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ADISINSIGHT REPORT

Nadofaragene Firadenovec: First Approval

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Abstract

Nadofaragene firadenovec (nadofaragene firadenovec-vncg; Adstiladrin®) is a non-replicating adenoviral vector-based gene therapy developed by Ferring Pharmaceuticals for the treatment of high-risk Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC). Nadofaragene firadenovec constitutes vector DNA that encodes for interferon (IFN)-α2b and is the first approved gene therapy in bladder cancer. The production of IFN-α2b by transfected urothelial cells is associated with anticancer activity, including immunostimulatory, antiangiogenic and apoptotic effects. In December 2022, nadofaragene firadenovec received its first global approval in the USA for the treatment of high-risk BCG-unresponsive NMIBC with carcinoma in situ (CIS) with or without papillary tumours in adults. This article summarizes the milestones in the development of nadofaragene firadenovec leading to this first approval for this indication.

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Nadofaragene firadenovec (Adstiladrin®): Key Points

A non-replicating adenoviral vector-based gene therapy is being developed by Ferring Pharmaceuticals for the treatment of bladder cancer

Received its first approval on 16 Dec 2022 in the USA

Approved for use in adults for the treatment of high-risk BCG-unresponsive NMIBC with CIS with or without papillary tumours

This profile has been extracted and modified from the *AdisInsight* database. *AdisInsight* tracks drug development worldwide through the entire development process, from discovery, through pre-clinical and clinical studies to market launch and beyond.

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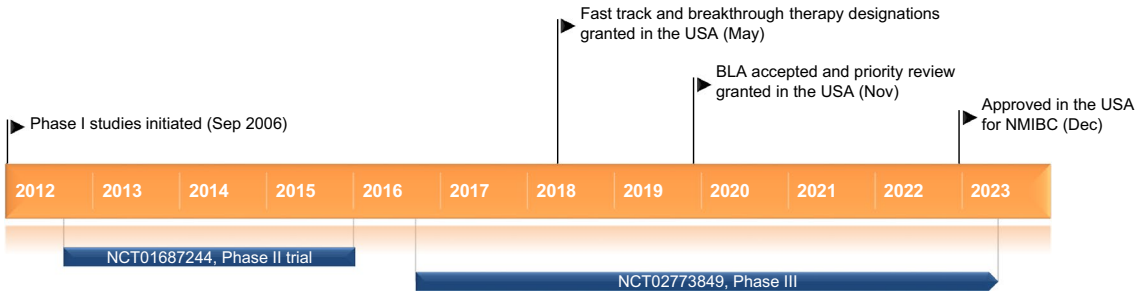
1 Introduction

Bladder cancer is a common type of cancer that is frequently (75–80%) diagnosed as non-muscle invasive bladder cancer (NMIBC) [1]. NMIBC involves the growth of cancer cells within the lining of the bladder without invasion into the muscle layer [1]. High-risk NMIBC, including carcinoma in situ (CIS), is typically treated with intravesical administration of Bacillus Calmette-Guérin vaccine (BCG) and surgical removal of tumours [1, 2]. Intravesical BCG has been successfully utilised in the treatment of NMIBC due to its immunostimulatory properties [2]. However, treatment options were limited in patients who did not respond to BCG [1].

Nadofaragene firadenovec (nadofaragene firadenovec-vncg; Adstiladrin®) is a non-replicating adenoviral vector-based gene therapy developed by Ferring Pharmaceuticals for the treatment of high-risk BCG-unresponsive NMIBC [1]. Nadofaragene firadenovec received its first approval on 16 Dec 2022 in the USA for the treatment of high-risk BCG-unresponsive NMIBC with CIS with or without papillary tumours in adults [1, 3]; it is the first gene therapy to be approved for the treatment of bladder cancer [3]. Nadofaragene firadenovec is also being developed by Trizell Ltd. and the Abramson Cancer Center of the University of



Key milestones in the development of nadofaragene firadenovec. *BLA* biologics license application, *NMIBC* non-muscle-invasive bladder cancer

Pennsylvania for the treatment of mesotheliomas including malignant pleural mesothelioma [4].

The recommended dosage of nadofaragene firadenovec is 3×10^{11} viral particles/mL in 75 mL instilled into the bladder via a urinary catheter once every 3 months [5]. The use of nadofaragene firadenovec is not recommended in patients who are immunocompromised or immunodeficient due to the risk of disseminated adenovirus infection. Delaying cystectomy may progress to potentially lethal metastatic disease; cystectomy is recommended in patients with CIS who do not achieve a complete response (CR) after 3 months or have recurrent CIS [5].

1.1 Company Agreements

Ferring Pharmaceuticals developed nadofaragene firadenovec for the treatment of high-grade NMIBC in patients who are unresponsive to BCG therapy with related companies, including FKD Therapies Oy, which acquired an exclusive license from Merck & Co to develop and commercialize nadofaragene firadenovec in September 2011 [6, 7].

2 Scientific Summary

2.1 Pharmacodynamics

The vector DNA in nadofaragene firadenovec encodes for interferon (IFN)-α2b, thus transfected urothelial cells produce and secrete IFN-α2b [2]. IFN-α2b induces the apoptosis of cancer cells via tumour necrosis factor-related apoptosis-inducing ligand-related pathways. Additionally, indirect antiangiogenic effects due to downregulation of basic fibroblast growth factor and matrix metalloproteinase-9 within tumour cells also contributes to apoptosis [2]. IFN-α signalling is involved in the stimulation of anticancer immune responses, which ultimately includes the activation of dendritic cells and subsequent priming of cytotoxic T cells and natural killer cells against cancer [8].

A dose-dependent increase of the excretion of IFN-α2b into urine was observed following intravesical administration of nadofaragene firadenovec in an animal model [9]. An additional dose on day 4 significantly ($p < 0.05$) increased IFN-α2b secretion in comparison with a single dose [9]. IFN-α2b was also detected in the urine of patients with recurrent NMIBC after intravesical administration of nadofaragene firadenovec [10]; however, no further improvements were observed with a second dose in patients with BCG-refractory NMIBC [11].

The magnitude of the antiviral response to the adenovirus vector was associated with improved outcomes during a phase III trial in patients with BCG-unresponsive NMIBC (NCT02773849) [12, 13]. In 55 patients with CIS (± high-grade T1 or Ta disease) who achieved a CR, significantly ($p = 0.0033$) more patients (43 vs 8) had a post-baseline immunogenic response (defined as a two-fold increase of anti-adenoviral antibodies from baseline). Similarly, in patients with high-grade T1 or Ta disease (without CIS) who achieved a CR, significantly ($p = 0.0003$) more patients (30 vs 4) had a post-baseline immunogenic response [12]. A significant ($p = 0.001$) difference in the proportion of patients who had on-treatment antibody titres > 800 against the vector was reported between responders and non-responders (89% and 59%, respectively) [13].

2.2 Pharmacokinetics

In patients receiving intravesical treatment with nadofaragene firadenovec 3×10^{11} viral particles/mL in 75 mL, vector DNA was detectable in the blood of one patient across two clinical trials (the patient numbers and trial identifiers were not reported) [5]. Detectable levels of vector DNA were reported in the urine of patients across both trials, with the frequency of positive detections correlating with higher dose levels. Vector DNA was detected in 1 of 4 patients during a phase I trial and 16 of 19 patients in a phase II trial [5].

Features and properties of nadofaragene firadenovec	
Alternative names	Adstiladrin®, Instiladrin, nadofaragene firadenovec-vncg, rAd-IFNa/Syn3, SCH-721015, TR-002
Class	Antineoplastics; IFNA2B gene therapies
Mechanism of action	Gene transference; IFNA2B expression stimulants
Route of administration	Intravesical (for bladder cancer), intrapleural (for mesotheliomas)
Pharmacodynamics	Interferon production following intravesical or intrapleural administration was reported in patients with bladder cancer or mesothelioma, respectively; in patients with bladder cancer, stronger anti-vector immune responses correlated with better clinical outcomes
Pharmacokinetics	Across two trials, vector DNA was detected in the blood of 1 patient (patient numbers were not reported); vector DNA was detected in the urine in 1/4 patients in one trial and 16/19 patients in another trial.
Adverse events	
Most frequent grade 1 or 2 events	Discharge around the catheter during instillation, fatigue, bladder spasm, micturition urgency, chills, dysuria, pyrexia
Grade 3 events	Micturition urgency, bladder spasm, syncope, hypertension, urinary incontinence
ATC codes	
WHO ATC code	L01 (antineoplastic agents)
EphMRA ATC code	L1 (antineoplastics)
Chemical name	Not available

2.3 Therapeutic Trials

In an open-label, single-arm, multicentre phase III trial in patients with BCG-unresponsive NMIBC, a CR was achieved in 53.4% (95% CI 43.3%–63.3%) of 103 patients in the CIS cohort [primary endpoint] (NCT02773849) [14]. The CR rate was significantly ($p < 0.0001$) higher than the prespecified rate of 27% in this cohort. In this trial, 157 patients aged ≥ 18 years with an Eastern Cooperative Oncology Group status of ≤ 2 were treated with an intravesical dose of nadofaragene firadenovec 75 mL at a concentration of 3×10^{11} viral particles/mL; repeat doses on months 3, 6 and 9 were administered in patients who had an absence of high-grade recurrent disease. Main exclusion criteria included the presence of upper urinary tract disease, urothelial carcinoma within the prostatic urethra, lymphovascular invasion, micropapillary bladder cancer or hydronephrosis caused by T1 disease. Patients were enrolled into one of two cohorts, the CIS with/without concomitant high-grade Ta or T1 disease cohort [referred to as the CIS cohort] ($n = 107$) or the high-grade Ta or T1 disease (without CIS) cohort [referred to as the high-grade Ta or T1 disease cohort] ($n = 50$); 4 and 2 patients from the respective cohorts were excluded from efficacy analyses as they did not meet the protocol-defined criteria for BCG-unresponsive NMIBC. In secondary endpoints, nadofaragene firadenovec treatment resulted in a CR rate of 72.9% (95% CI 58.2%–84.7%) in 48 patients of the high-grade Ta or T1 disease cohort. The median duration of CR was 9.69 months in the CIS cohort and the high-grade recurrence-free survival in the high-grade Ta or T1 disease cohort was 12.35 months. The median follow-up durations were 19.7 and 20.2 months in the respective cohorts (Jul 2019 data cutoff date) [14]. During longer-term follow-up (Sep 2020 data cutoff date), the 24-month cystectomy-free survival and overall survival (OS) rates were 64.6% and 94.4% in the CIS cohort, and 69.8% and 93.2% in the high-grade Ta or T1 disease cohort [15, 16].

In an open-label, multicentre phase II trial in BCG-refractory or relapsed NMIBC, the 12-month high-grade disease relapse-free survival rate was 33.3% in 21 patients receiving low dose (1×10^{11} viral particles/mL) nadofaragene firadenovec and 36.8% in 19 patients receiving high dose (3×10^{11} viral particles/mL) nadofaragene firadenovec [primary endpoint] (NCT01687244) [17]. All patients in the trial were treated with a single intravesical dose of nadofaragene firadenovec in 75 mL. Patients without high-grade disease recurrence received additional treatments with nadofaragene firadenovec on months 4, 7 and 10 [17].

In phase I trials, 2 of 7 (29%) patients with BCG-refractory NMIBC achieved a CR in a phase Ib trial following intravesical treatment with nadofaragene firadenovec 3×10^{11} viral particles/mL in 75 mL [secondary endpoint, the primary endpoint was to evaluate the transfection efficacy of a second dose] (NCT01162785) [11]. In a phase I trial, intravesical treatment with nadofaragene firadenovec 3×10^{9} to 3×10^{11} viral particles/mL in 75 mL resulted in a CR in 7 of 17 (41%) patients with BCG-refractory NMIBC [secondary endpoint, the primary endpoint was safety] (NCT00536588) [10].

Key clinical trials of nadofaragene firadenovec

Drug(s)	Indication	Phase	Status	Location	Identifier	Sponsor
Nadofaragene firadenovec	Bladder cancer	III	Active, not recruiting	USA	NCT02773849, rAd-IFN-CS003	Ferring Pharmaceuticals
Nadofaragene firadenovec	Bladder cancer	II	Completed	USA	NCT01687244, rAd-IFN-CS002	FKD Therapies Oy
Nadofaragene firadenovec	Bladder cancer	Ib	Completed	USA	NCT01162785	M.D. Anderson Cancer Center
Nadofaragene firadenovec	Bladder cancer	I	Completed	USA	NCT00536588	Merck Sharp & Dohme LLC
Nadofaragene firadenovec, celecoxib, gemcitabine	Mesothelioma	III	Active, not recruiting	Global	INFINITE, NCT03710876, EudraCT2017-003169-82, rAd-IFN-MM301	Trizell Ltd.
Nadofaragene firadenovec, celecoxib, chemotherapy	Mesothelioma	I[a]	Completed	USA	NCT01119664	Abramson Cancer Center of the University of Pennsylvania
Nadofaragene firadenovec	Mesothelioma	I	Completed	USA	NCT01212367	Abramson Cancer Center of the University of Pennsylvania

[a]Also reported as a phase II trial

2.4 Adverse Events

Nadofaragene firadenovec was generally well tolerated during a phase III trial in 157 patients with BCG-unresponsive NMIBC (NCT02773849) [14]. The safety population included all treated patients in the CIS and the high-grade Ta or T1 disease cohorts. Grade 1 or 2 drug-related adverse events (AEs) were reported in 66% of patients and grade 3 drug-related AEs were reported in 4% of patients; no grade 4 or 5 drug-related AEs were reported. The most common (incidence ≥ 10%) grade 1 or 2 TRAEs were discharge around the catheter during instillation (25%), fatigue (20%), bladder spasm (15%), micturition urgency (14%), chills (12%), dysuria (11%) and pyrexia (10%). Grade 3 drug-related AEs reported during the trial were micturition urgency (two patients; incidence 1%), bladder spasm, syncope, hypertension and urinary incontinence (one patient each; incidence 1%) [14].

Treatment discontinuation occurred in three patients due to AEs [14]. The reasons for discontinuation were due to discharge around the catheter during instillation, bladder spasms and drug-related urothelial hyperplasia (one patient each). Five off-treatment deaths were reported ≥ 4 months after the final dose of nadofaragene firadenovec, including three deaths following a cardiac event, one death due to pneumonia and an unknown cause of death [14].

2.5 Ongoing Clinical Trials

One phase III trial is currently evaluating nadofaragene firadenovec in BCG-unresponsive NMIBC [NCT02773849] (nadofaragene firadenovec single arm trial).

3 Current Status

Nadofaragene firadenovec received its first approval on 16 Dec 2022 for the treatment of adults with high-risk BCG-unresponsive NMIBC with CIS with or without papillary tumours in the USA [1].

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40265-023-01846-z.

Declarations

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Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability Not applicable.

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