Risk Management Plan

Active substance(s) (INN or common name):	Nadofaragene firadenovec
Pharmacotherapeutic group (ATC Code):	L01XL10
Name of Marketing Authorisation Applicant:	Ferring Pharmaceuticals A/S Amager Strandvej 405 DK-2770 Kastrup Denmark
Number of medicinal products to which this RMP refers:	1
Product concerned (brand name):	ADSTILADRIN

Data lock point for RMP:	03-Aug-2025	Version number:	1.0
Date of final sign off:	09-Apr-2026		

Rationale for submitting an updated RMP:	Not applicable
Summary of significant changes in this EU-RMP:	Not applicable

Other RMP versions under evaluation:

Not applicable

Details of the currently approved RMP:

Not applicable

QPPV name:

Lene Holdrup

QPPV oversight declaration:

The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file.

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Abbreviations

AE	adverse event
ALT	alanine aminotransferase
ADR	adverse drug reaction
ATC	anatomical therapeutic chemical classification system
ATMP	advanced therapeutic medicinal product
AST	aspartate aminotransferase
AUA	American Urological Association
AUC	area under the curve
BCG	Bacillus Calmette-Guérin
CIS	carcinoma in situ
C_{max}	maximum concentration
CR	complete response
CTR	clinical trial report
DLP	data lock point
DNA	deoxyribonucleic acid
EAU	European Association of Urology
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
GLP	good laboratory practice
GMO	genetically modified organism
hERG	human ether-a-go-go related gene
HG	high-grade
IFNα2b	interferon-α2b
INN	international nonproprietary name
IBCG	International Bladder Cancer Group
LG	low-grade
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute common terminology criteria for adverse events
NMIBC	non-muscle invasive bladder cancer
PBRER	periodic benefit-risk evaluation report
PL	package leaflet

PSUR	periodic safety update report
PT	preferred term
qPCR	quantitative polymerase chain reaction
QPPV	qualified person responsible for pharmacovigilance
RMP	risk management plan
SAE	serious adverse event
SAR	serious adverse reaction
SmPC	summary of product characteristics
SMQ	standardised MedDRA query
TEAE	treatment-emergent adverse event
TURBT	transurethral resection of bladder tumour
ULN	upper limit of normal
vp	viral particle

Definitions of terms

Nadofaragene firadenovec	Non-replicating recombinant type 5 adenovirus vector-based gene therapy containing the human interferon-α2b transgene
rAd-IFN	Nadofaragene firadenovec
Syn3NODA (excipient)	Polyamide surfactant that enhances an efficient entry of the adenovirus into the urothelial cells

Part I Product(s) overview

Table 1 Part I – Product(s) overview

Active substance(s) (INN or common name)	Nadofaragene firadenovec
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic cell and gene therapy (L01XL10)
Marketing Authorisation Applicant	Ferring Pharmaceuticals A/S Amager Strandvej 405 DK-2770 Kastrup Denmark
Medicinal product to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	ADSTILADRIN
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Nadofaragene firadenovec is a gene therapy medicinal product that embeds the gene for expression of the human interferon-α2b (IFNα2b) protein in bladder cells.
	Summary of mode of action: Nadofaragene firadenovec is a non-replicating recombinant type 5 adenovirus vector-based gene therapy containing the human IFNα2b transgene. Intravesical administration of nadofaragene firadenovec results in the entry of viral particles into the tumour cells and the urothelium that make up the luminal surface of the bladder, leading to the expression of IFNα2b protein by those cells. In the transduced cells, the viral DNA does not integrate into the genome. Treatment with nadofaragene firadenovec has shown anti-tumour effects in mice with bladder (cancer cell) xenografts.
	Important information about its composition: Nadofaragene firadenovec contains genetically modified organisms (GMOs). Nadofaragene firadenovec is a non-replicating recombinant type 5 adenovirus vector containing the cDNA of the IFNα2b transgene under the control of the cytomegalovirus immediate-early promoter. Nadofaragene firadenovec is produced in human embyonic kidney cells by recombinant DNA technology.

	Syn3NODA (excipient) is a polyamide surfactant that enhances an efficient entry of the adenovirus into the urothelial cells.
Hyperlink to the product information	1.3.1 SmPC
Indication(s) in the EEA	Current: ADSTILADRIN is indicated as monotherapy for the treatment of adult patients with Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumours.
	Proposed: Not applicable.
Dosage in the EEA	Current: The recommended dose of ADSTILADRIN is 75 mL at a concentration of 3×10^{11} viral particles (vp)/mL administered by intravesical instillation every three (3) months.
	Proposed: Not applicable.
Pharmaceutical form(s) and strengths	Current: Intravesical suspension, 3×10^{11} vp/mL.
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the EU?	Yes

ATC: anatomical therapeutic chemical classification system; EEA: European Economic Area; EU: European Union; INN: international nonproprietary name; RMP: risk management plan

Part II Safety specification

Ferring nadofaragene firadenovec has the invented name ADSTILADRIN. Ferring nadofaragene firadenovec is hereafter referred to as nadofaragene firadenovec.

Part II Module SI - Epidemiology of the indication(s) and target population(s)

Indication

Nadofaragene firadenovec is indicated as monotherapy for the treatment of adult patients with Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumours.

Incidence

Bladder cancer is the 9th most frequently diagnosed cancer worldwide with 614,298 new cases and 220,596 deaths estimated globally for 2022. The regions with the highest incidence rates are Europe (224,777 new cases), Asia (215,755 new cases) and North America (95,546 new cases).[1,2]

Approximately 75% of patients with bladder cancer present with disease confined to the mucosa (CIS and Ta) or submucosa (T1), defined as NMIBC. CIS is a flat, high-grade, non-invasive urothelial carcinoma that, without treatment, progresses to muscle-invasive disease in approximately 54% of patients. Ta and T1 are papillary tumours that can be high-grade. Ta is non-invasive and T1 invades the lamina propria.[3]

Prevalence

The 5-year prevalence of bladder cancer is more than 1,900,000 cases estimated worldwide, with 758,094 cases in Europe, 643,459 cases in Asia, 327,816 cases in North America, 105,577 cases in Latin America and the Caribbean, 97,605 cases in Africa, and 17,764 cases in Oceania.[1,2]

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease

Bladder cancer mainly occurs in the elderly, with a median age at diagnosis of 73 years.[4] Furthermore, it is approximately 4 times more common in men than women, with the age-standardised incidence rate of 9.3/100,000 for men and 2.4/100,000 for women.[2]

Based on data from the United States, the 5-year relative survival rate for bladder cancer is 77%, with 77% in white patients and 63% in black patients. Furthermore, the 5-year relative survival rate for CIS is 95%, with 95% in white patients and 91% in black patients.[5]

Risk factors for bladder cancer:[3]

- Tobacco smoking is the most important risk factor for bladder cancer, accounting for approximately 50% of the cases.
- Occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons, and chlorinated hydrocarbons is the 2nd most important risk factor for bladder cancer, accounting for approximately 10% of the cases. This type of exposure occurs during processing of e.g. paint, dye, metal, and petroleum products.
- Correlative evidence exists for other risk factors, such as pelvic ionization radiation.

The main existing treatment options

Transurethral resection of bladder tumour (TURBT) is a standard initial procedure in the management of NMIBC and is recommended by e.g. the American Urological Association (AUA), the European Association of Urology (EAU), and the International Bladder Cancer Group (IBCG).[3,6,7] A complete TURBT is critical for determining accurate tumour type, staging, grading, and optimising patient outcomes. A repeat TURBT is often needed if the initial TURBT was incomplete.

After TURBT, several guidelines recommend risk stratification to aid personalised treatment decisions and surveillance strategies.[3,6] EAU recommends stratifying patients into 4 risk groups based on their probability of progressing to muscle-invasive disease (i.e. low-risk, intermediate-risk, high-risk, and very high-risk).[3] Table 2 summarises the EAU primary treatment recommendations for high-risk and very high-risk NMIBC.

Table 2 European Association of Urology primary treatment recommendations for high-risk and very high-risk non-muscle invasive bladder cancer[3]

Risk group	Definition	Primary treatment
High-risk	• All T1 HG/G3 without CIS, except those included in the very high-risk group • All CIS, except those included in the very high-risk group • Ta LG/G2 or T1G1, no CIS with all 3 risk factors • Ta HG/G3 or T1 LG, no CIS with at least 2 risk factors • T1G2 no CIS with at least 1 risk factor	• Full-dose intravesical BCG[a] for 1-3 years should be offered • Immediate radical cystectomy may be discussed with these patients
Very high-risk	• Ta HG/G3 and CIS with all 3 risk factors • T1G2 and CIS with at least 2 risk factors • T1 HG/G3 and CIS with at least 1 risk factor • T1 HG/G3 no CIS with all 3 risk factors	• Immediate radical cystectomy should be discussed with these patients • Full-dose intravesical BCG[a] for 1-3 years should be offered if radical cystectomy is not feasible or refused by the patient

BCG: Bacillus Calmette-Guérin; CIS: carcinoma in situ; G1-3: grade 1-3 according to WHO 1973 or WHO 2004/2022; HG: high-grade; LG: low-grade, WHO: World Health Organization

Risk factors: Age >70 years, multiple papillary tumours, and tumour diameter >3 cm.

a: A complete BCG schedule comprises an induction phase of 6-weekly instillations followed by a maintenance phase of 3 weekly instillations at 3, 6, 12, 18, 24, 30, and 36 months.

Bacillus Calmette-Guérin immunotherapy

Intravesical immunotherapy with live attenuated BCG is the standard of care for patients with high-risk NMIBC and comprises an induction phase of 6-weekly instillations followed by a maintenance phase of 3-weekly instillations at 3, 6, 12, 18, 24, 30, and 36 months.[3]

BCG immunotherapy induces initial complete response rates of 70–75% in patients with CIS and of 55–65% in patients with high-risk papillary tumours. However, despite initial treatment success with BCG, 40% of patients will eventually relapse.[8]

BCG intravesical treatment is associated with both local and systemic side effects. However, serious side effects are encountered in <5% of patients and can be treated effectively in almost all cases. Furthermore, elderly patients do not seem to experience more side effects leading to treatment discontinuation.[3]

Radical cystectomy

Radical cystectomy is the most effective treatment against NMIBC, but is associated with significant risk of morbidity, mortality and impact on quality of life.[3,6] Thus, radical cystectomy is not feasible in all patients or may be refused by the patients.

In a retrospective study including 506 patients with bladder cancer undergoing radical cystectomy, 503 (99%) patients experienced a total of 2,485 complications within 30 days. The most commonly

reported complications were genitourinary (24%), gastrointestinal (19%), and infectious complications (15%), and a majority was classified as minor (Clavien-Dindo classification grade ≤IIIa). Overall, 12 (2.4%) patients died within 30 days.[9]

BCG-unresponsive NMIBC

According to EAU, BCG-unresponsive NMIBC is defined as all BCG refractory tumours[a] and those who develop T1/Ta high-grade recurrence within 6 months of completion of adequate BCG exposure[b] or develop CIS within 12 months of completion of adequate BCG exposure.[3] Similar definitions are provided by other guidelines.[7,10]

Patients with BCG-unresponsive NMIBC are unlikely to respond to further BCG therapy and radical cystectomy is therefore the standard and recommended treatment option for these patients.[3,7] Enrolment in clinical trials assessing new treatment strategies or bladder-preserving strategies may be offered if radical cystectomy is not feasible or is refused by the patient. A recent study reviewed oncologic outcomes in a large retrospective multi-centre cohort of 578 patients with BCG-unresponsive NMIBC, of whom 28% underwent upfront radical cystectomy and 72% received bladder-sparing therapy. This study showed that early initiation of bladder-sparing treatment is safe within the first 12 months of diagnosis of BCG-unresponsive NMIBC as comparable low rates of metastasis (2%) and death from bladder cancer (1%) were observed. Although bladder cancer death at 5 years was similar (14%) in the 2 groups, oncological outcomes began to increase 12 months after diagnosis.[11]

Follow-up

Due to the risk of recurrence and progression among patients with high-risk and very high-risk NMIBC, the EAU recommended surveillance strategy includes initial frequent cystoscopy and cytology and life-long follow-up.[3]

Natural history of the indicated condition in the untreated population, including mortality and morbidity

The survival prognosis for patients with NMIBC is relatively favourable, with the cancer-specific survival rate in high-grade NMIBC of 70-85% at 10 years.[6]

NMIBC (CIS, Ta and T1) is associated with a high risk of recurrence and progression. Without any treatment, approximately 54% of patients with CIS progress to muscle-invasive disease.[3] In a systematic review including 3,088 patients with high-risk NMIBC initially treated with TURBT and/or intravesical instillations, 659 (21%) patients progressed to muscle-invasive disease and

[a] BCG refractory tumour according to EAU:[3] If T1 high-grade/grade 3 tumour is present at 3 months, if Ta high-grade/grade 3 tumour is present after 3 months and/or at 6 months, after re-induction or 1st course of maintenance, if CIS (without concomitant papillary tumour) is present at 3 months and persists at 6 months after either re-induction or 1st course of maintenance, or if high-grade tumour appears during BCG maintenance therapy (low-grade recurrence during or after BCG treatment is not considered a BCG failure).

[b] Adequate BCG exposure according to EAU:[3] Completion of at least 5 of 6 doses of an initial induction course plus at least 2 out of 6 doses of a second induction course or 2 out of 3 doses of maintenance therapy.

428 (14%) patients died as a result of bladder cancer (median follow-up 48–123 months). Survival after progression to muscle-invasive disease was 35%. Progression to muscle-invasive disease and bladder cancer-related death mainly occurred within 48 months.[12]

Important co-morbidities

Bladder cancer mainly occurs in the elderly which have several co-morbidities. Important co-morbidities in patients with bladder cancer include:

- Cardiovascular disease[13]
- Diabetes[14]
- Chronic obstructive pulmonary disease[15]
- Acute kidney injury[16]
- Previous non-urothelial malignancy[17]

Part II Module SII - Non-clinical part of the safety specification

The results of a series of non-clinical studies provide evidence that the intravesical administration of nadofaragene firadenovec[c] can provide sustained local exposure to human IFNα2b in the bladder and urine and evoke an anti-tumour response in the bladder.

Syn3NODA and nadofaragene firadenovec

The collective non-clinical results indicate that, following intravesical administration, the excipient Syn3NODA is primarily retained in the bladder and urine. Nevertheless, toxicology studies demonstrated that Syn3NODA is rapidly cleared primarily as intact Syn3NODA via the faeces when intentionally introduced into the systemic circulation.

Following intravesical administration in monkeys, nadofaragene firadenovec DNA was detected in the bladder and human IFNα2b was detected in urine for several weeks post-administration. An antibody response was also generated toward nadofaragene firadenovec and human IFNα2b following intravesical administration in both rodent and monkey studies, over time reducing IFNα2b levels in urine and bladder.

Pharmacology

It was shown that the contact between the urothelial surface and the drug product was critical for the transduction of the urothelial cell, and data from a study in cynomolgus monkeys indicated that the dose strength of 3×10^{11} vp/mL enabled transduction of urothelial cells.

The repeat-dose pharmacology studies conducted in rats after intravesical administration indicated that longer time intervals between doses, such as 90 days, increases the duration and magnitude of urinary IFNα2b exposure after the 2nd dose. Results from the repeat-dose monkey study also indicated that monkeys could be re-dosed successfully, since despite the development of antibody responses against both the adenovirus vector and the human IFNα2b protein, detectable levels of human IFNα2b were secreted following a second dose 90 days after the first. Overall, these data support the clinical dosing schedule of once every 90 days.

Toxicology

The predominant safety finding after intravesical dosing was a reversible local irritation in the bladder.

In monkeys, intravesical administration of either Syn3NODA or nadofaragene firadenovec/Syn3NODA caused mild to moderate urinary tract inflammation, including chronic inflammation in the tunica muscularis, ulceration, and tissue changes (urothelial hyperplasia and cytoplasmic vacuolation) after the first and second doses. Following a 2-month recovery period

[c] Nadofaragene firadenovec and Syn3NODA were referred to as rAd-IFN and Syn3, respectively, in the non-clinical study reports.

after the second dose, partial resolution was observed, with minimal urothelial inflammation and fibrosis in the lamina propria of the bladder remaining in a few animals.

The cynomolgus monkey and the rat received dose concentrations of nadofaragene firadenovec that were higher in the monkey (1.7x) and lower in the rat (0.33x), respectively, with regard to the clinical dose concentration of viral particles. For Syn3NODA, identical concentrations were given to monkeys whereas rats received a higher dose concentration (4x). Overall, animals were exposed to higher concentrations of nadofaragene firadenovec and Syn3NODA compared with patients. Calculations of the exposure multiples (based on dose) are presented in Table 3 and Table 4. In addition, the systemic exposure multiples for Syn3NODA (based on area under the curve [AUC]) are presented in Table 5.

Table 3 Calculated exposure multiples of nadofaragene firadenovec and Syn3NODA based on dose

	Nado (vp/mL)	Syn3NODA (mg/mL)	Dose volume (mL)	Body weight (kg)	Nado total dose (vp)	Nado (vp/kg)	Syn3NODA total dose (mg)	Syn3NODA (mg/kg)
Species								
Monkey	5×10^{11}	1	25	3	1.25×10^{13}	4.17×10^{12}	25	8.33
Human	3×10^{11}	1	75	60	2.25×10^{13}	3.75×10^{11}	75	1.25
Exposure multiples (monkey versus human) based on dose								
Nado	$4.17 \times 10^{12} / 3.75 \times 10^{11} = 11.12$							
Syn3NODA	8.33 / 1.25 = 6.66							

nado: nadofaragene firadenovec; vp: viral particle

Table 4 Calculated local (bladder) exposure multiples of nadofaragene firadenovec and Syn3NODA based on dose

	Nado (vp/mL)	Syn3NODA (mg/mL)	Dose volume (mL)	Approx. bladder surface area (cm^2)	Nado total dose (vp)	Nado (vp/cm^2)	Syn3NODA total dose (mg)	Syn3NODA (mg/cm^2)
Species								
Rat	1×10^{11}	4	0.5	1	0.5×10^{11}	0.5×10^{11}	2	2
Monkey	5×10^{11}	1	25	45	1.25×10^{13}	2.8×10^{11}	25	0.56
Human	3×10^{11}	1	75	250	2.25×10^{13}	9.0×10^{10}	75	0.30
Local (bladder) multiples (monkey versus human) based on dose								
Nado	$2.8 \times 10^{11} / 9.0 \times 10^{10} = 3.11$							
Syn3NODA	0.56 / 0.30 = 1.87							

nado: nadofaragene firadenovec; vp: viral particle

Table 5 Systemic exposure multiples of Syn3NODA based on AUC

	AUC (ng*h/mL)	C_{max} (ng/mL)
Species		
Rat	74,800 (female)[a] 91,800 (male)[a]	Not calculated
Monkey	230,000 (female day 1)[b]	24,700 (female day 1)
Human	1,604[c]	118
Syn3NODA systemic exposure multiples based on AUC		
Rat (female) versus human	74,800 / 1,604 = 46.63	
Rat (male) versus human	91,800 / 1,604 = 57.23	
Monkey (female day 1) versus human	230,000 / 1,604 = 143.39	

AUC: area under the curve; C_{max}: maximum concentration

a. $AUC_{0\text{-}24hr}$

b. $AUC_{0\text{-}25hr}$

c. $AUC_{0\text{-}infinity}$

Given the low level of systemic exposure, no evidence of any systemic toxicity was seen in rats or cynomolgus monkeys following intravesical administration. The maximum clinical intravesical dose of Syn3NODA on a mg/kg basis is 1.25 mg/kg and no adverse systemic effects were seen in repeat-dose (~2-week) rat or monkey intravenous administration studies of Syn3NODA at dose levels up to 5 mg/kg/day. In this context, for alpha interferons, toxicities including effects on body weight and clinical pathology alterations, generally occur at relatively high exposure levels achieved after parenteral administration.

Syn3NODA was shown to be non-genotoxic in a good laboratory practice (GLP) compliant in vivo rat micronucleus test conducted in line with ICH S2 (R1) guidance. In addition, Syn3NODA did not inhibit the human ether-a-go-go related gene (hERG) channel tail current at doses of up to 4.53 micromolar in a GLP compliant in vitro assay conducted in line with ICH S7B guidance.

Safety pharmacology

Safety pharmacology studies were conducted with Syn3NODA in a conventional battery of safety pharmacology studies including intravenous administration at doses of 1 and 5 mg/kg in cynomolgus monkeys instrumented for measurement of cardiovascular function and electrocardiograms, and in separate studies of conscious rats monitored for changes in neurological and respiratory function. In these and in an in vitro hERG assay, no findings of concern were observed.

Conclusion

Collectively, the results obtained from a series of non-clinical studies indicate that the intravesical administration of nadofaragene firadenovec in animals is associated with the sustained and local expression of human IFN-α2b. Furthermore, no unacceptable toxicities were seen in animals

following intravesical or intravenous administration at doses/exposures beyond those anticipated clinically. The non-clinical studies showed the importance of contact between the urothelial surface and the drug product transduction of the urothelial cells and support the drug product concentration used in the clinical setting as well as a dose frequency of 90 days.

Part II Module SIII - Clinical trial exposure

As of DLP, 221 patients have been exposed to nadofaragene firadenovec in the completed clinical trials included in the NMIBC development programme.

Cumulative patient exposure to nadofaragene firadenovec in completed clinical trials in the NMIBC development programme is presented by sex, age, race, and ethnicity in Table 6. Table 7 summarises the cumulative patient exposure by dose, strength, and duration of exposure.

Table 6 Cumulative patient exposure to nadofaragene firadenovec in completed clinical trials in the non-muscle invasive bladder cancer development programme by sex, age, race, and ethnicity

	Phase 1 trials[a] (N=24)	Phase 2 trial[b] (N=40)	Phase 3 trial[c] (N=157)	Total (N=221)
Sex				
Males	23	33	129	**185**
Females	1	7	28	**36**
Age group (years)				
<65	6	10	38	**54**
65-74	5	16	64	**85**
≥75	13	14	55	**82**
Race				
White	17	38	146	**201**
Black or African American	0	1	8	**9**
Asian	0	1	3	**4**
Unknown	7	0	0	**7**
Ethnicity				
Hispanic or Latino	1	1	4	**6**
Not Hispanic or Latino	16	32	148	**196**
Not reported	0	2	1	**3**
Unknown	7	5	4	**16**

Note: This table does not include the phase 1 trial rAd-IFN-CS-004, as the single patient included in that trial had muscle-invasive bladder cancer. Furthermore, no ongoing trials are included in the table.

a: Phase 1 trials P03816 and 2009-0938.

b: Phase 2 trial rAd-IFN-CS-002.

c: Phase 3 trial rAd-IFN-CS-003.

Table 7 Cumulative patient exposure to nadofaragene firadenovec in completed clinical trials in the non-muscle invasive bladder cancer development programme by dose, strength, and duration of exposure

	Phase 1 trials[a] (N=24)	Phase 2 trial[b] (N=40)	Phase 3 trial[c] (N=157)	Total (N=221)
Dose				
75 mL	24	40	157	**221**
Strength				
3 x 10^9 vp/mL	3	0	0	**3**
1 x 10^{10} vp/mL	3	0	0	**3**
3 x 10^{10} vp/mL	3	0	0	**3**
1 x 10^{11} vp/mL	4	21	0	**25**
3 x 10^{11} vp/mL	11	19	157	**187**
Duration of exposure				
1 intravesical instillation	17	17	57	**91**
2 intravesical instillations[d]	7	6	24	**37**
3 intravesical instillations[d]	0	0	14	**14**
4 intravesical instillations[d]	0	17	20	**37**
≥5 intravesical instillations[d]	0	0	42	**42**

vp: viral particle

Note: This table does not include the phase 1 trial rAd-IFN-CS-004, as the single patient included in that trial had muscle-invasive bladder cancer. Furthermore, no ongoing trials are included in the table.

a: Phase 1 trials P03816 and 2009-0938.

b: Phase 2 trial rAd-IFN-CS-002.

c: Phase 3 trial rAd-IFN-CS-003.

d: Intravesical instillations once every 3 months.

Part II Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Table 8 Exclusion criteria in the pivotal phase 3 clinical trial (rAd-IFN-CS-003) within the development programme

Important exclusion criterion	Reason for exclusion criterion	Missing information (yes/no) Rationale if not missing information
Evidence of muscle invasive (muscularis propria) or metastatic disease Metastatic disease included, but was not limited to presence of lymphovascular invasion and/or micropapillary disease, and patients with T1 disease accompanied by the presence of hydronephrosis secondary to the primary tumour	Radical cystectomy is the recommended treatment option for patients with muscle invasive bladder cancer stage T2-T4a.[18]	No Not considered missing information as the proposed indication for nadofaragene firadenovec is adult patients with BCG-unresponsive NMIBC with CIS with or without papillary tumours.
Suspected hypersensitivity to IFNα2b	Known or suspected hypersensitivity to IFNα2b is not common. If a subject with known or suspected hypersensitivity is exposed to IFNα2b, a severe immunological response with a life-threatening condition could occur.	No Not considered missing information as only 1 unrelated SAE within the SMQ *Anaphylactic reaction* (narrow search) has been reported across the clinical development programme for nadofaragene firadenovec (PT *Anaphylactic reaction*). In addition, hypersensitivity to the active substance or to any of the excipients is listed as a contraindication in the product information for nadofaragene firadenovec (Section 4.3 of the EU-SmPC and Section 2 of the EU-PL). See further details in Table 12.
Clinically significant and unexplained elevated liver or renal function tests	Patients with clinically significant and unexplained elevated liver or renal function tests are considered to be a vulnerable group that usually receive specialised treatment and close monitoring. These patients were excluded to not jeopardise patient safety.	No Not considered missing information as the pivotal phase 3 trial rAd-IFN-CS-003 allowed patients with: • AST ≤1.5×ULN • ALT ≤1.5×ULN • Total bilirubin ≤1.5×ULN • eGFR ≥30 mL/min/1.73 m^2 In addition, it is highly unlikely that intravesical instillation of nadofaragene firadenovec would result in exposure of hepatic and renal tissues, since its pharmacological effect is highly restricted to the bladder.

Important exclusion criterion	Reason for exclusion criterion	Missing information (yes/no) Rationale if not missing information
Women who are pregnant or lactating or refuse to commit to use contraception	Pregnant and lactating women are considered to be a vulnerable group. These patients were excluded to not jeopardise patient safety.	No Not considered missing information as NMIBC is a disease that primarily affects elderly men and the following information is provided in the product information for nadofaragene firadenovec (see further details in Table 12): • Healthcare professionals who are pregnant should not prepare, administer, or come into contact with ADSTILADRIN due to the theoretical risk of adenoviral infection (Section 4.4 of the EU-SmPC and Section 2 of the EU-PL). • Pregnancy status in women of childbearing potential should be verified prior to initiating ADSTILADRIN (Section 4.6 of the EU-SmPC and Section 2 of the EU-PL). • Women of childbearing potential should use an effective (double) contraception method during treatment, and for 6 months following the last dose (Sections 4.4 and 4.6 of the EU-SmPC and Section 2 of the EU-PL). • Male patients with female partners of childbearing potential should use a barrier protection contraception method during treatment, and for 3 months following the last dose (Sections 4.4 and 4.6 of the EU-SmPC and Section 2 of the EU-PL). Male patients should also not donate sperm during this period (EU-PL Section 2).

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BCG: Bacillus Calmette-Guérin; eGFR: estimated glomerular filtration rate; EU: European Union; IFNα2b: interferon α2b; MedDRA: Medical Dictionary for Regulatory Activities; NMIBC: non-muscle invasive bladder cancer; PL: package leaflet; PT: preferred term; SAE: serious adverse event; SmPC: summary of product characteristics; SMQ: standardised MedDRA query; ULN: upper limit of normal

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions.

All trials in the clinical development program were open-label, and the pivotal phase 3 trial was designed as a single-arm trial due to ethical concerns about randomising patients with BCG-unresponsive NMIBC to a placebo control group. Given that the current standard of care for these patients is radical cystectomy, single-arm trials are considered appropriate for evaluating new therapies. However, the absence of a control group hinders the identification of safety risks and limits the ability to attribute any adverse events (AEs)/serious adverse events (SAEs) to nadofaragene firadenovec based on the causality assessment of each AE/SAE.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

An overview of special populations typically under-represented in clinical development programmes is presented in Table 9.

Table 9 Exposure of special populations included or not in the clinical trial development programme

Type of special population	Exposure
Patients ≥75 years	Of the 221 patients exposed to nadofaragene firadenovec in the completed clinical trials, 82 (37.1%) patients were ≥75 years. Furthermore, in the pivotal phase 3 trial rAd-IFN-CS-003 including 157 exposed patients, 55 (35.0%) patients were ≥75 years and the median age at informed consent was 71.0 years (minimum: 39 years, maximum: 89 years). Thus, there is no medical or scientific reason to expect a different safety profile of nadofaragene firadenovec in this population.
Female patients	Of the 221 patients exposed to nadofaragene firadenovec in the completed clinical trials, 36 (16.3%) patients were females. In addition, in the pivotal phase 3 trial rAd-IFN-CS-003, the safety profile was comparable between male and female patients. Thus, there is no medical or scientific reason to expect a different safety profile of nadofaragene firadenovec in this population.
Pregnant and lactating women	Pregnant and lactating women were excluded from the clinical development programme for nadofaragene firadenovec. There are no data from inadvertent exposure to nadofaragene firadenovec in this population.
Immunocompromised or immune-deficient patients	Not included in the clinical development programme.
Population with relevant different ethnic origin	Of the 221 patients exposed to nadofaragene firadenovec in the completed clinical trials, 201 were White, 9 were Black or African American, 4 were Asian, and 7 were unknown. Regarding the ethnicity of the patients in the completed clinical trials, 196 were not Hispanic or Latino, 6 were Hispanic or Latino, 3 were not reported, and 16 were unknown.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme.

Part II Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

As of DLP, nadofaragene firadenovec is approved in 1 country worldwide (United States). Furthermore, the Ministry of Health in Israel has granted license to import United States Food and Drug Administration (FDA)-approved nadofaragene firadenovec in advance of local regulatory approval. An early access program for nadofaragene firadenovec has also been approved by the Hainan Provincial Health Commission in China in advance of regulatory approval.

SV.1.1 Method used to calculate exposure

Calculation of patient exposure to nadofaragene firadenovec is based on sales up to 31 July 2025 as the sales database is limited to whole months. It is assumed that 100% of sales were administered to the patients.

Since a dose of ADSTILADRIN is administered once every 3 months, the calculations concerning patient exposure are based on the following range:

- Maximum exposure (1 dose = 1 treated patient): Assumes that each sold dose is given to a different patient.
- Minimum exposure (patient years): Assumes that the same patient is treated once every 3 months with 4 doses per year.

SV.1.2 Exposure

The cumulative exposure to nadofaragene firadenovec from marketing experience calculated up to 31 July 2025 is estimated to 3,350 treated patients, corresponding to 838 patient years (Table 10).

Table 10 Exposure table by region

Indication	Formulation	Dose	Strength	Region	Cumulative patient exposure (up to 31 July 2025)	
					1 dose = 1 treated patient	Patient years
Adult patients with high-risk BCG-unresponsive NMIBC with CIS with or without papillary tumours	Suspension for intravesical instillation	75 mL	3 x 10^{11} vp/mL	N. America	3,327	832
				Asia	23	6
				Total	3,350	838

BCG: Bacillus Calmette-Guérin; CIS: carcinoma in situ; NMIBC: non-muscle invasive bladder cancer; vp: viral particle

Note: 1 dose = 1 treated patient assumes that that each sold dose is given to a different patient. Patient years assumes that the same patient is treated once every 3 months with 4 doses per year.

Part II Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Nadofaragene firadenovec will only be available by restricted medical prescription and will be administered in highly specialised clinical settings.

Nadofaragene firadenovec is instilled into the bladder and results in transient local expression of the IFNα2b protein. The pharmacological effect is therefore highly restricted to the bladder and misuse for illegal purposes is considered very unlikely. Furthermore, as stipulated in Sections 4.2 and 6.6 of the EU-SmPC and in Section 3 of the EU-PL, after the treatment, ADSTILADRIN should be evacuated from the bladder via urinary catheter, or the patient may void and completely empty the bladder.

No cases of misuse or abuse of nadofaragene firadenovec were observed in the clinical development programme.

Part II Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Safety concerns in the initial RMP submission are listed in Table 11.

Table 11 Safety concerns in the initial RMP submission

Summary of safety concerns	
Important identified risks	None
Important potential risks	Disseminated adenovirus infection
Missing information	Long-term safety

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Risks that are not considered important for the purpose of planning of risk management for nadofaragene firadenovec are grouped based on the rationale for non-inclusion (Table 12). Overall, the impact of these risks on the risk-benefit balance of nadofaragene firadenovec is low and the risks are considered to be appropriately managed and mitigated in the proposed product information for nadofaragene firadenovec.

Table 12 Risks not considered important for inclusion in the list of safety concerns

Risk	Risk-benefit impact
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)	
Lower urinary tract signs and symptoms (PTs *Bladder spasm*, *Dysuria*, *Haematuria*, *Instillation site discharge*, *Micturition urgency*, *Nocturia*, and *Pollakiuria*)	The PTs *Bladder spasm*, *Dysuria*, *Haematuria*, *Instillation site discharge*, *Micturition urgency*, *Nocturia*, and *Pollakiuria* are listed as common (≥1/100 to <1/10) or very common (≥1/10) adverse reactions in the EU-SmPC and EU-PL for nadofaragene firadenovec. Across the clinical development programme for nadofaragene firadenovec, all ADRs reported for PTs *Bladder spasm*, *Dysuria*, *Haematuria*, *Instillation site discharge*, *Micturition urgency*, *Nocturia*, and *Pollakiuria* were non-serious and there were no ADRs that were NCI-CTCAE grade 4 or 5 in severity. As of DLP, 137 ADRs (5 serious and 132 non-serious) have been received from post-marketing sources on the beforementioned PTs on nadofaragene firadenovec. In the clinical development programme, these events were non-serious, transient, and mostly mild to moderate in severity, and have negligible impact on the benefit-risk profile. Consequently, these events are deemed non-important risks with minimal clinical significance and are also considered signs and symptoms associated with the underlying NMIBC and/or the instillation procedure. The risk will be monitored through routine pharmacovigilance activities, including single case reporting, PBRERs/PSURs and signal detection. No additional pharmacovigilance or risk minimisation activities are planned or deemed necessary.

Risk	Risk-benefit impact
Known risk that require no further characterisation and are followed-up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised)	
Urinary tract infection	The PT *Urinary tract infection* is listed as a very common (≥1/10) adverse reaction in the EU-SmPC and EU-PL for nadofaragene firadenovec. Across the clinical development programme for nadofaragene firadenovec, all ADRs reported for PTs *Escherichia urinary tract infection*, *Urinary tract infection*, *Urinary tract infection bacterial*, *Urinary tract infection enterococcal*, *Urinary tract infection neonatal*, *Urinary tract infection viral*, *Application site infection*, *Urogenital infection bacterial*, and *Post procedural infection* were non-serious and none were NCI-CTCAE grade 4 or 5 in severity. As of DLP, 1 serious ADR of PT *Urinary tract infection enterococcal* has been received from post-marketing sources on nadofaragene firadenovec. It is important to emphasise that most patients with nosocomial urinary tract infections have either had genitourinary or urological manipulation, and most catheter-associated urinary tract infections derive from the patient's own colonic flora.[19] Furthermore, it is highly unlikely for a non-replicating adenoviral vector to cause urinary tract infection. As stipulated in Section 4.4 of the EU-SmPC, urinary tract infection should be excluded before each bladder instillation (bladder mucous membrane inflammation may increase the risk of haematological dissemination of ADSTILADRIN). If a urinary tract infection is diagnosed during therapy, the therapy should be interrupted until the patient is asymptomatic and treatment with antibiotics is completed. In Section 2 of the EU-PL, patients are also informed that they will not receive ADSTILADRIN if they have a urinary tract infection. In addition, to further mitigate this risk, aseptic techniques should be used during preparation and insertion into the bladder (EU-SmPC Sections 4.2 and 6.6, and EU-PL information intended for health care professionals only). The risk is considered well-managed by the information shared to patients and healthcare professionals and will be monitored through routine pharmacovigilance activities, including single case reporting, PBRERs/PSURs and signal detection. No additional pharmacovigilance or risk minimisation activities are planned or deemed necessary.
Anaphylactic reaction	A total of 1 SAE (PT *Anaphylactic reaction*) unrelated to nadofaragene firadenovec has been reported within the SMQ *Anaphylactic reaction* (narrow search) across the clinical development programme for nadofaragene firadenovec. As of DLP, there were no cases reported within the SMQ *Anaphylactic reaction* (narrow search) from post-marketing sources on nadofaragene firadenovec. Hypersensitivity to the active substance or to any of the excipients is listed as a contraindication in the product information for nadofaragene firadenovec (EU-SmPC Section 4.3 and EU-PL Section 2). The risk is considered well-managed by the information shared to patients and healthcare professionals and will be monitored through routine pharmacovigilance activities, including single case reporting, PBRERs/PSURs and signal detection. No additional pharmacovigilance or risk minimisation activities are planned or deemed necessary.

Risk	Risk-benefit impact
Immunogenicity	Immunogenicity was evaluated through the measurement of anti-adenovirus type 5 antibody levels in serum in the phase 1 trial P03816, the phase 2 trial rAd-IFN-CS-002, and the pivotal phase 3 trial rAd-IFN-CS-003, and through the measurement of anti-IFNα2b antibody levels in serum in the phase 1 trial P03816 and the phase 2 trial rAd-IFN-CS-002. In the phase 3 trial rAd-IFN-CS-003, 72.4% of patients had a positive immunogenic response in anti-adenovirus type 5 antibody levels (i.e., a 2-fold increase in titre from baseline). Notably, there was a higher incidence of high-grade recurrence-free survival at month 3 in patients with a positive immunogenic response (77.7%) compared to patients without a positive immunogenic response (34.3%) Similar results were observed in the phase 2 trial rAd-IFN-CS-002, in which 55.0% of patients had a positive immunogenic response in anti-adenovirus type 5 antibody levels (i.e. a 2-fold increase in titre from baseline). Overall, there was a higher incidence of high-grade recurrence-free survival at month 12 in patients with anti-adenoviral antibodies present at baseline compared to patients without anti-adenoviral antibodies present at baseline, indicating that the presence of anti-adenoviral antibodies at baseline does not adversely impact the efficacy of nadofaragene firadenovec. In the phase 1 trial P03816, 29.4% of the patients had occasional occurrence of anti-adenovirus type 5 antibody titres >10-fold over baseline, with no measurable adverse clinical manifestations. Anti-IFNα2b antibody titres were evaluated in the phase 1 trial P03816 and the phase 2 trial rAd-IFN-CS-002. In the phase 1 trial, 1 patient had a positive antibody level at the pre-dose assessment and only 1 patient had a positive antibody level at the week 12 assessment. In the phase 2 trial, 1 patient only had a positive anti-IFNα2b antibody response with a 1:20 titre at 1 occasion following the first instillation of nadofaragene firadenovec, consistent with the expectation that human IFNα2b resulting from adenovirus-mediated transgene expression is not immunogenic. With regards to efficacy, these findings suggest a strong association between a positive clinical outcome and immunogenic response against the adenovirus part of nadofaragene firadenovec. With regards to safety, in a post-hoc evaluation of the phase 3 trial rAd-IFN-CS-003, a numerically higher incidence of TEAEs was reported in antibody-positive patients compared with antibody-negative patients. However, the safety profile in antibody-positive patients remained consistent with the overall safety findings in rAd-IFN-CS-003. Furthermore, 63.7% of the patients in rAd-IFN-CS-003 received at least 2 intravesical instillations of nadofaragene firadenovec and no clinically significant immune-mediated reactions were observed despite repeated administrations. As of DLP, there are no SAEs reported within the SMQ *Immune-mediated/ autoimmune disorders* (narrow search) in clinical trials with nadofaragene firadenovec. In addition, no cases have been reported within the beforementioned SMQ from post-marketing sources on nadofaragene firadenovec. The risk will be monitored through routine pharmacovigilance activities, including single case reporting, PBRERs/PSURs and signal detection. No additional pharmacovigilance or risk minimisation activities are planned or deemed necessary.

Risk	Risk-benefit impact
Other reasons for considering the risks not important	
Pregnancy and lactation	NMIBC is a disease that primarily affects elderly men. Of the 221 patients exposed to nadofaragene firadenovec in the completed clinical trials, only 36 (16.3%) patients were females and only 54 (24.4%) patients overall were <65 years. In the pivotal phase 3 trial rAd-IFN-CS-003 including 157 exposed patients, only 28 (17.8%) were females and only 38 (24.2%) patients overall were <65 years. Furthermore, in rAd-IFN-CS-003, the median age at informed consent was 71.0 years (minimum: 39 years, maximum: 89 years). Pregnant and lactating women were excluded from the clinical development programme for nadofaragene firadenovec. There are no data from inadvertent exposure to nadofaragene firadenovec in this population. As stipulated in Section 4.4 of the EU-SmPC and in Section 2 of the EU-PL, health care professionals who are pregnant should not prepare, administer, or come into contact with ADSTILADRIN due to the theoretical risk of adenoviral infection. In addition, as stipulated in Sections 4.4 and 4.6 of the EU-SmPC and in Section 2 of the EU-PL, pregnancy status in women of childbearing potential should be verified prior to initiating ADSTILADRIN. Furthermore, women of childbearing potential should use an effective (double) contraception method during treatment, and for 6 months following the last dose. Male patients with female partners of childbearing potential should use a barrier protection contraception method during treatment, and for 3 months following the last dose. Male patients should also not donate sperm during this period (EU-PL Section 2). The risk is considered well-managed by the information shared to patients and healthcare professionals and will be monitored through routine pharmacovigilance activities, including single case reporting, PBRERs/PSURs and signal detection. No additional pharmacovigilance or risk minimisation activities are planned or deemed necessary.
Traumatise the urinary tract	As of DLP, there were no SAEs reported in clinical trials with nadofaragene firadenovec within the PTs *Bladder injury*, *Bladder perforation*, *Foreign body in urogenital tract*, *Genital contusion*, *Genital injury*, *Haematuria traumatic*, *Pelvic organ injury*, *Penile contusion*, *Penis injury*, *Traumatic anuria*, *Traumatic haematoma*, *Traumatic haemorrhage*, *Urethral injury*, *Urethral stricture traumatic*, *Urinary bladder explosion*, *Urinary bladder haematoma*, *Urinary bladder rupture*, *Urinary tract injury*, and *Urethral perforation*. In addition, no cases have been reported within the beforementioned PTs from post-marketing sources on nadofaragene firadenovec. As stipulated in Section 4.4 of the EU-SmPC, care should be taken not to traumatise the urinary tract. The risk is considered well-managed by the information shared to patients and healthcare professionals and will be monitored through routine pharmacovigilance activities, including single case reporting, PBRERs/PSURs and signal detection. No additional pharmacovigilance or risk minimisation activities are planned or deemed necessary.

ADR: adverse drug reaction; DLP: data lock point; EU: European Union; IFNa2b: interferon-α2b; MedDRA: Medical Dictionary for Regulatory Activities; NCI-CTCAE: National Cancer Institute common terminology criteria for adverse events; NMIBC: non-muscle invasive bladder cancer; PBRER: periodic benefit-risk evaluation report; PL: package leaflet; PSUR: periodic safety update report; PT: preferred term; SAE: serious adverse event; SmPC: summary of product characteristics; SMQ: standardised MedDRA query; TEAE: treatment-emergent adverse event

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Risks considered important for inclusion in the list of safety concerns for further evaluation as part of the pharmacovigilance plan or risk minimisation activities are summarised in Table 13.

Table 13 Risks considered important for inclusion in the list of safety concerns

Safety concerns	Risk-benefit impact
Important identified risks	
None	
Important potential risks	
Disseminated adenovirus infection	Nadofaragene firadenovec is a non-replicating recombinant type 5 adenovirus vector transfected with the human IFN-α2b gene. The final adenoviral vector is non-replicating as a consequence of removing the adenovirus E1a and E1b regions. However, there is a potential risk of formation of replication-competent adenovirus through recombination or complementation which could potentially lead to a disseminated adenovirus infection. Any impact of this risk on the benefit-risk balance of nadofaragene firadenovec is anticipated to be reduced by the measures taken in the EU-SmPC and EU-PL to mitigate this risk. Furthermore, nadofaragene firadenovec will only be available by restricted medical prescription and will be administered in highly specialised clinical settings.
Missing information	
Long-term safety	To address the information gap, long-term safety is being evaluated in all ongoing clinical trials with nadofaragene firadenovec. Any impact of this risk on the benefit-risk balance of nadofaragene firadenovec is anticipated to be reduced by the fact that nadofaragene firadenovec will only be available by restricted medical prescription and will be administered in highly specialised clinical settings.

EU: European Union; IFN-α2b: interferon-α2b; PL: package leaflet; SmPC: summary of product characteristics

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable. This is the first RMP submitted to obtain marketing authorisation for nadofaragene firadenovec.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Important identified risk:

None.

Important potential risk: Disseminated adenovirus infection

Potential mechanisms:

Nadofaragene firadenovec is a non-replicating recombinant type 5 adenovirus vector transfected with the human IFN-α2b gene. The final adenoviral vector is non-replicating as a consequence of removing the adenovirus E1a and E1b regions. However, there is a potential risk of formation of replication-competent adenovirus through recombination or complementation which could potentially lead to a disseminated adenovirus infection.

Evidence sources and strength of evidence:

This is an advanced therapeutic medicinal product (ATMP) specific risk consideration.

The potential for generation of replication-competent adenovirus in humans has not been specifically monitored in the clinical development programme for nadofaragene firadenovec. However, shedding of nadofaragene firadenovec was investigated in the clinical development programme for nadofaragene firadenovec.

Clinical trials with nadofaragene firadenovec and post-marketing sources are the evidence sources of this risk.

Characterisation of the risk:

The true incidence of disseminated adenovirus infection is unknown. A literature survey reported that in none out of 201 patients treated in vivo or ex vivo with a replication-deficient adenoviral vector could the presence of replication-competent adenovirus be demonstrated.[20]

Shedding of vector (rAd-IFN)-derived DNA in blood and urine was assessed by quantitative polymerase chain reaction (qPCR) in 2 clinical trials with nadofaragene firadenovec (P03816 and rAd-IFN-CS-002), which measures the presence of DNA fragments in the biological sample but not necessarily intact viral particles.

In the phase 1 trial P03816, no rAd-IFN-derived DNA was detected in blood. In the phase 2 trial rAd-IFN-CS-002, only a single patient had detectable rAd-IFN-derived DNA in blood at a single time point after the second instillation of nadofaragene firadenovec, indicating limited systemic exposure of the vector. Measurable rAd-IFN-derived DNA in urine was observed in most of the patients in the phase 1 trial P03816 (with detection frequency and persistence increasing with dose level) and in all patients in the phase 2 trial rAd-IFN-CS-002. rAd-IFN-derived DNA was still detected in some patients at day 14 (P03816) and day 12 (rAd-IFN-CS-002). In rAd-IFN-CS-002, 3 (13%) patients had detectable rAd-IFN-derived DNA in urine at month 4 day 1 prior to the second instillation of nadofaragene firadenovec. Taken together, data from these trials indicate that rAd-IFN-derived DNA is likely to be excreted in urine in gradually decreasing levels. The ratio of intact to degraded vector fragments was not analysed and infectivity assessment of PCR-positive samples was not performed.

As of DLP, no events were reported in clinical trials with nadofaragene firadenovec on the disseminated adenovirus infection related preferred terms (PTs) *Adenoviral conjunctivitis*, *Adenoviral encephalitis*, *Adenoviral haemorrhagic cystitis*, *Adenoviral hepatitis*, *Adenoviral meningitis*, *Adenoviral upper respiratory infection*, *Pneumonia adenoviral*, *Adenovirus encephalomyeloradiculitis*, *Adenovirus infection*, *Adenovirus interstitial nephritis*, *Adenovirus reactivation*, *Adenovirus test*, *Adenovirus test positive*, and *Gastroenteritis adenovirus*.

As of DLP, 1 serious ADR (PT *Pneumonia adenoviral*) was received from post-marketing sources on nadofaragene firadenovec on the beforementioned PTs. However, the event was assessed as not related by Ferring. The outcome of the event was reported as recovered.

No case of third-party transmission has been reported in clinical trials with nadofaragene firadenovec or from post-marketing sources.

Risk factors and risk groups:

Patients who are immunocompromised or immune-deficient represent the most significant risk group.

Preventability:

The instructions included in the EU-SmPC and EU-PL are expected to limit the frequency of this risk:

- The risk related to disseminated adenovirus infection is presented in Section 4.4 of the EU-SmPC.
- Section 4.4 of the EU-SmPC stipulates that ‘Healthcare professionals who are immunocompromised, immune-deficient, or pregnant should not prepare, administer, or come in contact with ADSTILADRIN due to the theoretical risk of adenoviral infection’. Similar information is provided in EU-SmPC Section 6.6. Section 4.4 of the EU-SmPC also stipulates that ‘Immunocompromised patients, including those receiving immunosuppressant therapy, should not come into contact with ADSTILADRIN due to the theoretical risk of adenoviral infection’. In addition, Section 2 of the EU-PL provides information that patients who are immunocompromised or immune-deficient should talk to their doctor.
- Section 4.4 of the EU-SmPC stipulates that ‘Urinary tract infection should be excluded before each bladder instillation (bladder mucous membrane inflammation may increase the risk of haematological dissemination of ADSTILADRIN). If a urinary tract infection is diagnosed during therapy, the therapy should be interrupted until the patient is asymptomatic and treatment with antibiotics is completed’. Similar information is provided in Section 2 of the EU-PL.
- Section 4.4 of the EU-SmPC stipulates that ‘Patients should be instructed to add two cups of virucidal agent (e.g. household bleach such as 5 % sodium hypochlorite) to the toilet bowl prior to voiding and wait 15 minutes before flushing the toilet. This should be done for the first 2 days after each treatment. Patients should be instructed to wash their hands after toilet

use.' Similar information is provided in Sections 4.2 and 6.6 of the EU-SmPC and in Section 2 of the EU-PL.

- Section 4.4 of the EU-SmPC stipulates that 'Male patients with female partners of childbearing potential should use a barrier protection contraceptive method during treatment, and for 3 months following the last dose to avoid exposing sexual partners to virus.' Similar information is provided in Section 4.6 of the EU-SmPC and in Section 2 of the EU-PL. Male patients should also not donate sperm during this period (Section 2 of the EU-PL).
- Section 4.4 of the EU-SmPC stipulates that 'Women of childbearing potential should use an effective (double) contraceptive method during treatment, and for a period of 6 months following the last dose to avoid the theoretical risk of exposing foetal cells to virus.' Similar information is provided in Section 4.6 of the EU-SmPC and in Section 2 of the EU-PL.
- Section 4.4 of the EU-SmPC stipulates that 'Patients treated with ADSTILADRIN should not donate blood, organs, tissues, and cells for transplantation.' Similar information is provided in Section 2 of the EU-PL.

Furthermore, ADSTILADRIN will only be available by restricted medical prescription and will be administered in highly specialised clinical settings.

Impact on the risk-benefit balance of the product:

The clinical consequences to disseminated adenovirus infection could be significant. However, the impact on the risk-benefit balance of ADSTILADRIN is anticipated to be minimised based on the measures taken in the EU-SmPC and the EU-PL. To further mitigate this risk, ADSTILADRIN will only be available by restricted medical prescription and will be administered in highly specialised clinical settings.

Public health impact:

The public health impact is anticipated to be sufficiently minimised through the EU-SmPC and EU-PL. In addition, ADSTILADRIN will only be available by restricted medical prescription.

SVII.3.2 Presentation of the missing information

Missing information: Long-term safety

Evidence source

There have been no safety concerns observed with the re-administration of nadofaragene firadenovec in clinical trials or from post-marketing sources.

Long-term exposure data, defined as at least 4 doses of 3 x 10^{11} vp/mL nadofaragene firadenovec corresponding to at least 12 months of treatment, are available for 80 patients as of DLP (9 patients in the completed phase 2 trial rAd-IFN-CS-002, 62 patients in the completed phase 3 trial

rAd-IFN-CS-003, and 9 patients in the ongoing phase 3 trial 000381). In addition, the cumulative post-marketing exposure to nadofaragene firadenovec was estimated to 838 patient years.[d]

The overall long-term safety profile of nadofaragene firadenovec is consistent across the completed clinical trials. In the phase 3 trial rAd-IFN-CS-003, the long-term safety follow-up spanned up to 5 years of treatment with nadofaragene firadenovec. The majority of the ADRs/SARs had a short median duration (≤2 days) and there were no significant ADRs/SARs of long latency. In addition, the majority of the procedure-related AEs had a short median duration (≤1 day). There were no SAEs reported post month 24 that were considered related to nadofaragene firadenovec and only 1 SAE (PT *Pyrexia*) that was considered related to the procedure.

Anticipated risk/consequence of the missing information

Long-term safety is being evaluated in all ongoing clinical trials with nadofaragene firadenovec, including the post-authorisation efficacy study ABLE-22 presented in Part IV. In addition, this risk will be monitored through routine pharmacovigilance activities, including single case reporting, PBRERs/PSURs and signal detection. No additional pharmacovigilance or risk minimisation activities are planned or deemed necessary.

Any impact of this risk on the benefit-risk balance of nadofaragene firadenovec is anticipated to be reduced by the fact that nadofaragene firadenovec will only be available by restricted medical prescription and will be administered in highly specialised clinical settings.

[d] Calculation of patient years assumes that the same patient is treated once every 3 months with 4 doses per year.

Part II Module SVIII - Summary of the safety concerns

A summary of the safety concerns is presented in Table 14.

Table 14 Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Disseminated adenovirus infection
Missing information	Long-term safety

Part III Pharmacovigilance plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

The following routine pharmacovigilance practices are included at Ferring Pharmaceuticals A/S routine:

- Systems and processes ensure that information about all suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner
- The preparation of reports for regulatory authorities:
  - Adverse drug reaction (ADR) reports
  - Periodic safety update reports (PSURs)
- Continuous monitoring of the safety profile of nadofaragene firadenovec including signal detection, safety issue evaluation, updating of labelling, and liaison with regulatory authorities

Specific adverse reaction follow-up questionnaires for safety concerns:

Not applicable.

Other forms of routine pharmacovigilance activities for safety concerns:

Not applicable.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are planned.

Part IV Plans for post-authorisation efficacy studies

The monotherapy arm in ABLE-22 is a specific obligation in the context of a conditional marketing authorisation (Table 15). The protocol for ABLE-22 is provided in Annex 5.

Table 15 Planned and ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations

Study ***Status***	**Summary of objectives**	**Efficacy uncertainties addressed**	**Milestones**	**Due date**
Efficacy studies which are conditions of the marketing authorisation				
None				
Efficacy studies which are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
ABLE-22 A phase 3, randomised, multi-centre, open-label trial to evaluate the safety and efficacy of intravesical nadofaragene firadenovec alone or in combination with chemotherapy (gemcitabine and docetaxel) or immunotherapy (pembrolizumab) in subjects with high-grade Bacillus Calmette-Guerin (BCG) unresponsive non-muscle invasive bladder cancer (NMIBC) *Ongoing*	The primary objective is to evaluate the efficacy of intravesical instillation, including reinduction, of nadofaragene firadenovec alone or in combination with chemotherapy (gemcitabine and docetaxel) or immunotherapy (pembrolizumab) in subjects with HG BCG-unresponsive NMIBC with CIS with or without concomitant HG Ta or T1 papillary disease. The secondary objectives are to evaluate muscle-invasive progression of disease, incidence of and time to cystectomy (including pathological staging at cystectomy), overall survival, malignant lesions of the upper tract and/or prostatic urethra, as well as safety.	Long-term efficacy and safety	Primary CTR (after completion of the secondary endpoint CR at Month 6)	31-Mar-2029

BCG: Bacillus Calmette-Guérin; CIS: carcinoma in situ; CR: complete response; CTR: clinical trial report; HG: high-grade; NMIBC: non-muscle invasive bladder cancer

Part V Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

V.1. Routine risk minimisation measures

Table 16 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation measures
Important identified risks	
None	
Important potential risks	
Disseminated adenovirus infection	**Routine risk communication:** • The risk related to disseminated adenovirus infection is presented in Section 4.4 of the EU-SmPC. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Instructions that healthcare professionals who are immunocompromised, immune-deficient, or pregnant should not prepare, administer, or come into contact with ADSTILADRIN are provided in Sections 4.4 and 6.6 of the EU-SmPC and in Section 2 of the EU-PL. Instructions that immunocompromised patients should not come into contact with ADSTILADRIN are also provided in Section 4.4 of the EU-SmPC. • Instructions that urinary tract infection should be excluded before each bladder instillation are provided in Section 4.4 of the EU-SmPC and in Section 2 of the EU-PL. • Instructions that patients should add virucidal agent to the toilet bowl are provided in Sections 4.2, 4.4, and 6.6 of the EU-SmPC and in Section 2 of the EU-PL. • Instructions that male patients with female partners of childbearing potential should use a barrier protection contraceptive method during treatment and for 3 months following the last dose are provided in Sections 4.4 and 4.6 of the EU-SmPC and in Section 2 of the EU-PL. Male patients should also not donate sperm during this period (Section 2 of the EU-PL). • Instructions that women of childbearing potential should use an effective (double) contraceptive method during treatment and for 6 months following the last dose are provided in Sections 4.4 and 4.6 of the EU-SmPC and in Section 2 of the EU-PL. • Instructions that patients treated with ADSTILADRIN should not donate blood, organs, tissues, and cells for transplantation are provided in Section 4.4 of the EU-SmPC and in Section 2 of the EU-PL.

Safety concern	Routine risk minimisation measures
	Other routine risk minimisation measures beyond the product information: • ADSTILADRIN will only be available by restricted medical prescription. • ADSTILADRIN will be administered in highly specialised clinical settings.
Missing information	
Long-term safety	**Other routine risk minimisation measures beyond the product information:** • ADSTILADRIN will only be available by restricted medical prescription. • ADSTILADRIN will be administered in highly specialised clinical settings.

EU: European Union; PL: package leaflet; **S**mPC: summary of product characteristics

V.2. Additional risk minimisation measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table 17 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
None		
Important potential risks		
Disseminated adenovirus infection	**Routine risk communication:** • The risk related to disseminated adenovirus infection is presented in Section 4.4 of the EU-SmPC. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Instructions that healthcare professionals who are immunocompromised, immune-deficient, or pregnant should not prepare, administer, or come into contact with ADSTILADRIN are provided in Sections 4.4 and 6.6 of the EU-SmPC and in Section 2 of the EU-PL. Instructions that immunocompromised patients should not come into contact with ADSTILADRIN are also provided in Section 4.4 of the EU-SmPC. • Instructions that urinary tract infection should be excluded before each bladder instillation are provided in Section 4.4 of the EU-SmPC and in Section 2 of the EU-PL. • Instructions that patients should add virucidal agent to the toilet bowl are provided in Sections 4.2, 4.4, and 6.6 of the EU-SmPC and in Section 2 of the EU-PL.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** None proposed.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• Instructions that male patients with female partners of childbearing potential should use a barrier protection contraceptive method during treatment and for 3 months following the last dose are provided in Sections 4.4 and 4.6 of the EU-SmPC and in Section 2 of the EU-PL. Male patients should also not donate sperm during this period (Section 2 of the EU-PL). • Instructions that women of childbearing potential should use an effective (double) contraceptive method during treatment and for 6 months following the last dose are provided in Sections 4.4 and 4.6 of the EU-SmPC and in Section 2 of the EU-PL. • Instructions that patients treated with ADSTILADRIN should not donate blood, organs, tissues, and cells for transplantation are provided in Section 4.4 of the EU-SmPC and in Section 2 of the EU-PL. **Other routine risk minimisation measures beyond the product information:** • ADSTILADRIN will only be available by restricted medical prescription. • ADSTILADRIN will be administered in highly specialised clinical settings.	

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information		
Long-term safety	**Other routine risk minimisation measures beyond the product information:** • ADSTILADRIN will only be available by restricted medical prescription. • ADSTILADRIN will be administered in highly specialised clinical settings.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None proposed. **Additional pharmacovigilance activities:** None proposed.

EU: European Union; PL: package leaflet; **S**mPC: summary of product characteristics

Part VI Summary of the risk management plan

Summary of risk management plan for ADSTILADRIN (nadofaragene firadenovec)

This is a summary of the risk management plan (RMP) for ADSTILADRIN. The RMP details important risks of ADSTILADRIN, how these risks can be minimised, and how more information will be obtained about ADSTILADRIN's risks and uncertainties (missing information).

ADSTILADRIN's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how ADSTILADRIN should be used.

This summary of the RMP for ADSTILADRIN should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of ADSTILADRIN's RMP.

I. The medicine and what it is used for

ADSTILADRIN is proposed for the treatment of adult patients with Bacillus Calmette-Guérin (BCG) unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumours (see SmPC for the full indication). It contains nadofaragene firadenovec as the active substance and it is given by intravesical instillation.

Further information about the evaluation of ADSTILADRIN's benefits can be found in ADSTILADRIN's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/adstiladrin.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of ADSTILADRIN, together with measures to minimise such risks and the proposed studies for learning more about ADSTILADRIN's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities.*

II.A List of important risks and missing information

Important risks of ADSTILADRIN are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of ADSTILADRIN. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	Disseminated adenovirus infection
Missing information	Long-term safety

II.B Summary of important risks

No risks are classified as important identified risks in the RMP for ADSTILADRIN. The important potential risk and missing information are presented below:

Important potential risk: Disseminated adenovirus infection	
Evidence for linking the risk to the medicine	ADSTILADRIN is a medicine that uses an adenovirus to deliver a gene called IFNα2b into the cells in the surface of the bladder. The adenovirus has been modified not to replicate, which means that it cannot spread in the body and cause a widespread infection. However, there is a small potential chance that the adenovirus could start to replicate if 2 viruses (adenovirus in ADSTILADRIN and another virus) infect the same bladder cell. This in turn could lead to a widespread infection called ‘disseminated adenovirus infection’. The incidence of disseminated adenovirus infection caused by modified adenoviruses is not known. In a study including 201 patients who were treated with modified adenoviruses, no adenovirus was found that could replicate.

	It was not assessed if the modified adenovirus could start to replicate in the completed clinical trials with ADSTILADRIN. However, presence of ADSTILADRIN DNA fragments in blood and urine was assessed in patients treated with ADSTILADRIN in 2 clinical trials (P03816 and rAd-IFN-CS-002) using a test called qPCR. This test does not provide any information regarding if the ADSTILADRIN DNA fragments are intact adenovirus particles or just parts of the adenovirus, nor if the fragments can infect cells. In blood, ADSTILADRIN DNA fragments were only detected in a single patient at a single time point. In urine, ADSTILADRIN DNA fragments were detected in almost all patients treated with ADSTILADRIN and were detected up to 3 months after dosing. No case of disseminated adenovirus infection has been reported in patients included in the completed and ongoing clinical trials with ADSTILADRIN. In real-world use, 1 serious event of PT *Pneumonia adenoviral* has been reported as of DLP. The event was reported as being possibly caused by ADSTILADRIN, but Ferring does not consider the event to be caused by ADSTILADRIN. The event was reported as recovered.
Risk factors and risk groups	Patients who are immunocompromised or immune-deficient represent the most significant risk group.
Risk minimisation measures	**Routine risk communication:** • The risk related to disseminated adenovirus infection is presented in Section 4.4 of the EU-SmPC. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Instructions that healthcare professionals who are immunocompromised, immune-deficient, or pregnant should not prepare, administer, or come into contact with ADSTILADRIN are provided in Sections 4.4 and 6.6 of the EU-SmPC and in Section 2 of the EU-PL. Instructions that immunocompromised patients should not come into contact with ADSTILADRIN are also provided in Section 4.4 of the EU-SmPC. • Instructions that urinary tract infection should be excluded before each bladder instillation of ADSTILADRIN are provided in Section 4.4 of the EU-SmPC and in Section 2 of the EU-PL.

	• Instructions that patients should add virucidal agent to the toilet bowl are provided in Sections 4.2, 4.4, and 6.6 of the EU-SmPC and in Section 2 of the EU-PL. • Instructions that male patients with female partners of childbearing potential should use a barrier protection contraceptive method during treatment and for 3 months following the last dose are provided in Sections 4.4 and 4.6 of the EU-SmPC and in Section 2 of the EU-PL. Male patients should also not donate sperm during this period (Section 2 of the EU-PL). • Instructions that women of childbearing potential should use an effective (double) contraceptive method during treatment and for 6 months following the last dose are provided in Sections 4.4 and 4.6 of the EU-SmPC and in Section 2 of the EU-PL. • Instructions that patients treated with ADSTILADRIN should not donate blood, organs, tissues, and cells for transplantation are provided in Section 4.4 of the EU-SmPC and in Section 2 of the EU-PL. **Other routine risk minimisation measures beyond the product information:** • ADSTILADRIN will only be available by restricted medical prescription. • ADSTILADRIN will be administered in highly specialised clinical settings.
Missing information: Long-term safety	
Risk minimisation measures	**Other routine risk minimisation measures beyond the product information:** • ADSTILADRIN will only be available by restricted medical prescription. • ADSTILADRIN will be administered in highly specialised clinical settings.

DLP: data lock point; DNA; deoxyribonucleic acid; EU: European Union; IFNα2b: interferon-α2b; PL: package leaflet; PT: preferred term; qPCR: quantitative polymerase chain reaction; SmPC: summary of product characteristics

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

ABLE-22

Purpose of the study:

The main purpose of ABLE-22 is to evaluate how well ADSTILADRIN works alone or together with chemotherapy or immunotherapy in adults with NMIBC who did not respond to treatment with BCG.

ABLE-22 also evaluates:

- If the cancer spreads to the bladder muscle
- If patients undergo bladder removal surgery, including timing and cancer stage
- Patient survival
- If patients have cancer in the upper urinary tract or prostatic urethra
- Side effects

II.C.2 Other studies in post-authorisation development plan

There are no studies required for ADSTILADRIN.

Part VII Annexes

Annex 4 Specific adverse drug reaction follow-up forms

Not applicable. There are no specific adverse reaction follow-up forms in the RMP for nadofaragene firadenovec.

Annex 6 Details of proposed additional risk minimisation activities (if applicable)

Not applicable. There are no proposed additional risk minimisation activities in the RMP for nadofaragene firadenovec.