

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

OCE MORE Team BLA Supplementary Clinical Review and Evaluation

Application Type	Resubmission			
Application Number(s)	125700			
Priority or Standard	Priority			
Submit Date(s)	June 29, 2022			
Received Date(s)	June 30, 2022			
PDUFA Goal Date	December 30, 2022			
Division/Office	DCEPT/OTAT			
Review Completion Date	November 18, 2022			
Established Name	Nadofaragene firadenovec			
(Proposed) Trade Name	ADSTILADRIN			
Pharmacologic Class	TBD			
Code name	N/A			
Applicant	Ferring			
Formulation(s)	Component	Reference to Quality Standard	Function	Target Concentration (per ml)
	rAD-IFNα2b vector	In House	Active	3.0 x10 ¹¹ virus particles
	Sodium dihydrogen phosphate dihydrate	(b) (4)	Buffer agent	(b) (4)
	Tromethamine	(b) (4)	Buffer agent	(b) (4)
	Glycerol (Anhydrous)	(b) (4)	Stabilizer	(b) (4)
	Sucrose	(b) (4)	Stabilizer	(b) (4)
	Magnesium chloride hexahydrate	(b) (4)	Stabilizer	(b) (4)
	Syn3 [N-3-cholamidopropyl)-N-(3-lactobionamidopropyl)]-cholamide	In House	Surfactant	(b) (4)
	Hydroxypyl-beta-cyclodextrin	(b) (4)	(b) (4)	(b) (4)
	Citric acid monohydrate	(b) (4)	Buffer agent	(b) (4)
	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 3 x 10 ¹¹ vp/mL			
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.			
Recommended Indication(s)/Population(s) (if applicable)	Treatment of patients with high-risk Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors			

Product Introduction

ADSTILADRIN® (rAd-IFN/Syn3) is a gene-based therapy designed to deliver the gene encoding interferon- α 2b (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 x 10¹³ 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 biological product is:

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

Updated Conclusions on the Substantial Evidence of Effectiveness

We refer to OCE MORE Team BLA Clinical Review and Evaluation Memo, dated April 3, 2020, for comprehensive review of the original BLA application submitted on February 27, 2019.

The effectiveness claim of this original BLA is based on rAd-IFN-CS-003, a single-arm study that enrolled subjects with high-grade, BCG-unresponsive non-muscle invasive bladder cancer (NMIBC). The study population included subjects with CIS only, Ta/T1 high-grade disease with concomitant CIS, or Ta/T1 high-grade disease without concomitant CIS. Only subjects 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 subjects in the CIS cohort who showed CR at any time after the first administration of ADSTILADRIN.

As the application was resubmitted on June 29, 2022, FDA conducted analysis of response data as per the definition of CR put forth in FDA Guidance for Industry "BCG-Unresponsive Nonmuscle Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment," February 2018 which states:

"For single-arm trials of patients with BCG-unresponsive disease, the FDA defines a complete response as at least one of the following:

- *Negative cystoscopy and negative (including atypical) urine cytology*
- *Positive cystoscopy with biopsy-proven benign or low-grade NMIBC and negative*

cytology

For intravesical therapies without systemic toxicity, the FDA includes, in the definition of a complete response, negative cystoscopy with malignant urine cytology if cancer is found in the upper tract or prostatic urethra and random bladder biopsies are negative."

Additionally, although the protocol for the study did not require a specific imaging technology to be used by investigators by investigators during screening at study entry, FDA confirmed that all subjects included in the primary efficacy analysis had consistent imaging at screening and time of complete response. Thus, of the 107 subjects with CIS who were enrolled onto rAd-IFN-CS-003, 98 subjects were considered to be evaluable. Reasons that patients were considered unevaluable included no confirmation of BCG unresponsiveness (n=4), unknown cystoscopy imaging modality at screening (n=2), and positive cytology at CR determination without adequate evaluation of the upper and lower urinary tracts (n=3). As these latter two factors were not protocol violations but rather reflect FDA determination of the evaluable population subsequent to study initiation and conduct, these subjects were considered unevaluable for response and removed from the efficacy population. Fifty subjects had a CR at the first disease assessment (three months after the treatment start), leading to a CR rate of 51% (95% CI: 40.7, 61.3%). No subjects experienced a CR subsequently. The median duration of response was 9.7 months (range 3, 52+). Forty-six percent of subjects had duration of response lasting ≥ 12 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 subjects in CR had been followed for at least 12 months following response.

FDA also conducted review of submitted cystectomy reports through 36-month efficacy visit (cutoff date of September 9, 2021). The Applicant reported 44 subjects enrolled in Study CS-003 had received cystectomy. FDA received 43 cystectomy reports.

Of the 44 subjects with CIS treated with ADSTILADRIN on Study CS-003 who underwent subsequent radical cystectomy and for whom pathologic data were available, 14% (n = 6) had muscle-invasive (T2 or greater) disease at cystectomy. Two additional subjects who did not undergo cystectomy experienced progression to muscle-invasive disease during the treatment period. A Warning regarding the risk for muscle-invasive or metastatic bladder cancer if cystectomy is deferred in the setting of refractory or recurrent CIS reflecting these data was added to USPI Section 5.1. There were no clinically meaningful changes to the safety profile based on the updated data. A Warning regarding the risk of disseminated adenovirus infection with ADSTILADRIN exposure in immunocompromised persons due to exposure to low-level replication competent virus was added to USPI Section 5.2. This is a theoretical risk and there were no cases of disseminated adenovirus infection either in subjects or other exposed individuals that have been reported by the Applicant.

The OCE MORE Team concludes that ADSTILADRIN 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 ADSTILADRIN, an intravesical therapy without apparent systemic toxicity, is acceptable for this patient population, particularly given the alternative of cystectomy. In the context of a clinically meaningful complete 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 ADSTILADRIN in this patient population and recommends approval.

Signature Block

OCE MORE Team Clinical Efficacy Reviewer: Laronna Colbert, MD

Date:

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

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OCE MORE Team Leader: Daniel Suzman, MD

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OCE MORE Team Clinical Supervisor: Peter Bross, MD

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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.

OCE Signatory: Paul Kluetz, MD

Date:

Signature

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