	1 (0.6)
Sepsis	1 (0.9)	0 (0.0)	1 (0.6)
Injury, poisoning and procedural complications	0 (0.0)	1 (2.0)	1 (0.6)
Corneal abrasion	0 (0.0)	1 (2.0)	1 (0.6)
Renal and urinary disorders	1 (0.9)	0 (0.0)	1 (0.6)
Hematuria	1 (0.9)	0 (0.0)	1 (0.6)
Skin and subcutaneous tissue disorders	0 (0.0)	1 (2.0)	1 (0.6)
Subcutaneous emphysema	0 (0.0)	1 (2.0)	1 (0.6)

Note: CIS = CIS Only, Ta+CIS, T1+CIS; Papillary Disease = Ta & T1.

Percentage is calculated using the number of patients in the column heading as the denominator.

Treatment emergent adverse events (TEAEs) are defined as adverse events that occur or worsen in severity at or after the first dose of study drug.

If a patient experienced more than one adverse event within a preferred term, the patient is counted once in that preferred term. If a patient experienced more than one adverse event within an SOC, the patient is counted once in that SOC.

Abbreviations: AE = adverse event; CIS = carcinoma in situ

Source: Study Report rAd-IFN-CS-003, Post-text Table 14.3.1.4

Table 28: Listing of Serious Adverse Events – Safety Analysis Set (As of November 15, 2019 – 4 months safety update)

Cohort Patient	Preferred Term	Related to Study Drug/Procedure	NCI-CTCAE Grade	Resulted in Discontinuation
(b) (6)	CIS			
	Sepsis	No/Yes	4	No
	Syncope	No/No	3	No
	Coronary artery disease	No/No	3	No
	Hematuria	No/Yes	3	No
	Acute coronary syndrome	No/No	3	No
	Atrial Flutter	No/No	3	No
	Brain edema	No/No	3	No
	Atrial fibrillation	No/No	1	No
	Dehydration	No/No	3	No
	Arrhythmia	No/No	3	No
	Papillary disease			
	Hypoglycemia	No/No	3	No
	Corneal abrasion	No/No	2	No
	Coronary artery disease	No/No	3	No
	Pericarditis	No/No	3	No
	Pericarditis	No/No	3	No
	Lung neoplasm malignant	No/No	3	No
	Pancreatic carcinoma	No/No	3	No
	Pneumonia	No/No	3	No
	Transitional cell cancer of the renal pelvis and ureter	No/No	3	No
	Subcutaneous emphysema	No/No	3	No
	Lung cancer metastatic	No/No	3	No
	Syncope	Yes/No	3	No
	Bile duct stone	No/No	3	No
	Cardiac failure	No/No	3	No
	Myocardial infarction	No/No	3	No
	Anaphylactic reaction	No/No	4	No
	Pyrexia	No/Yes	2	No
	Transient global amnesia	No/No	1	No
Note: CIS = CIS only, Ta + CIS, and T1 + CIS; papillary disease = Ta and T1. CIS = carcinoma in situ; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events. Sources: Post-text Tables 14.3.2.1 and 14.3.2.3				

The Applicant's Position:

SAEs were reported by two patients in Phase 1 study P03816; no patients in Phase 1 study 2009-0938 experienced a SAE. Five patients in rAd-IFN-002 experienced 10 SAEs, all of which were Grade 3, with two (diarrhea and acute renal failure; see rAd-IFN-CSR-002, Section 14.3.3 for narratives) considered to be related to study drug by the Investigator. One SAE (Grade 3 back pain) led to discontinuation of ADSTILADRIN.

In the Phase 3 study, 13 patients had an SAE, all of which were Grade 1-3, with the exception of one Grade 4 event (anaphylactic reaction, suspected by the investigator to be due to Cysview® that had been instilled pre-operatively prior to a planned TURBT); only one event (Grade 3 syncope) was considered to be related to the study drug by the Investigator, but considered unrelated by the Applicant. Only one SAE (Grade 2 pericarditis) led to discontinuation of ADSTILADRIN. In total, two (1.3%) patients had a study procedure-related serious TEAE (see [rAd-IFN-CS-003, Post-text Table 14.3.1.5.1](#) and [rAd-IFN-CSR-003, Section 14.3.3](#) for narratives).

The FDA's Assessment:

In total, 31 (19.7%) patients had an NCI-CTCAE Grade 3/4 TEAE: 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 TEAE was hypertension (4 [2.5%] patients). Overall, 2 (1.3%) patients had an NCI-CTCAE Grade 4 TEAE and no patient had an NCI-CTCAE Grade 5 TEAE.

The overall incidence of SAEs was low in both cohorts. No single SAE occurred at a significantly higher incidence to suggest the occurrence of a treatment-related SAE.

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

In study [P03816](#) no patient discontinued the study due to an AE, and in study [2009-0938](#) there was a single discontinuation due to worsening urinary tract symptoms.

In study [rAd-IFN-CS-002](#) one patient experienced a serious TEAE of back pain (Grade 3) that led to the discontinuation of the study drug; the event was considered by the Investigator to be unrelated to study drug. The primary reason for withdrawal from the study was recorded as due to a safety reason.

In study [rAd-IFN-CS-003](#), four patients had a TEAE leading to discontinuation of the study drug, in whom 3 of which the events (bladder spasm and instillation site discharge, instillation site discharge, and benign neoplasm) were considered to be related to study drug. Of the four patients who had a TEAE leading to discontinuation of the study drug, 3 of the 4 patients were high grade recurrence-free at the last assessment prior to withdrawal.

Table 29: Listing of Adverse Events Leading to Discontinuation of Study Drug – Safety Analysis Set (As of November 15,2019 – 4 months safety update)

Cohort Patient	Preferred Term	Related to Study Drug/Procedure	NCI-CTCAE Grade	SAE
CIS				
(b) (6)	Bladder spasm	Yes/No	3	No
	Chills	Yes/No	1	No
	Instillation site discharge	Yes/Yes	2	No
Papillary disease				

(b) (6)	Benign neoplasm of bladder	Yes/No	2	No
	Note: CIS = CIS only, Ta + CIS, and T1 + CIS; papillary disease = Ta and T1. CIS = carcinoma in situ; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; SAE = serious adverse event. Source: Post-text Table 14.3.2.3			

The FDA's Assessment:

FDA agrees with the applicant's position above. The incidence of discontinuation was low in patients treated with the study drug and were local in nature. Of note, the benign neoplasm was reported as urothelial hyperplasia, a potential precursor lesion for low-grade NMICBC, which the investigator did not consider to represent disease progression.

Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:

No dose reductions were permitted in the Phase 2 and 3 studies. Adjustments to the dwell time or splitting of the dose (e.g. 37.5 mL volume x 2) were allowed based upon assessments of local tolerability. Only 3 patients (7.5%) had a dose split and no patient had a dose delay or dosing discontinued in the Phase 2 study rAd-IFN-CS-002. In the Phase 3 study rAd-IFN-CS-003, 56 (35.7%) patients experienced a dose interruption, primarily due to adverse events. Two (1.9%) patients experienced a dose split.

The FDA's Assessment:

Based on the 4-month safety update and FDA review, a total of 57 (36.3%) patients experienced a dose interruption: 41 (38.3%) patients in the CIS cohort and 16 (32.0%) patients in the papillary disease cohort due to a preceding adverse event. Two (1.9%) patients in the CIS cohort experienced a dose split. These would have minimal effect on the overall interpretation of safety of ADSTILADRIN.

Significant Adverse Events

The Applicant's Position:

Across the clinical program, the results of clinical laboratory evaluations have been unremarkable.

No dose-limiting changes in laboratory parameters were reported in the Phase 1 study in 17 patients (study [P03816](#)). Transient decreases in total white blood cell count, neutrophil count,

and lymphocyte counts were observed; no pattern was evident, and none of the abnormal values were considered clinically significant. Similarly, in the Phase 2 and 3 studies, no clinically significant changes were found for mean values. Clinical laboratory findings are presented in the individual clinical study reports and summarized in [Module 2.7.4, Section 3](#).

Significant events leading to withdrawal of or delay to administration of ADSTILADRIN, other than those reported as SAEs, are discussed in Section 5.2.4.

The FDA's Assessment:

Laboratory abnormalities observed in patients treated with ADSTILADRIN were mild to moderate. There were no grade 4 or grade 5 laboratory abnormalities, refer to Table 31 below.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Table 30: Adverse Reactions Occurring in ≥5% of Patients Following Treatment with ADSTILADRIN

System Organ Class/Preferred Term	Study 1 (N=40)		Study 2 2.25 x 10 ¹³ vp N=157 n (%)
	7.5 x 10 ¹² vp N=21 n (%)	2.25 x 10 ¹³ vp N=19 n (%)	
Renal and urinary disorders			
Micturition urgency	10 (47.6)	5 (26.3)	24 (15.3)
Dysuria	5 (23.8)	6 (31.6)	16 (10.2)
Pollakiuria	6 (28.6)	5 (26.3)	10 (6.4)
Nocturia	4 (19.0)	4 (21.1)	4 (2.5)
Bladder spasm	NR	NR	24 (15.3)
Hematuria	3 (14.3)	1 (5.3)	7 (4.5)
Urinary incontinence	3 (14.3)	1 (5.3)	4 (2.5)
Bladder pain	0 (0.0)	1 (5.3)	8 (5.1)
Incontinence	0 (0.0)	1 (5.3)	1 (0.6)
Renal failure acute	0 (0.0)	1 (5.3)	NR
General disorders and administration site conditions			
Fatigue	3 (14.3)	6 (31.6)	31 (19.7)
Chills	0 (0.0)	5 (26.3)	18 (11.5)

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System Organ Class/Preferred Term	Study 1 (N=40)		Study 2 2.25 x 10 ¹³ vp N=157 n (%)
	7.5 x 10 ¹² vp N=21 n (%)	2.25 x 10 ¹³ vp N=19 n (%)	
Pyrexia	1 (4.8)	5 (26.3)	16 (10.2)
Instillation site discharge	NR	NR	39 (24.8)
Influenza-like illness	2 (9.5)	0 (0.0)	6 (3.8)
Pain	0 (0.0)	1 (5.3)	10 (6.4)
Asthenia	1 (4.8)	1 (5.3)	3 (1.9)
Infusion site reaction	0 (0.0)	1 (5.3)	NR
Gastrointestinal disorders			
Nausea	1 (4.8)	3 (15.8)	6 (3.8)
Abdominal pain	0 (0.0)	2 (10.5)	1 (0.6)
Diarrhea	2 (9.5)	2 (10.5)	9 (5.7)
Abdominal distension	0 (0.0)	1 (5.3)	NR
Frequent bowel movements	0 (0.0)	1 (5.3)	NR
Vomiting	0 (0.0)	1 (5.3)	2 (1.3)
Nervous system disorders			
Headache	0 (0.0)	0 (0.0)	14 (8.9)
Dizziness	1 (4.8)	1 (5.3)	6 (3.8)
Infections and infestations			
Urinary tract infection	0 (0.0)	1 (5.3)	3 (1.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain	0 (0.0)	1 (5.3)	NR
Skin and subcutaneous tissue disorders			
Hyperhidrosis	0 (0.0)	1 (5.3)	1 (0.6)
Musculoskeletal and connective tissue disorders			
Myalgia	0 (0.0)	1 (5.3)	7 (4.5)

NR = term not reported for the population

0 = event reported at a frequency of 0 (0.0%) in subgroup

Source: [Study Report rAd-IFN-CS-002, Post-text Table 14.3.1.3](#)
[Study Report rAd-IFN-CS-003, Post-text Table 14.3.1.11](#)

The Applicant's Position:

In the Phase 1 study [P03816](#), the most commonly reported treatment-related AEs were micturition urgency (88%), fatigue (47%), and headache (41%). No dose-limiting treatment-related AEs were reported.

In 34/40 patients (85.0%) in the Phase 2 study [rAd-IFN-CS-002](#), TEAEs occurred that were considered related to the study drug with 18/21 patients (85.7%) in the 7.5×10^{12} vp dose group and 16/19 patients (84.2%) in the 2.25×10^{13} vp dose group. By preferred term, the most frequently reported TEAEs were dysuria and micturition urgency in 16 patients (40.0%), fatigue in 13 patients (32.5%) and pollakiuria in 11 patients (27.5%). Most TEAEs considered related occurred in only one or two patients overall. However, the most frequently reported study-drug related TEAEs by preferred term were micturition urgency (15/40 patients; 37.5%), dysuria and pollakiuria (each in 11 patients; 27.5%), fatigue (9 patients; 22.5%) and nocturia (8 patients; 20.0%).

In the overall Phase 3 population, the most common TEAEs were instillation site discharge (49 [31.2%] patients), fatigue (37 [23.6%] patients), bladder spasm (30 [19.1%] patients), micturition urgency (28 [17.8%] patients), and hematuria (27 [17.2%] patients). Study drug-related TEAEs were experienced by 110 (70.1%) patients, 77 (72.0%) of whom were in the CIS cohort and 33 (66.0%) in the papillary disease cohort. A total of 7 patients (7/157; 4.5%) had a drug-related NCI-CTCAE Grade 3/4/5 TEAE, four of whom belonged to the CIS cohort (and reported micturition urgency (2), bladder spasm (1) and urinary incontinence (1)), and three of whom belonged to the papillary disease cohort (and reported micturition urgency (1), syncope (1) and hypertension (1)).

As the Phase 2 and Phase 3 studies were not prospectively designed to be pooled, and the inclusion criteria are different, as discussed with FDA at the Initial Comprehensive Multidisciplinary Breakthrough Therapy teleconference held on June 29, 2017 (Ref: CRMTS [10712](#)), the data, rather than being pooled, are included as side-by-side tabular presentations in Table 30. Across both the Phase 2 and Phase 3 studies, the most common treatment-emergent adverse reactions occurring in $\geq 10\%$ of patients were micturition urgency, dysuria, fatigue, pollakiuria, chills, pyrexia, instillation site discharge, nocturia, nausea, bladder spasm, hematuria, urinary incontinence, abdominal pain, and diarrhea (Table 30). In general, very common adverse reactions (those occurring in $\geq 10\%$ of patients) were reported more frequently in the Phase 2 study than in the Phase 3 study, including reports of urinary symptoms (micturition urgency, dysuria, pollakiuria, and nocturia); however, two events (instillation site discharge and bladder spasm) were only reported in the Phase 3 study. There is no obvious explanation for the difference in frequencies across studies; there were no substantive differences in the patient populations studied or the initial treatment duration (12 months).

In the Phase 3 study, the majority of adverse reactions occurring in $\geq 5\%$ of patients had a median duration of 1.0 day (instillation site discharge, bladder spasm, micturition urgency, bladder pain)

or 2.0 days (chills, pyrexia, headache, pain, diarrhea); other adverse reactions occurring in ≥5% of patients were dysuria (median duration 4.5 days), fatigue (11.0 days) and pollakiuria (41.0 days).

Based on the Phase 2 and Phase 3 data, the adverse reaction profile is considered to be manageable in the hospital setting. Specifically, there are no signals from the Phase 2 and 3 study data that indicate a need for specific warnings, precautions or contraindications to be provided to physicians prior to the administration of ADSTILADRIN.

The FDA's Assessment:

In summary, the most common TEAEs for the safety population were instillation site discharge, fatigue, bladder spasm, micturition urgency, and hematuria. FDA agrees with the applicant.

Laboratory Findings

The Applicant's Position:

There were no laboratory findings indicative of actual or possible serious medical effects across the clinical program.

The FDA's Assessment:

Table 31: Study Drug-Related TEAEs in Laboratory Results (Source: FDA Analysis)

	[Group1:acohort=CIS] N=107			[Group2:acohort=Papillary Disease] N=50			[Group3:saffl=Y] N=157		
	1-2	3-4	4	1-2	3-4	4	1-2	3-4	4
[Alanine Aminotransferase (U/L)] Increased	14.15	0	0	14	0	0	14.1	0	0
[Aspartate Aminotransferase (U/L)] Increased	12.26	0	0	16	0	0	13.46	0	0
[Bilirubin (mg/dL)] Increased	2.83	0	0	12	0	0	5.77	0	0
[Cholesterol (mmol/L)] Increased	14.85	0	0	10.41	0	0	13.42	0	0
[Creatinine (mg/dL)] Increased	15.09	0	0	18	0	0	16.02	0	0
[Glucose (mg/dL)] Increased	27.36	6.6	0	36	6	0	30.13	6.41	0
[Hemoglobin (g/dL)] Decreased	16.03	0	0	14	2	0	15.38	0.64	0
[Leukocytes (10 ⁹ /L)] Decreased	18.87	0	0	20	0	0	19.23	0	0
[Lymphocytes (10 ⁹ /L)] Decreased	11.42	0	0	18.36	0	0	13.63	0	0
[Neutrophils (10 ⁹ /L)] Decreased	8.57	1.9	0	12.24	2.04	0	9.74	1.95	0
[Platelets (10 ⁹ /L)] Decreased	14.15	0	0	22	0	0	16.67	0	0
[Prothrombin Intl. Normalized Ratio (ratio)] Increased	6.93	1.98	0	2.08	6.25	0	5.37	3.36	0
[Triglycerides (mg/dL)] Increased	30.69	1.98	0	16.66	0	0	26.17	1.34	0

Laboratory abnormalities observed in patients treated with ADSTILADRIN were mild to moderate. There were no grade 4 or grade 5 laboratory abnormalities.

Vital Signs

The Applicant's Position:

No notable changes were observed in any of the assessments performed to assess vital signs or physical/other observations related to safety across the clinical program.

The FDA's Assessment:

FDA agrees.

Electrocardiograms (ECGs)

The Applicant's Position:

There were no notable changes in 12-lead ECGs across the clinical program.

The FDA's Assessment:

FDA agrees.

QT

The Applicant's Position:

A thorough QT study has not been performed with ADSTILADRIN owing to the lack of systemic exposure and the product's mechanism of action. This approach is consistent with FDA guidance, which, although generally applicable to new drugs with systemic bioavailability, notes that if a product has a highly localized distribution, and nonclinical data do not indicate any signals, the absence of such studies can be justified.

The FDA's Assessment:

Not applicable.

Immunogenicity

The Applicant's Position:

In study [P03816](#), 5 of 17 patients had occasional occurrence of anti-adenovirus type 5 antibody titers >10-fold over baseline, with no measurable adverse clinical manifestations. One patient had a positive anti-IFN α 2b antibody level at the pre-dose assessment.

In [rAd-IFN-CS-002](#), anti-adenovirus type 5 antibody levels were measured in serum from each patient. Based on this assessment, 22 patients (55.0%) had a significant anti-adenovirus antibody

response. A definitive antibody titer for any of the positive patients was not determined. Anti-IFN α 2b antibody levels were measured in serum from each patient. With the exception of one patient who had a very weak 1:20 titer at Month 1 Day 12, no other patient at any time point had measurable anti-IFN α 2b antibodies.

In addition to evaluating the overall safety of ADSTILADRIN, the Phase 3 study will determine the anti-adenoviral antibody levels for correlation to response rate, and data will be reported at the time of the 12 month analysis. However, no analyses for safety are planned, as the Phase 2 data are considered sufficient to inform on the potential for generation of anti-IFN α 2b antibodies, and there is no indication from the available safety data to indicate that generation of anti-adenovirus or anti-IFN α 2b antibodies presents a safety risk for patients.

The FDA's Assessment:

Phase 2 safety data showed no indication that generation of anti-adenovirus or anti-IFN α 2b antibodies presents a safety risk for patients. A by-patient listing of immunogenic response in anti-adenoviral antibody at post-baseline in the Phase 3 study was provided by the applicant. However, as planned, no safety analysis was done.

5.2.5. Analysis of Submission-Specific Safety Issues

The Applicant's Position:

No potential safety issues warranted a more thorough or specific evaluation during the clinical development of ADSTILADRIN. Therefore, this section is not applicable.

The FDA's Assessment:

The applicant had no events of special interest that were prospectively identified prior to the conduct of the Phase 2 and Phase 3 studies. However, FDA had some concerns that an alternative treatment with the study agent instead of standard care of radical cystectomy could provide an opportunity for NMIBC to progress to MIBC. To mitigate this concern, FDA requested further information from the applicant and analyzed the number of patients who had progression to muscle-invasive bladder cancer (MIBC) and pathological staging at time of radical cystectomy.

Table 32: Time from last dose of ADSTILADRIN to cystectomy reported as of July 8, 2019

Unique Subject Identifier	Analysis Cohort	Date of Last Exposure to Treatment (dd/mm/yy)	Date of Cystectomy (dd/mm/yy)	Time From Last Dose Until Cystectomy (Days)	Stage at Recurrence	Stage at Cystectomy
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(b) (6)	CIS	(b) (6)	383	0A	NK
	CIS		128	I	pT1; pN0
	CIS		252	IV	Bladder pT1 Prostate pT2 pN0
	CIS		308	0is	pT2b; pN1
	CIS		471	0is	pTis; pN0
	CIS		109	0is	pTis; pN0
	CIS		161	0is	pT0; pN0
	CIS		158	I	pTis; pN0
	CIS		126	0is	pTis; pN0
	CIS		176	0is	pTis; pN2
	CIS		127	0is	pTis; pN0
	CIS		454	0is	pTis; pN0
	CIS		206	0is	pTis; pN0
	CIS		275	0is	pT1; pN0
	CIS		105	0is	pTis; pN0
	CIS		315	0is	pTis; pN0
	CIS		140	0is	pTis; pN0
	CIS		91	N/A*	pT0; pN0
	CIS		104	0is	pTis; pN0
	CIS		140	0is	pTis; pN0
	CIS		113	II	pT3a; pN0
	CIS		126	0is	pTis; pN0
	CIS		150	I	pTis; pN0
	CIS		181	0is	pTis; pN0
	CIS		242	0is	pTis; pN0
	CIS		128	0is	pTis; pN0

(b) (6)	CIS	(b) (6)	324	0is	pTis; pN0
	CIS		154	0is	pTis; pN0
	Papillary		193	0is	pTis; pN0
	Papillary		117	0A	pTa; pN0
	Papillary		126	0is	pTis; pN0
	Papillary		207	0is	pTis; pN0
	Papillary		149	0A	pT1; pN0
	Papillary		145	0is	pT2b; pN0
	Papillary		169	0A	NK
	Papillary		176	0A	pT1; pN0
	Papillary		193	I	pT2a; pN0
	Papillary		119	I	pTis; pN0
	Papillary		147	0A	pT0, pN0

Table 33: Time from last dose of ADSTILADRIN to cystectomy in the four additional patients undergoing cystectomy reported from July 8, 2019 to November 15, 2019

Unique Subject Identifier	Analysis Cohort	Date of Last Exposure to Treatment (dd/mm/yyyy)	Date of Cystectomy (dd/mm/yyyy)	Time From Last Dose Until Cystectomy (Days)	Stage at Recurrence	Stage at Cystectomy
(b) (6)	CIS	(b) (6)		170	0is	pTis; pN0
	CIS	(b) (6)		128	0is	NK
	CIS	(b) (6)		193	0is	pTis; pN0
	CIS	(b) (6)		161	0is	pTis; pN0

In summary, in 32/43 (74%) patients who underwent cystectomy (25/32 patients in the CIS cohort and 7/11 patients in the papillary cohort), there was no change in overall stage between recurrence and cystectomy. In 6/43 (14%) patients who underwent cystectomy (3/32 in the CIS cohort and 3/11 in the papillary cohort) there was a change in overall stage between recurrence and cystectomy; 4 patients were up-staged (2 patients in the CIS cohort and 2 patients in the papillary cohort) and 2 patients were down-staged (1 patient in the CIS cohort

and 1 patient in the papillary cohort). Of particular note, 1 patient in the CIS cohort who was up-staged had received pembrolizumab in the KEYNOTE-057 trial prior to cystectomy; in the remaining 3 patients who were up-staged, the interval between recurrence and cystectomy ranged from 113 – 193 days. Of the other 5 patients, information on the outcome at cystectomy is unavailable in 3 patients and the remaining 2 patients did not have muscle-invasive disease at cystectomy.

Excluding the patient who underwent an additional therapy prior to cystectomy, the incidence of upstaging at cystectomy in the CIS cohort (2/31; 6.5%) was not worse than would be expected based on the literature.

In the CIS cohort of 103 patients, 97 subjects were in the study follow-up at the time of data cut-off November 15, 2019. These subjects had a minimum follow-up of 7 months from last patient enrolled to data cut-off and a median follow-up of 24 months. There were two subjects among the 55 (3.6%) who achieved CR who experienced progression to extravesical or muscle invasive disease.

Table 34: Summaries of Muscle invasive/Extra-vesical disease in CIS cohort, N=55

Progression Event	Brief Narrative
Extravesical disease	A 69-year-old male with relapsed TIS at study entry and duration of response recorded as 5.6 months. At the 9-month efficacy visit the patient was found to have high-grade carcinoma consistent with urothelial carcinoma in a pelvic lymph node at biopsy. No information provided on treatment the study subject received after recurrence.
MIBC	A 53 year-year-old male with refractory TA/CIS had confirmed duration of response of 4.4 months. Subject was diagnosed with invasive high-grade urothelial carcinoma invading the muscularis propria at the 6-month efficacy visit by biopsy. No information provided on treatment received after recurrence.

The number of progression events among the responding subjects at 24 months median follow-up may not be fully indicative of the long-term risk of progression in subjects with high-risk NMIBC. The natural history of high-risk bladder cancer captures the majority of progression

events within 48 months. However, this data in conjunction with the low incidence of upstaging recorded at cystectomy mitigates the FDA concerns described above and supports a favorable benefit/risk profile of ADSTILADRIN in the intended population for marketing approval.

5.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:

Patient-reported outcomes were not included in the Phase 3 study.

The FDA's Assessment:

Patient reported outcomes were not assessed.

5.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:

No subgroup analyses were performed for the Phase 1 and 2 studies owing to the small number of patients recruited to the trials. The final subgroups for analysis in the Phase 3 study were selected based on the mechanism of action of ADSTILADRIN and/or the lack of systemic exposure to the vector. The analysis of the Phase 3 data is, therefore, limited to gender, weight, age, height, and race. With the exception of age, all other subgroup analyses will be performed as exploratory analyses and the data will be available in the full clinical study report based on the 12 month data. As of the cut off date for the Phase 3 study, a comparison of the most frequently reported TEAEs by age group (TEAEs occurring in $\geq 10\%$ of patients in either group) indicated a generally comparable safety profile in patients aged ≥ 65 years versus patients aged < 65 years, although there was a possible increased frequency of urinary tract infection and diarrhea in patients aged ≥ 65 years versus younger patients (see [Module 2.7.4, Section 5.1](#)).

The FDA's Assessment:

Overall AEs occurred at a similar frequency across age ranges. Incidences of urinary tract infection and diarrhea in patients aged ≥ 65 years were numerically lower than that in patients aged < 65 years. However, it is difficult to make comparisons regarding the incidence of AEs between these age groups on trial due to the small number of patients aged < 65 years.

5.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:

No specific safety concerns were identified for ADSTILADRIN that warranted evaluation in a specific safety study.

The FDA's Assessment:

None.

5.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

Nonclinical studies to evaluate the carcinogenic and genotoxic potential of ADSTILADRIN have not been performed. As ADSTILADRIN is administered intravesically every 3 months to NMIBC patients, carcinogenicity studies are not considered warranted taking into account the nature of the replication deficient adenoviral vector and the limited systemic exposure to Syn3, which has shown no evidence of genotoxicity.

The FDA's Assessment:

Not applicable.

Human Reproduction and Pregnancy

The Applicant's Position:

The average age of patients with NMIBC at diagnosis is 73 years. As agreed with FDA, the risk for toxicity to reproductive organs was satisfactorily addressed by assessing the exposure to reproductive organs following intravesical administration in addition to the histopathological evaluation of reproductive organs in the various toxicology studies. Appropriate information has been included in the proposed USPI.

The FDA's Assessment:

Not applicable.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

NMIBC primarily occurs in the elderly. No studies in the pediatric population have been conducted and a Pediatric Waiver was agreed with FDA in March 2016.

The FDA's Assessment:

Not applicable.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

There are no human data on overdose. No events of overdose were reported in study rAd-IFN-CS-003 for any patient. No adverse reactions specifically associated with ADSTILADRIN overdose have been identified, and no cases of drug abuse were reported during the clinical trials with ADSTILADRIN. As ADSTILADRIN is administered by a urologist in the hospital setting, the likelihood of overdose or abuse is considered to be negligible. Further, withdrawal and rebound effects, although not studied, are not anticipated based on the mechanism of action.

The FDA's Assessment:

The likelihood of overdose or abuse is negligible.

5.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Not applicable for this initial BLA.

The FDA's Assessment:

Not applicable for this initial BLA.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Based on the clinical safety profile observed in the Phase 2 and 3 studies, labelling and routine pharmacovigilance procedures alone are sufficient to ensure the safe use of ADSTILADRIN. Therefore, no additional measures are proposed for the postmarket setting.

The FDA's Assessment:

No additional measures are proposed for the postmarket setting.

5.2.11. Integrated Assessment of Safety

The Applicant's Position:

The AEs in the clinical program (involving a total of 221 patients) were generally short-lived in duration and reversible. In the Phase 3 clinical study, [rAd-IFN-CS-003](#), the most frequent TEAEs were instillation site discharge (20.4%), fatigue (19.7%), bladder spasm (14.6%), micturition urgency (14.6%), chills (11.5%), pyrexia (10.2%), and dysuria (10.2%). Treatment-emergent SAEs comprised coronary artery disease (1.3%), and acute coronary syndrome, atrial fibrillation, cardiac failure, pericarditis, brain edema, syncope, transient ischemic attack, dehydration,

hypoglycemia, bile duct stone, anaphylactic reaction, sepsis, corneal abrasion, and hematuria, each occurring in 0.6% of patients and only one of which (syncope) was considered related to treatment by the investigator, but which was considered unrelated by the Sponsor. There were no deaths due to TEAEs.

This side effect profile is consistent with that observed in the Phase 2 study [rAd-IFN-CS-002](#), and is considered to be manageable in the hospital setting. Bladder-related adverse events were typically short-lived, did not usually lead to discontinuation of treatment and can be managed using concomitant therapies, if necessary, for symptomatic relief. Adverse events such as fatigue, chills and pyrexia may reflect patient response to interferon, but these were similarly typically transient, not severe, and can be managed by concomitant therapies, if necessary, for symptomatic relief.

There is no discernible pattern of SAEs in the studies; rather, the events reported are considered to be reflective of the age of the patient population and the associated degree of co-morbidities. Similarly, there was a generally comparable safety profile in patients aged ≥ 65 years versus patients aged < 65 years. As noted in Section 5.1.2, the patient population recruited to the Phase 3 study is representative of that proposed for commercialization and, as such, the safety of ADSTILADRIN has been evaluated in all relevant patient populations (see also [Module 2.4, Section 4.5](#) for discussion on the Prescribing Information recommendations on use in specific populations).

Patients will continue to be followed to assess long-term safety in the Phase 3 study. However, no safety issues were identified during the long-term follow up period in the Phase 2 study. This observation is consistent with the expectation, based on its mechanism of action, that the long-term safety of ADSTILADRIN will not be associated with risks related to long-term dosing; no signals of long-term adverse sequelae have been identified in the clinical program to date. It is anticipated that ADSTILADRIN will be administered by urologists in the hospital setting, which would mitigate any risks associated with its use. Based on the safety profile and anticipated context of use, there is no need for additional risk mitigation measures, beyond appropriate labelling and routine pharmacovigilance activities.

In summary, the safety profile for ADSTILADRIN is acceptable considering the lack of alternative effective medical therapies for this condition. The vast majority of the adverse reactions are not serious, are short-lived and reversible, and can be managed by symptomatic therapies. The observed serious adverse reactions are rare and reversible. There were no deaths attributed to ADSTILADRIN. In contrast, the standard of care therapy for these patients is radical cystectomy which has both significant morbidity and mortality. Moreover, patients strongly prefer effective therapies that allow them to keep their bladder.

The FDA's Assessment:

A single Phase 3 trial of nadofaragene firadenovec in patients with BCG-unresponsive NMIBC was included in this application and safety data from Phase 2 trial were not integrated. Data for

nadofaragene firadenovec in patients with high risk, BCG-unresponsive NMIBC are discussed in Section 5.2.4. FDA agrees with the applicant that there is no need for additional risk mitigation measures, beyond appropriate labelling and routine pharmacovigilance activities.

5.3. Statistical Issues

The FDA's Assessment:

See separate statistical review for review of statistical issues. There were no major statistical issues with the study design, statistical analysis plan, or efficacy results for this single-arm trial. The study's primary and key secondary endpoints of CR rate of patients with CIS and response duration in patients with CIS were consistent with what is recommended in FDA guidance. The DFS results in patient with papillary-only NMIBC cannot be interpreted since they are evaluated in the context of a single-arm trial.

5.4. Conclusions and Recommendations

The FDA's Assessment:

The safety profile of nadofaragene firadenovec in patients with BCG-unresponsive NMIBC containing CIS is acceptable. The size of the safety database and duration of exposure of nadofaragene firadenovec in rAd-IFN-CS-003 as well as in the earlier phase trials were sufficient to characterize the safety of nadofaragene firadenovec for the treatment of a serious and life-threatening condition. The proportion of patients experiencing serious or high-grade adverse events or experiencing discontinuation due to an adverse event were low. The incidence of pathologic upstaging in patients who underwent subsequent cystectomy was low in comparison to historical controls in the literature, indicating the safety of delaying cystectomy in patients with BCG-unresponsive NMIBC with CIS receiving nadofaragene firadenovec. In the context of a clinically meaningful response rate and duration in patients with CIS, the OCE MORE team determines that there is a favorable risk-benefit profile for the use of nadofaragene firadenovec in this patient population and recommends approval. However, due to issues related to manufacturing and product quality, a complete response for this application is anticipated.

6 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

There were no advisory committee or external consultations for this application.

7 Pediatrics

The Applicant's Position:

NMIBC primarily occurs in the elderly. No studies in the pediatric population have been conducted and a Pediatric Waiver was agreed with FDA in March 2016.

The FDA's Assessment:

FDA agrees with the above.

8 Labeling Recommendations

The FDA's Assessment:

As a complete response will be issued for this application, labeling was not reviewed.

9 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

No REMS are recommended for this application.

10 Postmarketing Requirements and Commitment

The FDA's Assessment:

As a complete response will be issued for this application, there are no post-marketing requirements or commitments.

11 Signature Block

OCE MORE Team Clinical Efficacy Reviewer: Laronna Colbert, MD

Date: 4-15-2020 Signature

Laronna S. Colbert -S
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Date: 2020.04.15 10:43:31 -04'00'

OCE MORE Team Clinical Safety Reviewer: Yuxia Jia, MD, PhD

Date: 4-15-2020 Signature

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Date: 2020.04.15 10:30:21 -04'00'

OCE MORE Team Leader: Daniel Suzman, MD

Date: 4-15-2020 Signature

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Date: 2020.04.15 10:35:18 -04'00'

OCE MORE Team Clinical Supervisor: Ke Liu, MD, PhD

Date: 4-15-2020 Signature

Ke Liu -S
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Date: 2020.04.15 17:49:24 -04'00'

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE. However, due to issues related to manufacturing and product quality, a complete response for this application will be issued.

OCE Signatory: Paul Kluetz, MD

Date: 4-15-2020 Signature

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Date: 2020.04.15 12:58:24 -04'00'

12 Appendices

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